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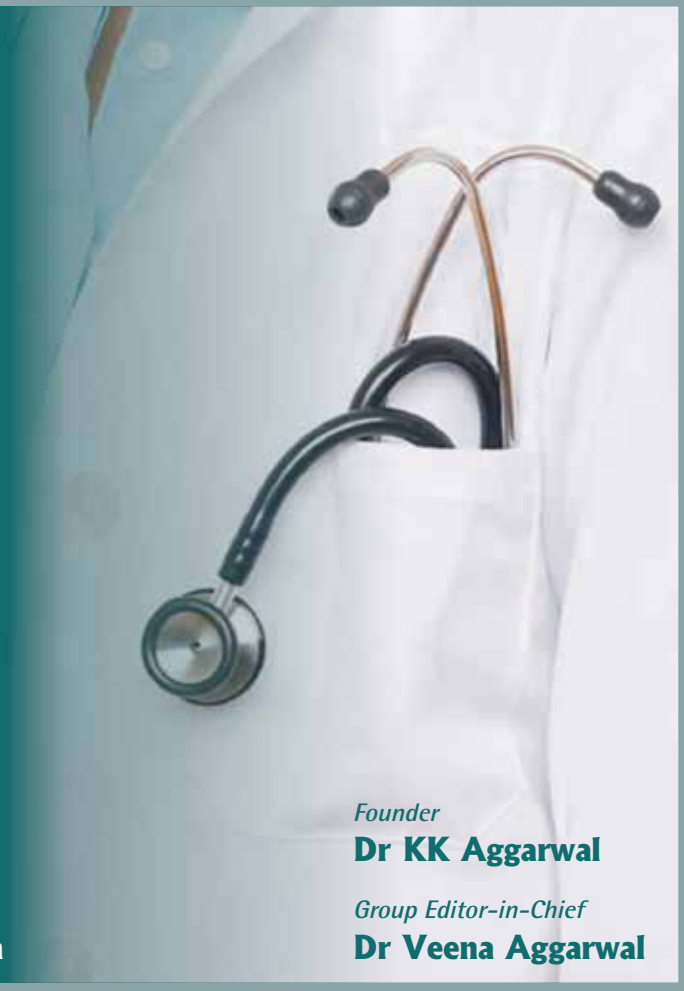

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Predisposing Factors for Ectopic Pregnancy

Patients with a previous history of ectopic pregnancy are nine times more likely to have ectopic pregnancy, according to a new study published in the *International Journal of Gynecology & Obstetrics*[1]. Likewise, a history of pelvic inflammatory disease (PID) increases the likelihood of ectopic pregnancy by fourfold.

The systematic review and meta-analysis aimed to determine risk factors associated with the occurrence of ectopic pregnancy. Observational studies published from 2000 onward in English and Portuguese were included in the analysis after a search of electronic databases, including MEDLINE/PubMed, LILACS, The Cochrane Library, and the Virtual Health Library (VHL). Studies with undefined methodologies or published before 2000 were excluded. A total of 16 risk factors were evaluated. Eleven studies conducted between 2003 and 2019, with a total of 25,051 patients were analyzed.

The study identified several strong risk factors for ectopic pregnancy, including a history of ectopic pregnancy (odds ratio [OR] 9.03), PID (OR 4.00), infertility (OR 3.70), abdominal and pelvic surgeries (OR 5.60), and previous tubal ligation (OR 5.59).

Additionally, advanced maternal age, smoking, multiple sexual partners, history of spontaneous and induced abortion, emergency contraception use, and intrauterine devices were found to slightly increase the risk of ectopic pregnancy. Advanced maternal age, specifically between 30 to 34 years (OR 1.13) and ≥40 years (OR 1.46), as well as marital status (OR 1.19) were associated with a slight increase in the risk of ectopic pregnancy. Oral contraceptive use was linked to a reduced risk (OR 0.77), while condom use had a negligible impact (OR 0.93).

The findings emphasize the need for screening policies for women at high-risk to improve early detection and outcomes. Women with a history of ectopic pregnancy, PID, infertility, prior tubal surgery, or tubal ligation should be particularly closely monitored due to their significantly increased risk. Targeted patient counseling, and preventive measures to reduce the associated morbidity and mortality can improve maternal outcomes.

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■■■■

GUEST EDITORIAL

The Smart 4S Ratio – The Sleep, Sit, Stand, and Stride System

SANJAY KALRA*, MADHUR VERMA†, NITIN KAPOOR‡

ABSTRACT

To translate evidence into meaningful outcomes, emphatic, and effective public health messaging is essential. Such messaging must be strong, yet simple, easy to explain, and friendly to follow. With due credit to earlier researchers, we suggest a Smart 4S (Sleep: Sit: Stand: Stride) ratio for smart health. Sleeping for 8 hours (1/3 of the day), sitting for 6 hours (1/4 of the day), standing for 5 hours (1/5 of the day), and being in stride (structured physical activity, sports, strenuous exercise) for 4 hours (1/6 of the day) may be suggested as a mantra for a healthy daily routine.

Keywords: Cardiovascular outcomes, exercise, physical activity, sitting, sleeping

Physical activity, sleep duration, and sedentary time have all been linked with cardiovascular and metabolic health[1]. Most research in this field is unifocal, and tries to assess the impact of one of these variables on health. Daily life, however, is an amalgam of various activities. Researchers have explored the influence of these on long-term outcomes. Based upon this, Brakenridge et al suggest ideal times for sleeping sitting, standing, and light as well as moderate physical activity[2].

This important research has significant implications, both for public and clinical care. The necessity for adequate sleep is a "discovery" that has been rediscovered by modern medicine, and rightfully so[3]. The need to ensure regular physical activity, and avoid prolonged, uninterrupted sitting, is also documented[4]. The importance of exercise, or structured physical activity, is also well known, as is the advantage of introducing diversity in physical activity, exercise, and sports[5].

4S MESSAGING

To translate this evidence and information into meaningful benefit for the public, emphatic, and effective public health messaging is essential. Such messaging must be strong, yet simple, easy to explain, and friendly to follow. With due credit to Brakenridge et al[2], we take the liberty of crafting a Smart 4S statement, or a smart ratio for smart health (Box). Sleeping for 8 hours (1/3 of the day), sitting for 6 hours (1/4 of the day), standing for 5 hours (1/5 of the day), and being in stride (structured physical activity, sports, strenuous exercise) for 4 hours (1/6 of the day) may be suggested as a mantra for a healthy daily routine.

The Smart 4S Ratio	Structured as follows
Sleeping: 8 hours/day	**Sleeping:** 1/3 of the day
Sitting: 6 hours/day	**Sitting:** 1/4 of the day
Standing: 5 hours/days	**Standing:** 1/5 of the day
Sports and strenuous activities: 4 hours/day	**Sports and strenuous activities:** 1/6 of the day

Simplified as follows: Sleep: Sit: Stand: Stride = 8:6:6:4 = 4:3:3:2

STRENGTH IN SMARTNESS

While we acknowledge that these ratios are not exactly accurate, they are a fair approximation of Brakenridge's findings. The choice of hours/day, or fractions, allows the ratio to be used as per individual choice. The simplicity

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of numbers adds strength to the health message, and ensures robustness and resilience to the conviction.

Similar messaging had led to advantageous dividends in public health, including maternal and child health[6]. Such number-based concepts have been used to guide healthy food choices, and have been incorporated in obesity guidelines as well[7]. Such a proposal lives up to the tenets of quinary prevention[8]. We hope, therefore, that the Smart 4S solution we share will help enhance healthy behaviors and lifestyles, incorporating both rest and recreation, as well as structured activity and sports.

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REVIEW ARTICLE

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

H SUDARSHAN BALLAL

ABSTRACT

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

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

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

RENAL REPLACEMENT THERAPY

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

The RRTs available for all patients with ESRD are:

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

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

HEMODIALYSIS FOR DIABETIC ESRD

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

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

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

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frequent but also has a more aggressive course than in nondiabetic patients. In view of this, aggressive measures to manage CVD need to be adopted in all diabetic patients even before they reach the stage of dialysis.

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

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

DIET IN DIABETIC PATIENTS ON DIALYSIS

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

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

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

[a]All intakes calculated on the basis of normalized body weight (i.e., the average body weight of normal persons of the same age, height and sex as the patient).

[b]These levels of caloric intake are rarely attained in practice.

[c]Includes glucose absorbed from dialysis solutions.

[d]Carbohydrate intake should be decreased in patients with hypertriglyceridemia.

HD = Hemodialysis; PD = Peritoneal dialysis; LUO = Liters of urine output per day.

BLOOD SUGAR CONTROL IN DIABETIC DIALYSIS PATIENTS

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

Altered Insulin Metabolism

In uremic patients (both diabetic and nondiabetic), insulin secretion by the beta-cells of the pancreas is reduced and the responsiveness of peripheral tissues (e.g., muscle) to insulin is depressed. On the other hand, the rate of insulin catabolism (renal and extrarenal) is decreased, and therefore, the half-life of any insulin present in the circulation is prolonged. All of these abnormalities are only partially corrected after institution of maintenance dialysis therapy.

Increased Sensitivity to Insulin

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

Insulin Therapy

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

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

Oral Hypoglycemic Agents

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

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

Metformin, a biguanide, is associated with increased incidence of lactic acidosis in dialysis patients and should not be used. Acarbose inhibits alpha-glucosidase in the enteric mucosa and moderates postprandial hyperglycemia. It may prove to be a useful adjunct to other diabetic medications in diabetic patients.

Troglitazone and other thiazolidinediones sensitize the target tissues to insulin and may be of help in obese, type 2 diabetics with insulin resistance. However, the use of this class of drugs may be associated with the risk of severe hepatotoxicity.

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

Specific problems of hemodialysis in diabetic patients:

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

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

the patient as fit as possible even before they reach dialysis.

TIMING OF DIALYSIS IN DIABETIC ESRD

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

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

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

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

ROLE OF CAPD

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

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

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

Table 2. Dialysis Modalities for Diabetics

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

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

SURVIVAL ON HEMODIALYSIS AND PERITONEAL DIALYSIS

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

TRANSPLANTATION

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

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

RECOMMENDATIONS FOR TREATMENT OF DIABETIC ESRD PATIENTS

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

CAPD is recommended for patients with:

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

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

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CLINICAL STUDY

To Study Endothelial Dysfunction by Brachial Artery Flow-mediated Dilatation and Its Relationship with Microalbuminuria in Hypertensive Individuals

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ABSTRACT

Introduction: Hypertension remains a central pathophysiologic contributor to cardiovascular morbidity and mortality. In its earliest stage, the principal endothelial alteration is merely functional and addressed as "endothelial dysfunction". Flow-mediated dilatation (FMD) of the brachial artery has been widely used as a noninvasive marker to vascular reactivity. Both microalbuminuria and endothelial dysfunction are expressions of an endothelial pathology; however, it is still uncertain whether they are interrelated, or if the two phenomena are caused in parallel by the cardiovascular risk burden. **Aim:** To study the relationship of brachial artery flow-mediated dilatation (BAFMD) with microalbuminuria in hypertensive subjects. **Method:** Total 120 subjects were included in the study comprising 80 hypertension cases and 40 controls. All subjects were subjected to anthropometric measurements and routine biochemical tests – hemogram, urea, serum creatinine, liver function test, lipid profile, BAFMD and urinary albumin to urinary creatinine ratio (30-300 mg/g Cr). **Conclusion:** Mean % FMD was lower in patients with abnormal microalbuminuria compared to normal and this was statistically verified, with p = 0.016, thereby verifying the central hypothesis of this study.

Keywords: Hypertension, microalbuminuria, brachial artery flow-mediated dilatation

Hypertension remains a central pathophysiologic contributor to cardiovascular morbidity and mortality. Although the precise cascade of events from the development of hypertension to adverse cardiovascular events remains to be elucidated, cardiovascular risk factors, including hypertension, are clearly associated with the development of vascular endothelial dysfunction. Endothelial dysfunction is a phenotypical alteration of the endovascular lining of blood vessels that is characterized by a prothrombotic, proinflammatory and proconstrictive phenotype. Endothelial function is readily measurable through multiple modalities and is an established barometer of cardiovascular risk. Further, interventions aimed at reducing cardiovascular risk, including antihypertensive therapy, are more effective if they concomitantly improve endothelial function. These data support the provocative hypothesis that reductions in cardiovascular risk secondary to antihypertensive therapy may relate independently to a particular intervention's beneficial effects on endothelial function as well as to its absolute effect on blood pressure[1].

Recent studies have established microalbuminuria as an important cardiovascular risk factor. Data reported thus far clearly underpin the importance of measuring urinary albumin in patients with hypertension.

More importantly, patients with hypertension may benefit from prevention of the onset or progression of albuminuria, and to this end, further characterization of albuminuria in hypertensive patients or of possible risk factors affecting urinary excretion of albumin, could provide useful information.

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In disease conditions, including cardiovascular risk factors, the vascular endothelium undergoes functional and structural alterations. In its earliest stage, the principal endothelial alteration is merely functional and addressed as "endothelial dysfunction". The fundamental feature of this condition is impaired nitric oxide (NO) bioavailability. This can be evaluated in humans by measuring the downstream effects, namely vasodilatation through vascular reactivity tests. In the last decade, flow-mediated dilatation (FMD) of the brachial artery has been widely used as a noninvasive marker for this purpose[2].

Both microalbuminuria and endothelial dysfunction are expressions of an endothelial pathology; however, it is still uncertain whether they are interrelated, or if the two phenomena are caused in parallel by the cardiovascular risk burden. Although endothelial dysfunction is constantly present in advanced renal disease, its association in mild renal dysfunction is still uncertain[3].

AIMS AND OBJECTIVES

- To assess endothelial dysfunction by brachial artery flow-mediated dilatation (BAFMD) in hypertensive individuals and normotensive controls.
- To study microalbuminuria in the study population.
- To study the relationship of BAFMD with microalbuminuria.

MATERIAL AND METHODS

The present study was conducted in the Dept. of General Medicine, Cardiology and Radiology, Gajra Raja Medical College, Gwalior (Madhya Pradesh) in between January 2016 and September 2017.

Target sample size of 120 was divided into the following groups according to their age:

- Cases: Eighty individuals (40 male and 40 female) between age 30 and 50 with hypertension.
- Controls: Forty individuals (20 male and 20 female) between age 30 and 50 without hypertension.

Hypertension among the subjects was defined as per the seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VII) (systolic BP [SBP] >140 mmHg and diastolic BP [DBP] >90 mmHg).

All subjects were subjected to anthropometric measurements and routine biochemical tests – hemogram, urea, serum creatinine, liver function test and lipid profile.

Patients were subjected to BAFMD study in the Dept. of Radiology. The procedure involved placing a pneumatic sphygmomanometer cuff on the forearm distal to the brachial artery and inflating it to suprasystolic levels and subsequently releasing it 5 minutes later. FMD was assessed by Doppler ultrasound with high resolution. FMD_{max} value was used in the present study.

Patient's urine sample was collected for detection of microalbuminuria. A single-void, urine sample was used to measure urinary excretion of albumin. Urinary albumin concentrations were measured by turbidimetric immunoassay and were as ratio of concentrations of urinary albumin-creatinine ratio (UACR). Microalbuminuria was defined according to recommendations of the American Diabetes Association and National Kidney Foundation (300 > UACR >30 mg/g Cr).

Inclusion Criteria

- **Cases**: Individuals having age between 30 and 50 years suffering from hypertension.
- **Controls:** Individuals having age between 30 and 50 years with no history of hypertension.

Exclusion Criteria

- Age below 30 and above 50 years.
- Documented or detected cases of type 1 or type 2 diabetes mellitus, chronic kidney disease, chronic inflammatory conditions, coronary artery disease, heart failure, acute febrile illnesses and on angiotensin-converting enzyme (ACE) inhibitors.
- Subjects who did not provide consent for the study.

Statistical Methods

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented as mean ± SD (Min-Max) and results on categorical measurements are presented in number (%). Significance is assessed at 5% level of significance. Student *t*-test has been used to find the significance of study parameters between the two groups of patients. Chi-square/Fisher exact test has been used to find the significance of study parameters on categorical scale between the two groups. Pearson's correlation test was used for exploring correlation.

OBSERVATIONS

In cases and controls, most of the subjects belonged to age groups of 46 to 50 years (34 [42.5%]) and 36 to 40 years (13 [32.5%]), respectively (Table 1). Age of the

Table 1. Distribution of Subjects According to Age and Gender

Age group	Cases		Controls	
	Male	Female	Male	Female
30-35	4 (5)	2 (2.5)	5 (12.5)	4 (10)
36-40	11 (13.8)	9 (11.2)	9 (22.5)	4 (10)
41-45	8 (10)	12 (15)	4 (10)	7 (17.5)
46-50	17 (21.2)	17 (21.2)	2 (5)	5 (12.5)

study population was restricted to 30 to 50 years to avoid the confounding influence of age-related atherogenic changes on the measurement of BAFMD. Equal number of males and females were selected within the cases and controls for comparability.

Amongst the cases, 57.5% of the subjects belonged to the Stage 1 hypertension (HTN) group as per the JNC VII criteria (Table 2). More number of females than males was present in Stage 2 HTN group while the inverse was true for Stage 1 HTN. Subjects were distributed equally among the normal and prehypertensive categories in the control group with no female preponderance. Figure 1 depicts the distribution of study participants according to stage of hypertension.

Mean baseline lumen diameter (mm) in male and female cases and controls was 3.65 ± 0.86 vs. 3.75 ± 0.71 and 3.67 ± 0.66 vs. 3.70 ± 0.66, respectively. After occlusion cuff release, among male and female cases and controls, the diameter was 3.97 ± 0.92 vs. 4.15 ± 0.74 and 4.05 ± 0.71 vs. 4.10 ± 0.79, respectively. Mean BAFMD (%) in male and female cases and controls was 6.85 ± 2.86 vs. 10.75 ± 2.38 and 7.2 ± 3.12 vs. 10.35 ± 2.76, respectively (Table 3 and Figs. 2-4). Although the baseline diameter showed no significant difference among the hypertensive and normotensive groups, the mean post occlusion diameter was much lower in the hypertensive subjects, which was thereby reflected in a much lower mean % FMD amongst them. The lowest baseline diameter, post occlusion diameter and % BAFMD were recorded in the male hypertensives while the highest of these parameters were recorded amongst the male control group.

All cases of microalbuminuria were present in the hypertensive group. Among them, more males were observed to have abnormal levels than females (Table 4 and Fig. 5).

Mean values of body mass index (BMI), total cholesterol (TC), triglycerides (TGs), low-density lipoprotein cholesterol (LDL-C) and microalbuminuria (UACR) were higher in the case group when compared to the controls. Additionally, % BAFMD was lower in hypertensives when compared to the normotensive subjects (Table 5). On applying Students *t*-test, this difference in mean values between the cases and controls was statistically significant with each of them having a p value of <0.05.

Mean FMD (%) was significantly different across the age groups (p = 0.001), with FMD (%) showing a declining trend as age increases, whereas distribution of microalbuminuria was comparable across the age groups (p = 0.52) (Table 6; Figs. 6 and 7).

Table 2. Distribution of Subjects According to Blood Pressure

Blood pressure (mmHg)	Cases		Controls	
	Male	Female	Male	Female
Normal				
SBP <120 mmHg	0 (0)	0 (0)	10 (25)	10 (25)
DBP <80 mmHg				
Prehypertension				
SBP 120-139 mmHg	0 (0)	0 (0)	10 (25)	10 (25)
DBP 80-89 mmHg				
Stage 1 HTN				
SBP 140-159 mmHg	24 (30)	22 (27.5)	0 (0)	0 (0)
DBP 90-90 mmHg				
Stage 2 HTN				
SBP ≥160 mmHg	16 (20)	18 (22.5)	0 (0)	0 (0)
DBP ≥100 mmHg				

SBP = Systolic blood pressure; DBP = Diastolic blood pressure; HTN = Hypertension.

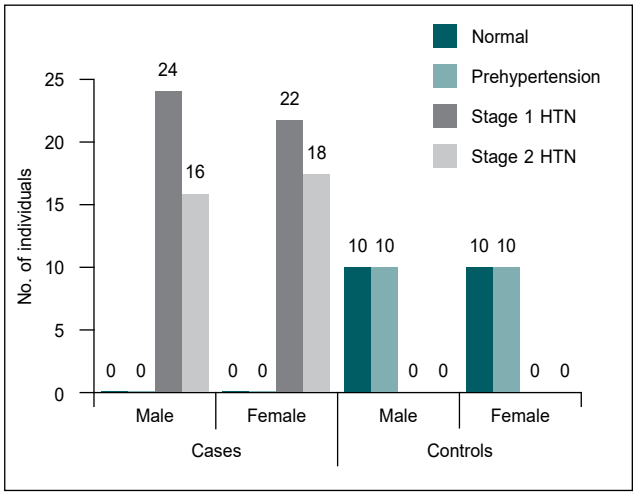

Figure 1. Distribution according to stage of hypertension.

Table 3. Comparison of Assessment of FMD Between Cases and Controls

Variable	Cases		Controls	
	Male (mean ± SD)	Female (mean ± SD)	Male (mean ± SD)	Female (mean ± SD)
Baseline lumen diameter (mm)	3.65 ± 0.86	3.67 ± 0.66	3.75 ± 0.71	3.70 ± 0.66
Diameter after occlusion release (mm)	3.97 ± 0.92	4.05 ± 0.71	4.15 ± 0.74	4.10 ± 0.79
BAFMD (%)	6.85 ± 2.86	7.2 ± 3.12	10.75 ± 2.38	10.35 ± 2.76

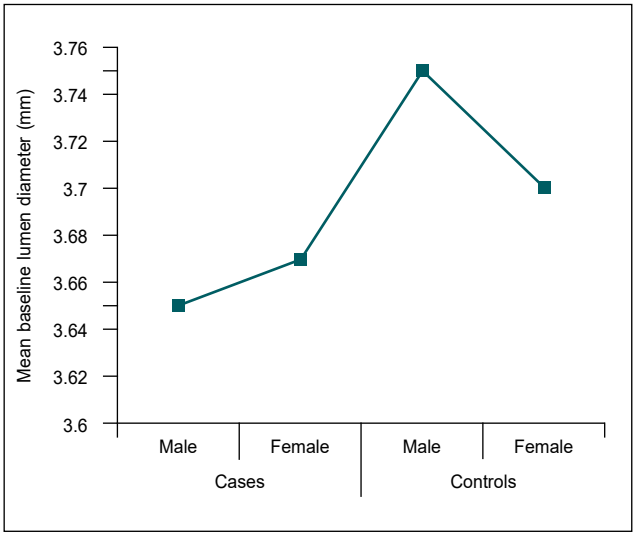

Figure 2. Mean baseline lumen diameter in study population.

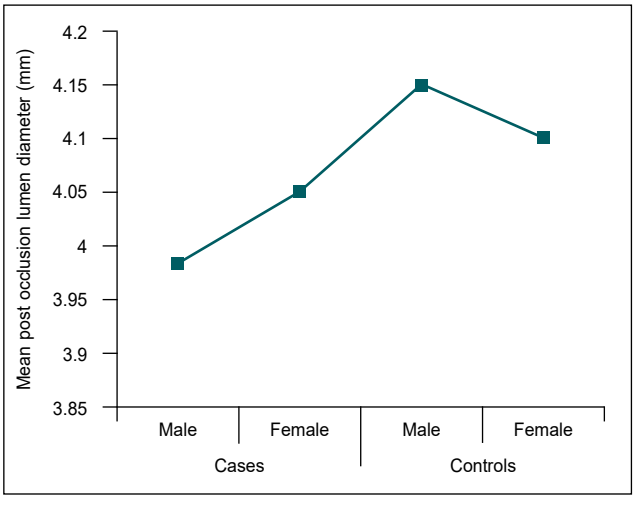

Figure 3. Mean post occlusion lumen diameter in study population.

Mean FMD was insignificantly higher among males (7.05 ± 2.55) compared to females (7 ± 3.38) (p = 0.87), whereas microalbuminuria was significantly higher among females (20 [25%]) compared to males (11 [13.8%]) (p = 0.039) in relation to smoking (Table 7).

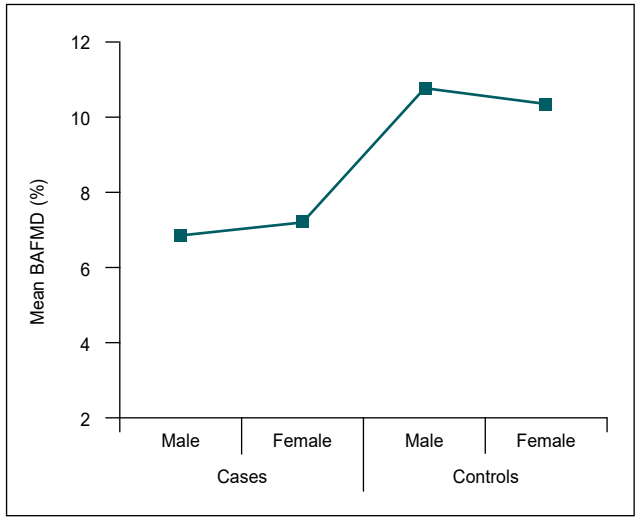

Figure 4. Mean BAFMD (%) in study population.

Table 4. Distribution of Subjects According to Microalbuminuria Levels

Microalbuminuria	Cases		Controls	
	Male	Female	Male	Female
Normal (<30)	20 (25)	29 (36.2)	20 (50)	20 (50)
Abnormal (>30)	20 (25)	11 (13.8)	0 (0)	0 (0)

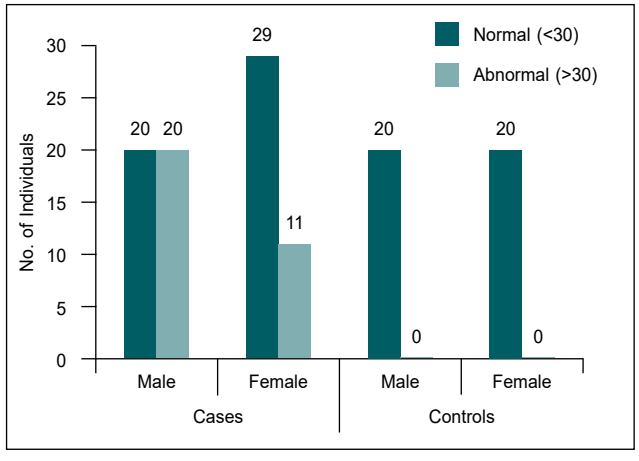

Figure 5. Distribution according to microalbuminuria.

Table 5. Comparison Between Cases and Controls

Variable	N	Mean	SD	P value
BMI				
Case	80	26.08	2.79	0.031*
Control	40	22.68	2.25	
TC				
Case	80	173.76	29.03	<0.001*
Control	40	162.77	6.19	
HDL-C				
Case	80	44.95	5.88	0.056
Control	40	44.08	28.83	
TG level				
Case	80	119.25	32.06	<0.001*
Control	40	97.58	23.50	
LDL-C				
Case	80	104.95	24.73	<0.001*
Control	40	97.57	16.25	
Microalbuminuria (ACR)				
Case	80	27.44	38.86	<0.001*
Control	40	3.73	0.68	
FMD %				
Case	80	7.04	2.173	<0.001*
Control	40	10.61	1.19	

*Significant

BMI = Body mass index; TC = Total cholesterol; HDL-C = High-density lipoprotein cholesterol; TG = Triglyceride; LDL-C = Low-density lipoprotein cholesterol; ACR = Albumin-to-creatinine ratio; FMD = Flow-mediated dilatation; N = Number; SD = Standard deviation.

Table 6. Relation of BAFMD and Microalbuminuria with Age in Cases

Age	FMD (%)		Microalbuminuria	
	Mean	SD	Normal	Abnormal
30-35	9.2	3.09	6 (7.5)	0
36-40	9.27	3.54	12 (15)	8 (10)
41-45	8.03	2.7	10 (12.5)	10 (12.5)
46-50	7.1	3.27	21 (26.2)	13 (16.2)
P value	0.001*		0.52	

The FMD % showed a secular and significant decrease in mean value in the progressively higher JNC VII stages of hypertension with computed p value of 0.038 (Table 8 and Fig. 8). The prevalence of microalbuminuria

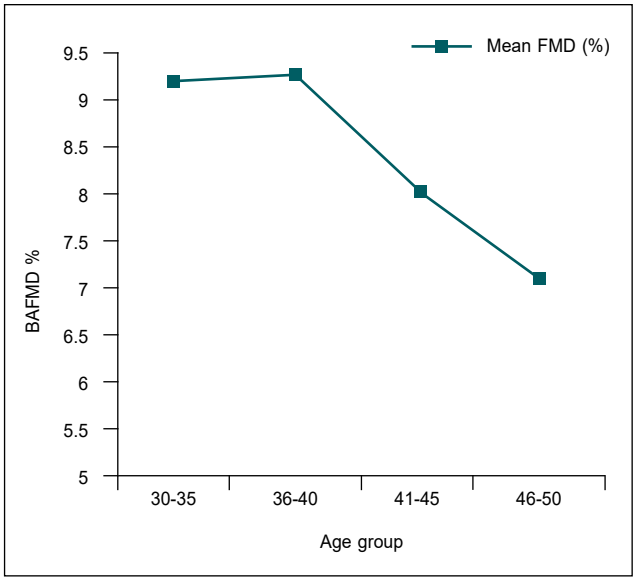

Figure 6. Age and BAFMD %.

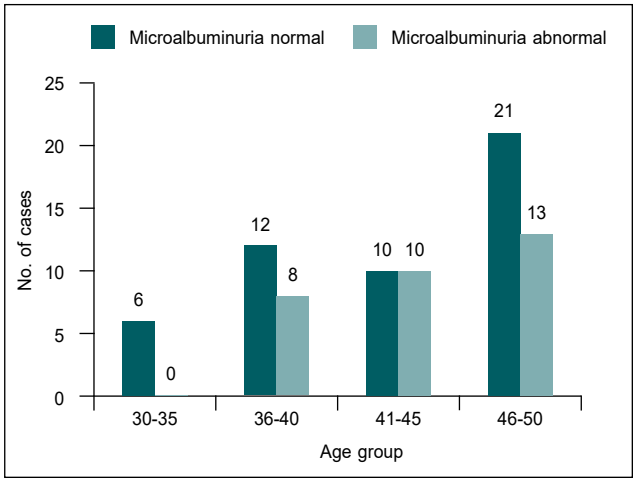

Figure 7. Age and microalbuminuria.

Table 7. Relation of BAFMD and Microalbuminuria with Smoking Habit in Cases

Smoking habit	FMD (%)		Microalbuminuria	
	Mean	SD	Normal	Abnormal
Male	7.05	2.55	20 (25)	20 (25)
Female	7	3.38	29 (36.2)	11 (13.8)
P value	0.87		0.039*	

was higher in Stage 2 HTN than Stage 1 HTN, with a significant p value of 0.009 (Table 8).

Mean FMD was significantly lower in patients with abnormal SBP (>140 mmHg) compared to normal SBP (Table 9 and Fig. 9). Microalbuminuria was significantly

Table 8. Relation of BAFMD and Microalbuminuria with Stage of Hypertension in Cases

Blood pressure (mmHg)	FMD (%)		Microalbuminuria	
	Mean	SD	Normal	Abnormal
Normal	10.61	3.72	0 (0)	0 (0)
Prehypertension	8.73	3.55	0 (0)	0 (0)
Stage 1 HTN	7.53	2.81	34 (42.5)	12 (15)
Stage 2 HTN	6.58	2.91	20 (25)	14 (17.5)
P value	0.038*		0.009*	

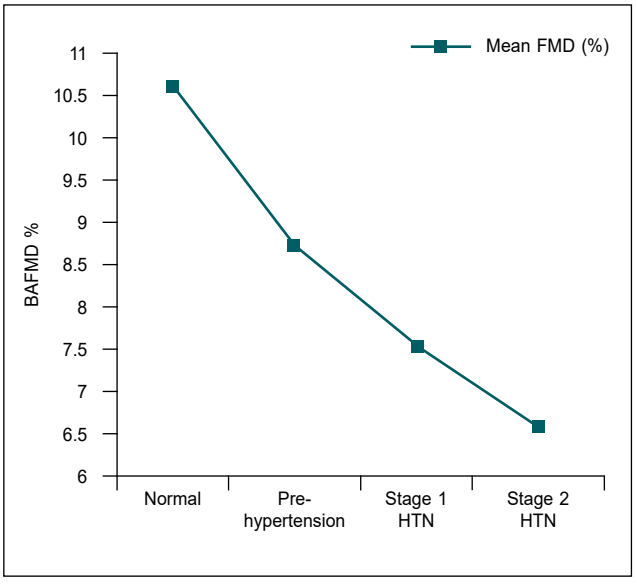

Figure 8. Stage of hypertension and BAFMD %.

Table 9. Relation of BAFMD and Microalbuminuria with SBP in Cases

SBP	FMD (%)		Microalbuminuria	
	Mean	SD	Normal	Abnormal
Normal (<140)	8	2.91	12 (15)	1 (1.2)
Abnormal (>140)	6.84	2.97	37 (46.2)	30 (37.5)
P value	0.002*		0.001*	

higher in patients with abnormal SBP (p = 0.001) (Table 9).

Mean FMD was significantly lower in patients with abnormal DBP (>90 mmHg) compared to normal DBP (p = 0.027) (Table 10 and Fig. 10). Also, microalbuminuria was significantly higher in patients with abnormal DBP (p = 0.005) (Table 10).

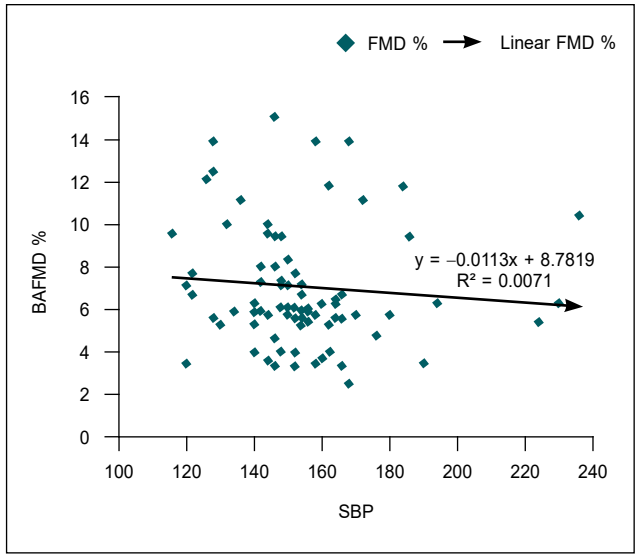

Figure 9. Systolic blood pressure and BAFMD %.

Table 10. Relation of BAFMD and Microalbuminuria with DBP in Cases

DBP	FMD (%)		Microalbuminuria	
	Mean	SD	Normal	Abnormal
Normal (<90)	7.27	2.99	36 (45)	13 (16.2)
Abnormal (>90)	6.65	2.96	13 (16.2)	18 (22.5)
P value	0.027*		0.005*	

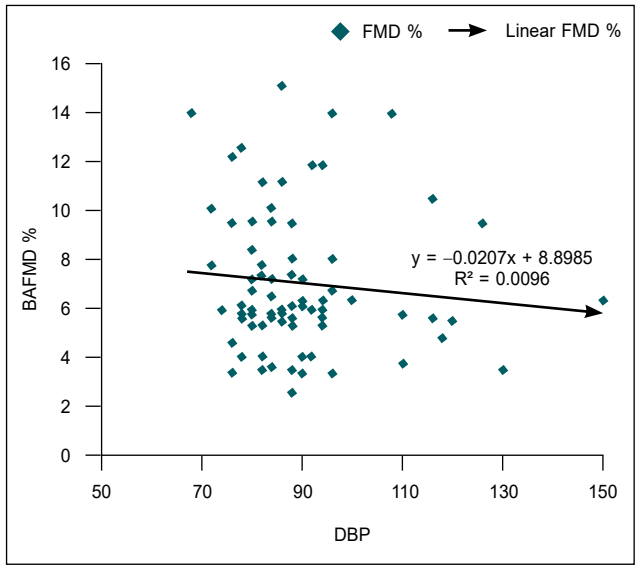

Figure 10. Diastolic blood pressure and FMD %.

Mean % FMD was significantly lower in patients with longer history of hypertension compared to patients with no history of hypertension (p = 0.022) (Table 11 and Fig. 11). The most precipitous dip in mean %

Table 11. Relation of BAFMD and Microalbuminuria with Duration of Hypertension

Duration of hypertension	FMD (%)		Microalbuminuria	
	Mean	SD	Normal	Abnormal
No history of hypertension (control group)	10.55	2.55	40 (100)	0
1 year	6.89	2.91	33 (41.25)	10 (12.5)
1-3 years	7.8	3.51	10 (12.5)	5 (6.25)
3-5 years	7.36	2.76	5 (6.25)	9 (11.25)
5-7 years	4.5	1.29	0 (0)	4 (5)
>7 years	3.91	1.01	1 (1.25)	3 (3.75)
P value	0.022*		0.036*	

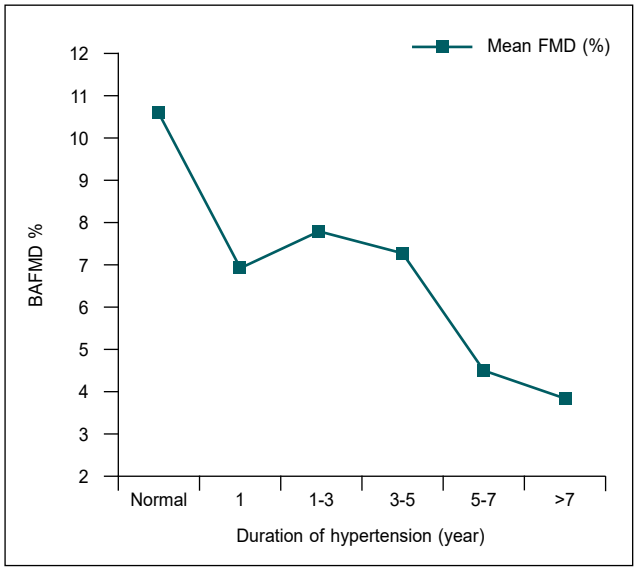

Figure 11. Duration of hypertension and FMD %.

BAFMD value in hypertensives occurred when the duration of hypertension exceeded 5 years. Similarly, the tendency for abnormal levels of microalbuminuria was significantly higher in patients with longer hypertensive history (p = 0.036) (Table 11).

When multiple cardiovascular risk factors (hypertension, dyslipidemia, smoking and obesity) were combined, it was noted that the cases tended to have a progressively lower mean % FMD and a higher mean level of microalbuminuria as the number of risk factors increased (Table 12; Figs. 12 and 13). In the case of % FMD, the decreasing trend was more or less secular in nature, with the most precipitous fall in % FMD value occurring when smoking was added as a risk factor. When the

Table 12. Impact of Various Risk Factors on BAFMD and Microalbuminuria

Risk factors	N	Mean FMD (%)	Mean level of microalbuminuria
Hypertension	80	7.03 ± 2.98	27.12 ± 38.58
Dyslipidemia	45	7.13 ± 2.96	67.49 ± 72.61
Smoking	23	7.06 ± 2.99	85.01 ± 71.23
Obesity	46	7.09 ± 2.89	56.23 ± 69.83
HTN + Obesity	46	7.09 ± 2.89	62.95 ± 69.83
HTN + Dyslipidemia	45	7.01 ± 2.97	73.82 ± 68.59
HTN + Smoking	23	7.06 ± 2.99	94.76 ± 71.23
HTN + Dyslipidemia + Obesity	25	7.05 ± 2.08	83.51 ± 70.12
HTN + Obesity + Smoking	13	5.78 ± 2.13	106.47 ± 75.88
HTN + Smoking + Dyslipidemia	10	5.69 ± 2.14	105.428 ± 69.87
HTN + Dyslipidemia + Obesity + Smoking	5	4.85 ± 1.89	103.74 ± 88.52

trend of mean levels of microalbuminuria was plotted, the trend showed general increase in the mean levels of microalbuminuria, and peaked at the points where smoking was added as risk factor.

Mean % FMD was lower in patients with microalbuminuria compared to those with normal values and this was statistically verified (Table 13 and Fig. 14), with p = 0.016, thereby verifying the central hypothesis of this study.

DISCUSSION

Our core question was whether hypertension related endothelial dysfunction detected in peripheral circulation by high frequency ultrasound measurement of BAFMD independently favors the progressive loss of albumin through urine, which shall be an indicator of early hypertensive renal disease. Moreover, we have also outlined the various cardiovascular determinants of BAFMD and microalbuminuria.

The present study limited the age of the participants within 30 to 50 years, with a deliberate intent of avoiding the confounding influence that age has been demonstrated to have on endothelial function. In spite of this, BAFMD showed a significant decline moving

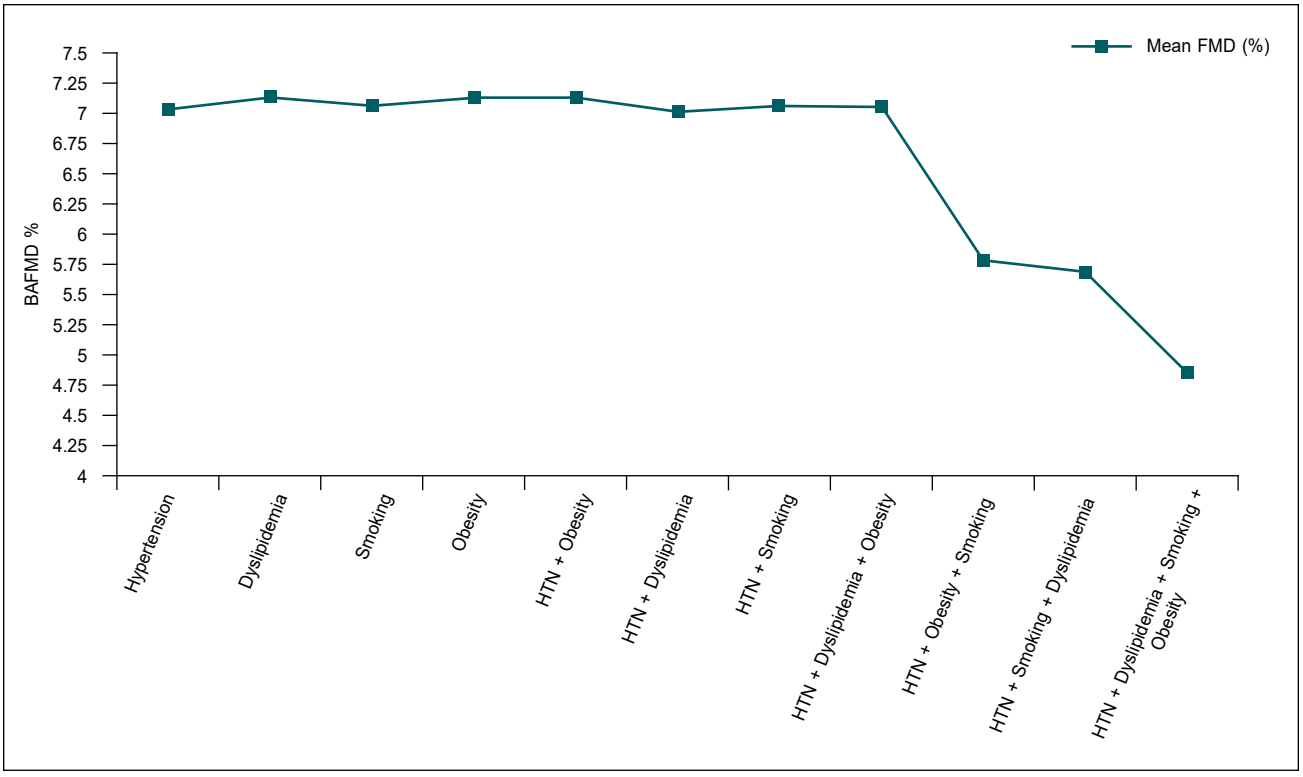

Figure 12. Combination of cardiovascular risk factors and BAFMD %.

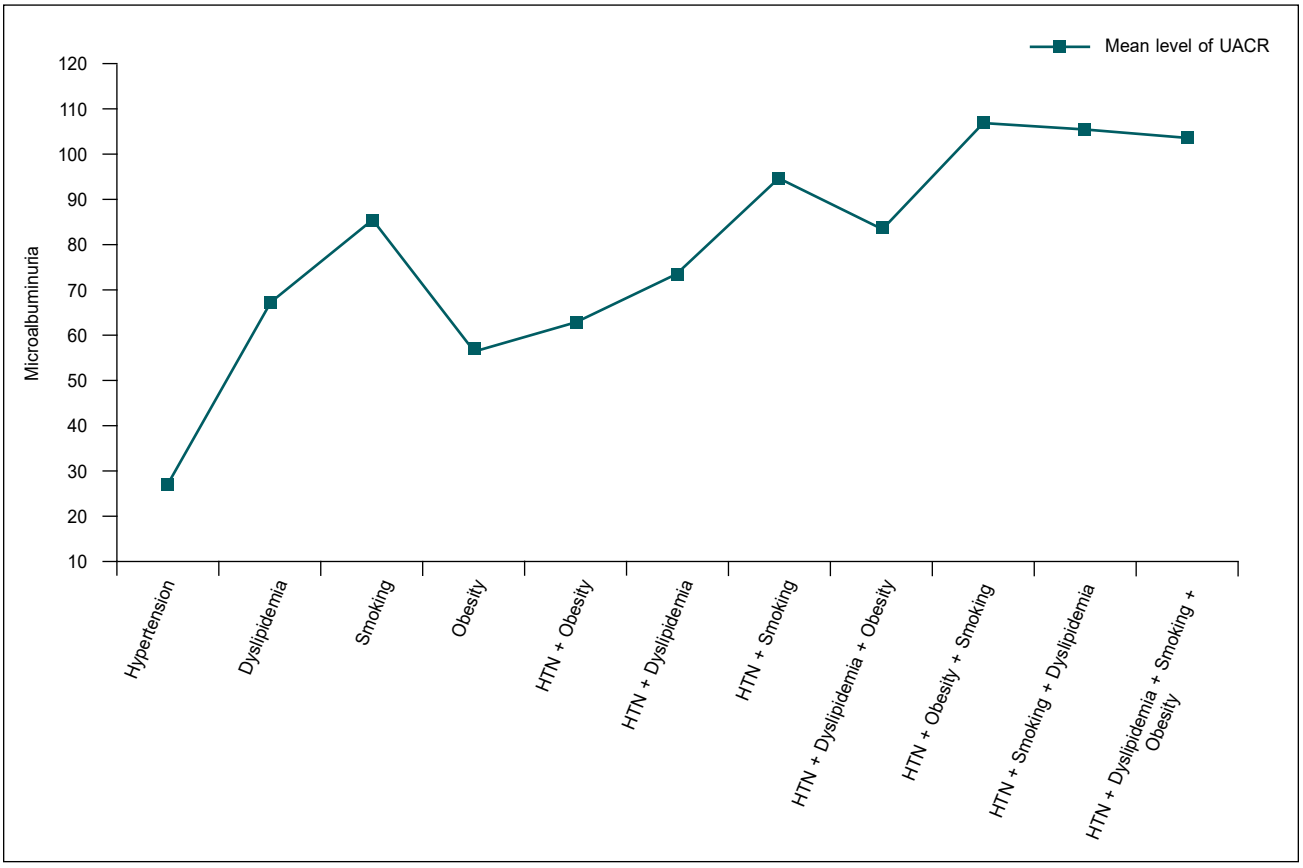

Figure 13. Combination of cardiovascular risk factors and microalbuminuria.

Table 13. Relationship of BAFMD and Microalbuminuria in Cases

Microalbuminuria	FMD %	
	Mean	SD
Normal	7.69	3.001
Abnormal	5.97	2.664
P value	0.016*	

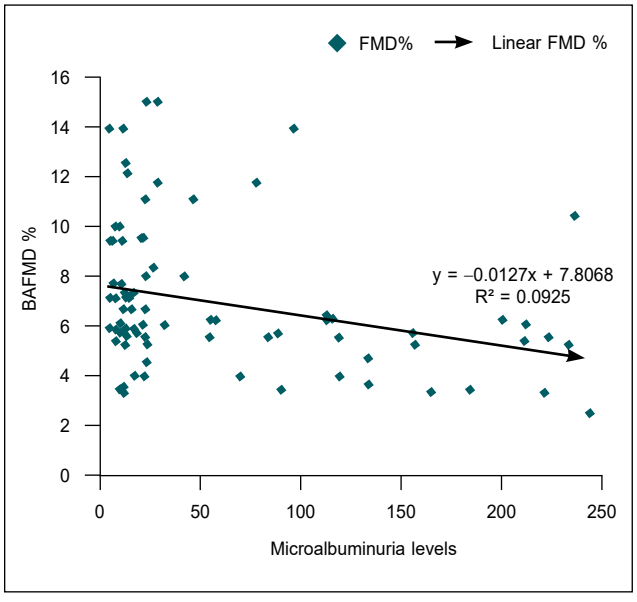

Figure 14. Microalbuminuria and BAFMD %.

towards the higher age groups, with a precipitous decline occurring at the 45 age cut-off. This trend across the age groups was statistically verified with a 'p' value = 0.001.

The number of males and females were equally distributed within the case and control group for comparability purposes. The prevalence of microalbuminuria reported by Sabharwal et al in males and females was found to be 34% and 30.7%, respectively[4]. In the present study, microalbuminuria was significantly higher among females (25%) compared to males (13.8%) (p = 0.039). Although various pathophysiological mechanisms have been propounded for this observation, it has to be pointed out that this may also reflect a certain fallacy arising in the nature of measurement of microalbuminuria, i.e., UACR. Urinary creatinine is a reflection of the overall body muscle mass and its metabolism, i.e., individuals with more muscle bulk tend to excrete higher levels of creatinine. In the measurement of UACR, as creatinine is placed in the denomination, and with middle-aged Indian females tending to have a decreased muscle bulk than their male counterparts, a higher UACR may be observed in females due to this inherent flaw.

Yang et al[5] studied the relationship of several cardiovascular risk factors (CVRF) to BAFMD in Chinese subjects and reported that according to multivariate analysis, negative FMD correlated with age ($\beta = -0.29$, $p < 0.001$), gender ($\beta = -0.12$, $p < 0.001$), BMI ($\beta = -0.12$, $p = 0.001$), waist circumference (WC) ($\beta = -0.10$, $p = 0.011$), SBP ($\beta = -0.12$, $p < 0.001$), fasting glucose ($\beta = -0.04$, $p = 0.009$), TC ($\beta = -0.04$, $p = 0.014$), smoking ($\beta = -0.05$, $p = 0.003$) and baseline brachial artery diameter ($\beta = -0.35$, $p < 0.001$). FMD decreased with increasing age in both genders. In women, FMD was higher than men and age-related decline in FMD was steepest after age 40; FMD was similar in men above 55 years old. In the present study, FMD was significantly different across the age groups (p = 0.001), lower among smokers (5.73 ± 2.69), higher among male (7.05 ± 2.55) compared to female (7 ± 3.38) (p = 0.87), lower in obese Grade I patients (7.16 ± 2.73) compared to obese Grade II (7.38 ± 2.72) and overweight (8.35 ± 3.37) (p = 0.007), lower in patients with Stage 2 HTN (6.58 ± 2.91) compared to Stage 1 HTN (7.53 ± 2.81) and prehypertension (8.73 ± 3.35) (p = 0.038), lower in patients with abnormal TC (>200 mg/dL), significantly lower in patients with abnormal TG (>150 mg/dL) compared to normal TC (p = 0.047) and significantly lower in patients with abnormal baseline diameter (>5) compared to normal baseline diameter (p < 0.001).

Multivariate analyses resulted in different conclusions. Schnabel et al noted that FMD was associated with age, sex, BMI, SBP, DBP, TC, HDL-C, TG, C-reactive protein, hypertension, hypertension treatment and dyslipidemia, whereas Philpott et al. argued FMD was only associated with SBP[6,7]. Although Mizia-Stec et al agreed FMD was associated with CVRF, he insisted that such correlations were limited among populations at high risk of cardiovascular disease[8].

As observed in the current study, FMD was correlated with the traditional CVRFs including BP, blood lipid, obesity and smoking, in particular the baseline brachial artery diameter; however, it was not correlated with serum creatinine and uric acid. In our study, we further listed dyslipidemia, hypertension and smoking as the major risk factors. Grouping based on the number of risk factors showed that the FMD value declined along with the increase of the number of risk factors which means lower FMD was recorded in patients with multiple risk factors.

In the study by Yang et al, women had higher FMD values than men, which was consistent with a previous study[9], suggesting the endothelial function is better in women than in men[5,10]. Contrary to these, in the present study, FMD was comparable between males (7.05 ± 2.55) and females (7 ± 3.38) (p = 0.87).

Gupta et al assessed the various factors affecting endothelial function in essential hypertensives and reported that endothelial dysfunction was significantly more quantified in Stage 2 HTN as compared with Stage 1 HTN (p < 0.01)[11]. Similar to that, in our study, mean FMD was lower in patients with Stage 2 HTN (6.58 ± 2.91) compared to Stage 1 HTN (7.53 ± 2.81) and prehypertension (8.73 ± 3.35) (p = 0.038). Shimbo et al examined the cross-sectional and longitudinal relationships between endothelial dependent BAFMD and hypertension prevalence and incidence in 3,500 participants from the Multi-Ethnic Study of Atherosclerosis (MESA) and reported that reduced FMD was not an independent predictor of hypertension incidence, suggesting that impaired endothelial function does not play a major role in the development of hypertension[12]. Contrary to Shimbo et al, in the present study, FMD significantly decreased as we progressed to the higher stages of hypertension.

Mean FMD was significantly lower in patients with Stage 2 HTN (6.85 ± 2.91) compared to Stage 1 HTN (7.53 ± 2.81), prehypertension (8.73 ± 3.35) (p = 0.038) and the normotensive controls (10.61 ± 3.72). Whereas microalbuminuria was significantly distributed across the hypertensive ranges (p = 0.009). Mean FMD was significantly lower in patients with abnormal SBP (>140 mmHg) compared to normal BP, whereas microalbuminuria was significantly higher in patients with abnormal SBP (p = 0.001). Mean FMD was significantly lower in patients with abnormal DBP (>90 mmHg) compared to normal BP (p = 0.027), whereas abnormal microalbuminuria was significantly higher in patients with abnormal DBP (p = 0.005). Stehouwer et al concluded that both in nondiabetic and diabetic subjects, microalbuminuria is associated with an increased cardiovascular risk, independent of known risk determinants. As such, microalbuminuria is potentially useful for improved cardiovascular risk stratification[13]. Dinneen and Gerstein[14], in a systematic review, showed microalbuminuria among individuals with type 2 diabetes to be associated with a 2.4-fold (95% confidence interval [CI] 1.8-3.1) increased risk for cardiovascular death as compared with normoalbuminuria. In addition, similar associations exist in hypertensive individuals (without diabetes) and in the general population[15].

In the present study, mean FMD was lower in patients with abnormal microalbuminuria compared to normal (p = 0.016). Yokoyama et[16] measured FMD, carotid intima-media thickness (IMT) and pulse-wave velocity (PWV) in 158 subjects with type 2 diabetes (normo- 49, micro- 64, macroalbuminuria 45), explored the determinants of FMD and analyzed the relationship of FMD with traditional cardiovascular risk factors according to IMT and PWV levels.

They reported that microalbuminuria was significantly associated with lower FMD, higher IMT and higher PWV compared to normoalbuminuria (p < 0.001 for all). FMD was significantly correlated with IMT and PWV, and also with traditional risk factors, urinary albumin excretion (UAE), glomerular filtration rate, diabetic retinopathy and neuropathy. Multivariate regression analysis revealed that UAE remained a significant determinant of FMD independent of traditional risk factors, metabolic control and renal function. The relationship of FMD with IMT and PWV was less pronounced in subjects with increased IMT and PWV[16]. A report of Foster et al showed that microalbuminuria was associated with decreased hyperemic mean flow (47.2 ± 1.4 vs. 51.4 ± 0.5 mg/g, p = 0.005), but the association was not significant after multivariable adjustment (p = 0.09)[2]. In agreement to this, in the present study, mean FMD was lower in patients with microalbuminuria compared to those with normal values (p = 0.016).

CONCLUSION

Traditional cardiovascular risk factors were significantly associated with both BAFMD and microalbuminuria. BAFMD had a significant inverse relationship with age (0.001), smoking (0.009), BMI (0.007), higher JNC VII stage of hypertension (0.038), duration of hypertension (0.002), SBP (0.027), DBP (0.022), abnormal TG levels (0.047) and a positive relationship with baseline diameter (<0.001).

Microalbuminuria was positively associated with female gender (0.039), smoking (0.001), stage of hypertension (0.009), duration of dypertension (0.001), SBP (0.005), DBP (0.036), abnormal TG levels (0.037), abnormal LDL-C levels (0.001).

Combination of more than one cardiovascular risk factor produced lower mean levels of BAFMD and higher levels of UAE.

BAFMD and microalbuminuria were significantly associated and the relationship was inverse in nature.

Based on the observations of the study, we can infer that:

- Both BAFMD as well as microalbuminuria can be used as surrogate markers in assessing increasing cardiovascular risk.
- BAFMD can be used as an effective tool to detect early hypertensive target organ damage, especially to the kidney.
- Hypertensive patients should be advised to maintain a within normal limit BMI.
- Effective therapeutic control of hypertension to prevent progress to higher stages of hypertension can prevent target organ damage.
- Hypertensive patients should be advised to cease smoking.
- Aggressive pursuit of target organ damage should be done in hypertensives, especially if the duration of hypertension exceeds 5 years.

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CLINICAL STUDY

The Usefulness of Ultrasound Guidance in Fresh Embryo Transfers: A Retrospective Study

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ABSTRACT

Objective: To evaluate retrospectively the efficacy of ultrasound-guided embryo transfer method on pregnancy and implantation rate and compare with clinical touch method. **Material and methods:** The results of 582 cycles from our *in vitro* fertilization and embryo transfer (IVF-ET) program conducted at Jaipur Fertility Centre, an Infertility Unit of Mahatma Gandhi University of Medical Sciences and Technology, Jaipur, Rajasthan were analyzed retrospectively and comparison was made between those carried out using ultrasound guidance and those by clinical touch method. **Results:** Higher pregnancy and implantation rates (37.19% and 19.66%, respectively) were found in the group using the transabdominal ultrasound guidance during ET compared with those in the group using the clinical touch method (30.92% and 16.22%, respectively). The difference was not statistically significant. **Conclusion:** Older women (>35 years) and in the subgroup when the clinician rated the transfer procedure as easy with some difficulty, there appeared to be a substantial improvement in the pregnancy rate and the difference was statistically significant. We believe that ultrasound-guided ET should be used in these subgroups.

Keywords: Clinical touch, embryo transfer, *in vitro* fertilization, retrospective study, ultrasound-guided, air bubble

Transabdominal ultrasound-guided embryo transfer (ET) has been described by various authors since 1985 to improve the pregnancy rate[1-4]. However, significantly higher pregnancy rates following transabdominal ultrasound guidance have not been consistently demonstrated. Lindheim et al, first reported that ultrasound guidance improved pregnancy outcome only in easy transfer[5]. Subsequently, two studies demonstrated significant differences between the clinical touch method and transabdominal ultrasound-guided ET retrospectively[6] and prospectively[7].

Most studies trying to address the issue of whether ultrasound guidance is beneficial to ET conclude that although pregnancy rates may not be significantly raised, ultrasound guidance provides both the clinicians and patients with greater degree of confidence in the ET procedure[3,4,8]. We divided our study population according to: i) Number of embryo transferred; ii) age of patient; and iii) ease of transfer to delineate a subgroup of patients that would particularly benefit from their embryo being transferred under ultrasound guidance.

MATERIAL AND METHODS

A retrospective study of *in vitro* fertilization and embryo transfer (IVF-ET) cycles from June 2011 to August 2012 was performed. Between June 2011 to December 2011 the clinical touch method had been adopted for 262 cycles in our IVF-ET program. Between January 2012 and August 2012, 320 cycles of IVF-ET were performed under transabdominal ultrasound guidance. During both periods, there was no change in ovarian stimulation method, oocyte retrieval, culture media and culture system. For ET, Wallace and Cook echo tip catheters were used. Exclusion criteria were: age 45-year-old, more than three previous assisted conception cycles and transfer requiring general anesthesia for the patients. One clinician and three ultrasonographers were involved in the study. All ultrasonographers were specialists in infertility. An ultrasound machine with 3.75 MHz transabdominal probe was used on all women in ultrasound group.

Controlled ovarian hyperstimulation (COH) was carried out in more than 85% of patients with recombinant

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follicle-stimulating hormone (FSH) and human menopausal gonadotropin (hMG) with half-dose of gonadotrophin-releasing hormone (GnRH) agonist after down regulation with GnRH agonist in the preceding late luteal phase. Rest of the patients were induced by short protocol with GnRH agonist along with recombinant FSH or hMG. Follicular growth was followed by transvaginal ultrasonography and once adequate follicular maturation was obtained, human chorionic gonadotropin (hCG) was administered and oocyte retrieval was performed about 36 hours later under transvaginal sonographic guidance and general anesthesia. ET was carried out on Day 3 or Day 5 after oocyte retrieval. Frozen ETs were excluded from the study.

THE EMBRYO TRANSFER PROCEDURE

We carried out all the ET in the operation theater. Three embryos were usually prepared for transfer. In case, where numbers of embryos formed were less than three, less number of embryos, i.e., one or two were transferred. The patients arrived with semi-filled bladder in ultrasound-guided group and with empty bladder in clinical touch group. In both clinical touch and ultrasound group, the clinicians started the ET in the same way, i.e., cleaning the external genitalia with a dry swab before insertion of a sterile speculum into the vagina. The external cervical os was then cleaned with a dry cotton swab and mucus in the cervical canal was removed with a mucus extractor. Embryos were loaded into Wallace sure view and Cook echo tip catheter. The catheter was then handed over to the clinician who inserted it through the cervical canal. At this stage, there was a difference between the two groups.

In the clinical touch group, when the clinician was satisfied with that he had placed the catheter as close to the fundus as possible without touching it, the plunger was depressed; but in the ultrasound group, the ultrasonographer used a transabdominal ultrasound to guide the clinician in the positioning of the tip of the catheter to ~15 mm from the fundus of the uterine cavity. The plunger was then depressed and the air bubbles observed to be expelled from the catheter tip. The embryos were injected over 30 seconds, allowing observation of the movement of the air bubbles into uterine cavity. Removal of the catheter was also monitored by ultrasound and retention of the air bubbles was observed in the fundal position. The catheter was carefully checked under microscope and the embryo retained within the lumen or adherent to the surface of the catheter were reharvasted. The embryo can be clearly identified by air bubbles inserted on either side, which are seen as bright echoes on the ultrasound image.

The clinician was then required to rate the ET procedure in terms of ease of transfer before they left the ET room. The rating system guidelines were:

- **Very easy:** Transfer catheter went straight through the cervix.
- **Easy with some difficulty:** Required the separation of the transfer catheter to advance the sheath of a stiffer catheter to facilitate the transfer.
- **Difficult:** Required in tenculum in addition to those requirement in easy category.

A positive pregnancy outcome was a positive blood pregnancy test performed 2 weeks after the ET and an ultrasound scan showing at least one sac in the uterine cavity 2 weeks after the positive pregnancy test. Statistical analysis: A p value <0.05 was considered to be statistically significant.

RESULTS

The pregnancy rate and implantation rate appeared higher in the ultrasound-guided group but not significant statistically (Tables 1 and 2).

When the analysis was performed controlling for the number of embryos transferred, there was no significant difference in the two groups whether one, two, three

Table 1. Clinical Data of IVF Cycles in Clinical Touch and Transabdominal Ultrasound Groups

Variables	Clinical touch (n = 262)	Ultrasound-guided (n = 320)
Age in years	34.2	33.9
Primary infertility (%)	142/262 = 54.2	165/320 = 51.6
Mean infertility duration in years	6.0	5.6
Cause of infertility		
Unexplained (%)	44/262 = 16.8	63/320 = 19.7
Male %	92/262 = 35.1	112/320 = 35
Only female %	98/262 = 37.4	127/320 = 39.7
Combined %	28/262 = 10.7	18/320 = 5.6
Mean number of embryos available	7.8	6.9
Mean number of embryos transferred	2.56	2.37
Mean number of oocyte retrieved	13.2	12.3
Days after retrieval	3.1	3.2

No significant difference was observed between the two groups.

Table 2. Outcome of ETs Performed with Clinical Touch and Ultrasound Guidance

	Clinical touch (n = 262)	Ultrasound-guided (n = 320)	P value
Pregnancy rate (%)	81/262 = 30.92%	119/320 = 37.19%	0.134 NS
Implantation rate (%)	109/672 = 16.22%	149/758 = 19.66%	0.103 NS

NS = Not significant.

Table 3. Outcome of ET in Subgroups

Pregnancy rate in subgroups	Clinical touch (n = 262)	Ultrasound-guided (n = 320)	P value
Number of embryo transferred			
One	3/21 = 14.3%	15/55 = 27.27%	0.327 NS
Two	15/72 = 20.8%	24/92 = 26.1%	0.549 NS
Three	63/169 = 37.3%	80/173 = 46.24%	0.116 NS
Age of patients			
≤35-year-old	53/141 = 37.6%	69/186 = 37.1%	0.981 NS
>35-year-old	28/121 = 23.14%	50/134 = 37.31%	0.021 S
Ease of ET			
Very easy	65/174 = 37.4%	85/225 = 37.8%	0.986 NS
Easy with some difficulty	12/62 = 19.35%	25/68 = 36.8%	0.045 S
Difficult	4/26 = 15.38%	9/27 = 33.33%	0.231 NS

NS = Not significant; S = Significant.

Table 4. Pregnancy Rate According to the Position of the Air Bubbles

	Distance of air bubbles from fundus (mm)						No air bubbles	Total
	0-5	6-10	11-15	16-20	21-25	26-30		
Total	13	34	49	14	6	5	4	**125**
Pregnancy	4	13	21	5	2	1	0	**46**
Pregnancy rate (%)	30.77	38.24	42.86	35.71	33.33	20	0	**36.8**

embryos were transferred. When controlled for age of women (≤35 and >35 years old) again the results were not significantly different in ≤35 years of age group but they were statistically significant in age group >35 years old (23.14% vs. 37.31%, respectively). Pregnancy rate in 'easy with some difficulty' ultrasound group was 36.8% vs. 19.35% in comparison to clinical touch group (statistically significant $p < 0.05$). It may be due to precise recognition of position of uterus in ultrasound-guided cases. If we only examined the cases, which were rated 'difficult' the difference in favor of the ultrasound group appeared nonsignificant (Table 3).

Out of 320 ultrasound-guided ET, in 125 patients, distance of air bubbles from fundus was noted. Pregnancy rate according to the position of the air bubbles was calculated. Maximum pregnancy rate was achieved when the distance of air bubble was between 11-15 mm from the fundus. Four cycles were excluded from this analysis because there was no description of the location of air bubbles in these cases (Table 4).

DISCUSSION

Since the IVF pregnancy was achieved, some aspects of the technique have remained largely unchanged,

whilst other have been constantly evolving, the most significant development being in ovulation induction, the use of intracytoplasmic sperm injection (ICSI) and in the development of culture media. Despite these improvements, the majority of the transferred embryos fail to implant. This failure may be due to poor quality embryo, lack of uterine receptivity or the technique of ET itself[9,10]. Defining the factors that are important for successful ET after IVF has been a major issue. Based on the questionnaires distributed amongst highly experienced IVF clinical, Kovacs summarized the answers[11]. The factor that got highest votes was the need to remove hydrosalpinx before treatment. The other important factors in order of priority included absence of bleeding, type of catheter used, not touching the fundus, avoid the use of a tenaculum, removal of all mucus from the cervix, ultrasound details of the cavity before treatment, leaving the catheter in place for at least 1 minute, 30 minutes rest after transfer, dummy transfer before treatment, ultrasonic monitoring of transfer and antiprostaglandins to prevent contractions. Although the clinician rated the importance of ultrasound guidance as 11th of 12 factors, the role of ultrasound monitoring during transfer should receive more emphasis. The cause of low priority of this factor might be due to the inconvenience and inaccuracy of transabdominal ultrasound guidance.

Generally, the positions of air bubble indicate the position of the embryos. It was recommended that the tip of the catheter be positioned 15 mm from the fundus of the uterine cavity to avoid placement of embryos close to the uterine fundus[7]. In our study, the point of placement of embryo was also 15 mm from the fundal limit of the uterine cavity. We could transfer the embryos to the precise place under transabdominal ultrasound guidance. There was no pregnancy in four cases in which air bubbles could not be identified. It is likely that these embryos were misplaced probably due to uterine contractions or technical errors. In two cases embryos remained in the lumen of catheter. In other cases, we suppose that the catheter was inadvertently abutting the internal tubal os and the bubbles disappeared in the tubal canal. Furthermore, we experienced some cases in which the air bubbles moved towards the cornue or the cervix from the position of the tip of the catheter. These observations also suggest that adequate monitoring by ultrasound guidance is very important during ET.

Evidence emerging from 17 to 20 randomized controlled trials comparing ultrasound guidance versus the 'clinical touch' method for ET have been evaluated. Clinical pregnancy rates were found to be statistically significant higher (odd ratio [OR] 1.31-1.50) with transabdominal ultrasound guidance[7,12]. It has been reported that high frequency uterine contractions on the day of embryo transfer hinder IVF-embryo transfer outcome[13]. It was reported that tactile assessment of catheter placement was unreliable[14].

The outer guiding catheter inadvertently abutted the fundal endometrium or the internal tubal os and intended the endometrium. The transfer catheter was seen to be embedded within the endometrium. Transabdominal ultrasound-guided ET can minimize these endometrial traumas and thus reduce the uterine contractions. As transabdominal ultrasound can supply fine picture of the flexion of the uterus and the curve of the uterine endometrial midline, the clinician can insert the catheter smoothly without endometrial trauma under the monitoring, and stop the catheter before reaching the fundus. If the curve of the uterine endometrial midline is sharp, we stop the outer sheath before intending the endometrium and advance only the inner catheter, which is softer than the outer sheath, upto 15 mm from the uterine fundus. These atraumatic procedures probably contributed to successful ET in the present study because bleeding from the endometrium or the uterine cervix is a significant negative factor for ET, as suggested by Kovacs[11].

The procedure was readily accepted by the patients who were reassured by the visualization of the transfer process. The acceptance by the clinician was also high with no significant added time, and the procedure was done with more confidence as the catheter is advanced to the fundus of the uterus under ultrasound scan guidance. Furthermore, ultrasound-guided ET may have two additional advantages over clinical touch ET when considering that: i) Blind catheter placement has been shown to result in a malposition of the catheter in >25% of cases, thus indicating that tactile assessment of ET catheter position is unreliable[14] and ii) the depth of the embryo replacement into the uterine cavity influences implantation rates, with high pregnancy rates obtained when the embryos are replaced 15-20 mm from the fundal endometrial surface[7]. Ultrasound assistance in the ET is a pivotal tool for improving pregnancy rate in assisted reproduction irrespective of whether embryos are fresh or frozen and replaced in spontaneous, stimulated or artificially prepared cycles. A report showing that ultrasound-guided ET improves outcome in patients with previous failed IVF cycles provides further evidence in this regard[12].

CONCLUSION

There was no significant difference in the pregnancy rate when the number of embryos transferred was controlled. Based on the results obtained from the present study, transabdominal ultrasonography guidance appears to be an essential factor for improving the results of ET especially in case of easy with some difficulty ET and in older women.

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CASE REPORT

Robot-Assisted Laparoscopic Surgery for Pheochromocytoma in a Dilated Cardiomyopathy Patient

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ABSTRACT

Pheochromocytomas are rare endocrine tumors which secrete catecholamines leading to severe cardiovascular complications. Dilated cardiomyopathy (DCM) is known to exist in patients with pheochromocytomas. The presence of these two conditions makes the anesthetic management of such cases even more complex. In this article, we present the case of a young male who had both pheochromocytoma and DCM, and who underwent robot-assisted laparoscopic surgery. The challenges in managing this case are discussed.

Keywords: Adrenal pheochromocytoma, retroperitoneal mass, catecholamines, catecholamine-induced cardiomyopathy

Dilated cardiomyopathy (DCM) is an idiopathic clinical condition characterized by left ventricular or biventricular dilation and impaired contractions. DCM is a potentially lethal disease and its 5-year mortality rate is above 50%[1]. The anesthetic management of patients with DCM is challenging for anesthesiologists because of poor left systolic function, risk of arrhythmias, chamber enlargement and risk of sudden cardiac death[2]. Pheochromocytomas are rare tumors of the adrenal medulla. The catecholamines secreted by the tumor can lead to serious cardiovascular complications including paroxysmal hypertension and cardiac failure. In individuals with pheochromocytomas, activities such as movement, endotracheal intubation, pneumoperitoneum, and compression of the tumor during surgery can trigger the release of significant amounts of catecholamines[3]. The substantial fluctuations in blood pressure that occur during surgery are the primary reason why pheochromocytoma resection is deemed a high-risk procedure. A rapid decline in catecholamine levels following tumor removal may result in difficult-to-manage hypotension, particularly during the induction of anesthesia or the surgical excision of pheochromocytomas. However, if the pheochromocytoma is removed swiftly, the prognosis is generally very favorable[4].

Additionally, patients with these tumors may experience severe complications, such as DCM, which poses considerable challenges and requires more extensive preoperative evaluation and anesthesia management[5]. In this report, we discuss a rare case of DCM in an adult patient who underwent a highly risky pheochromocytoma resection.

CASE REPORT

A 23-year-old male was admitted due to a left retroperitoneal mass identified via computed tomography (CT) scan while investigating left-sided abdominal pain (Fig. 1). The lesion measured 5.6 cm in diameter, and the patient exhibited no additional symptoms such as palpitations, fatigue, central obesity, or purple striae. Laboratory tests indicated elevated catecholamine levels and their metabolites, suggesting a diagnosis of pheochromocytoma. The patient had a history of DCM for 2 years and reported recent shortness of breath during stair climbing. There was no other significant medical history.

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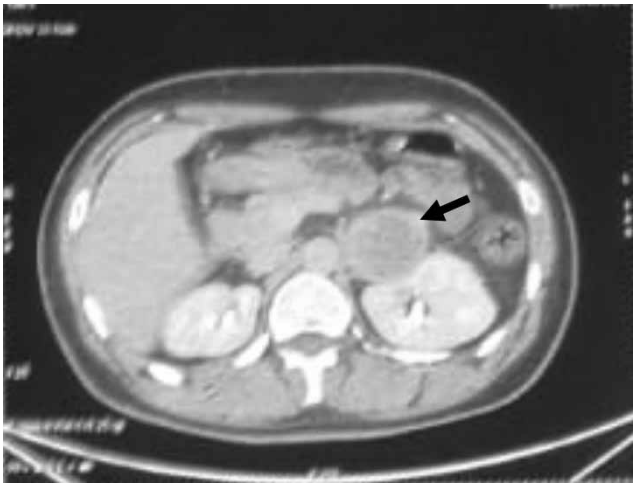

Figure 1. Noncontrast CT scan of abdomen showing left adrenal mass (*solid arrow*).

Upon admission, the physical examination revealed the following: height 172 cm, weight 89 kg, pulse rate 78 bpm, and blood pressure 112/78 mmHg. The patient was alert with a regular heart rhythm, clear lung sounds, and no lower limb edema. Other medical tests showed no significant abnormalities. Blood analysis indicated normal platelet counts, white and red blood cell counts, coagulation parameters, and liver and kidney functions. Urinary tests showed a 24-hour normetanephrine level of 1,005 μg/g creatinine (normal range: 70.00- 335.00 μg/g), and metanephrine level of 178 μg/g creatinine (normal range: 20.0-150.0 μg/g). Plasma normetanephrine was at 526 ng/L (normal range: 20.1-135.40 ng/L), while plasma metanephrine was significantly elevated at 3,910 ng/L (normal range: 7.90-88.7 ng/L). A DOTANOC-PET/CT scan indicated increased uptake in the left adrenal mass with no abnormal uptake elsewhere in the body (Fig. 2). A two-dimensional echocardiogram revealed an ejection fraction of 20%, along with dilation of the left atrium and ventricle and global hypokinesia.

The preoperative diagnosis was established as left pheochromocytoma with DCM. The patient underwent a Da Vinci robot-assisted laparoscopic resection of the left adrenal pheochromocytoma (Fig. 3). General anesthesia induction was planned during endotracheal intubation, along with invasive arterial pressure monitoring, central venous pressure monitoring, intraoperative transesophageal echocardiography (TEE), and bispectral index monitoring. Preoperative multidisciplinary consultation included administering prazosin (20 mg/day for 2 weeks) and metoprolol (25 mg/day for 1 week), along with echocardiography and N-terminal pro-B-type natriuretic peptide (NT-proBNP) assessments every 2 days to manage blood pressure and provide volume

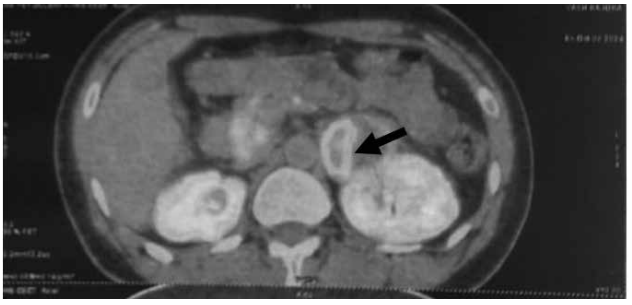

Figure 2. DOTANOC PET-CT image showing uptake in left adrenal mass (*solid arrow*).

Figure 3. Da Vinci robot-assisted laparoscopic resection of pheochromocytoma in progress.

expansion therapy for 1 week, while continuously monitoring cardiac function.

Anesthesia induction involved intravenous administration of midazolam (1 mg), etomidate (20 mg), cisatracurium (16 mg), dexmedetomidine (0.5 μg/kg/h for 30 minutes), and fentanyl (100 μg). Maintenance included propofol (3-5 mg/kg/h), fentanyl (0.5μg/kg/h), cisatracurium (6 mg/h), and sevoflurane (1%) inhalation. Throughout the procedure, intraoperative cardiac function and left heart volume status were monitored using TEE following general anesthesia induction with endotracheal intubation. Invasive arterial blood pressure, central venous pressure, depth of anesthesia, and temperature were also monitored during surgery.

To prevent stress ulcers and potential esophageal damage from the TEE probe, intravenous omeprazole was administered, along with methylprednisolone to enhance stress response capability during the operation; human serum albumin was also given. Intraoperative TEE showed a left ventricular ejection fraction ranging from 27% to 31% and a normal inferior vena cava diameter (16-18 mm). The total operative time was 2 hours and 15 minutes, with uneventful procedures performed throughout.

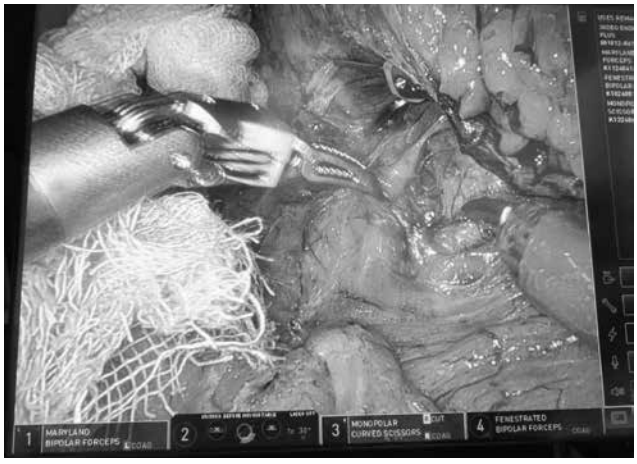

Figure 4. Intraoperative image of pheochromocytoma resection.

Intraoperative anesthesia remained stable with parameters including invasive arterial blood pressure between 110 to 130 mmHg/66 to 78 mmHg; central venous pressure between 6 to 10 cmH_2O; intraoperative blood loss at 250 mL; urine output at 400 mL and infusion volume at 1,500 mL. The adrenal mass was successfully excised, with postoperative histopathology confirming pheochromocytoma (Fig. 4). Postoperative analgesia was initiated under close observation, leading to the patient's transfer to the intensive care unit for further monitoring before returning to the general ward 3 days post-operation. He was discharged 4 days later in good condition and expressed satisfaction with his treatment and recovery.

DISCUSSION

This report outlines the successful execution of a rare, high-risk surgical procedure assisted by robotic technology, along with the optimization of anesthesia management through comprehensive preoperative evaluation and preparation. Intraoperative monitoring of cardiac function and hemodynamics was crucial for accurately guiding fluid therapy and the administration of vasoactive medications. An effective multidisciplinary team, comprising hospital physicians, anesthetists, urologists, and cardiovascular specialists, is essential in managing patients with DCM and pheochromocytoma[6]. Optimal anesthetic management for patients with DCM necessitates comprehensive preoperative assessment, vigilant perioperative monitoring, appropriate anesthesia techniques, refined fluid management, and maintenance of stable hemodynamic conditions.

Pheochromocytoma releases catecholamines that can lead to catecholamine-induced cardiomyopathy, including DCM; however, this complication is rarely reported[7]. Chronic use of adrenaline inhalers may also contribute to DCM development[8]. The mechanisms behind cardiomyopathy in pheochromocytoma patients include catecholamine-induced vasoconstriction of small arterioles, direct toxic effects from catecholamines and their metabolites, as well as receptor-mediated pathways[9]. Pheochromocytoma may result in myocardial fibrosis along with both systolic and diastolic dysfunction. While impaired myocardial function can often be improved through medical treatment or surgery, complete restoration may not be achievable in all patients[10].

Early surgical intervention is critical for managing catecholamine-induced cardiomyopathy associated with pheochromocytoma, with laparoscopic tumor removal being the preferred approach. Robot-assisted laparoscopy can significantly enhance perioperative conditions by reducing stress and energy expenditure while minimizing complications[11]. This precision surgical technique lessens stimulation from pheochromocytomas, thereby improving safety during the procedure. Consequently, we successfully performed a Da Vinci robot-assisted laparoscopic resection of the adrenal pheochromocytoma. There are documented cases indicating that surgical treatment can reverse myocardial dysfunction[12].

Preoperative preparation for pheochromocytoma resection must meet stringent standards, including maintaining blood pressure below 120/80 mmHg, a heart rate of 60 to 80 bpm, and ensuring electrocardiographic recovery from ventricular premature contractions. Additionally, there should be a decrease in hematocrit of more than 5% following volume expansion therapy, alongside improvements in hypermetabolic syndrome and correction of impaired glucose metabolism[13]. Elevated catecholamine levels can cause sustained vasoconstriction and reduced effective circulating blood volume, leading to hypertension, tachycardia, hypovolemia, and hemoconcentration in patients. In this case, the patient had DCM with a low ejection fraction of 20%, necessitating careful monitoring and gradual volume expansion therapy to avoid exacerbating heart failure. Preoperative blockade with alpha-blockers is recommended for all patients with hormonally active paragangliomas, and combining these with calcium antagonists may further stabilize intraoperative blood pressure. Proper preoperative anesthesia preparation is essential for maintaining stable circulation during the surgical procedure[14].

The perioperative mortality rate for pheochromocytomas is notably high, with risks including hypertensive crises and heart failure. However, hypotension and

hypoglycemic shock can occur following tumor resection. Additionally, the patient presented with DCM. To optimize anesthesia induction and management, we closely monitored the depth of anesthesia, cardiac function, and hemodynamics, maintaining systolic blood pressure between 90 and 140 mmHg and diastolic blood pressure between 60 and 90 mmHg. The patient was susceptible to hypotension and tachycardia after anesthesia induction, prompting the administration of norepinephrine via a micropump to stabilize his condition. These measures ensured that the surgery proceeded safely and smoothly.

Anesthesia induction was conducted smoothly, ensuring adequate sedation, analgesia, and muscle relaxation. We utilized intravenous anesthesia while continuously monitoring the depth of anesthesia to maintain stability throughout the procedure.

Perioperative hemodynamic instability is a significant challenge during pheochromocytoma surgery, especially in patients with compromised cardiac function[15]. To manage this, an intraoperative TEE probe was used for real-time monitoring of left heart function and volume, which is crucial for guiding fluid management. TEE revealed a stable left ventricular ejection fraction of 28% to 32%, and careful monitoring of invasive arterial and central venous pressures allowed for timely adjustments in vasoactive drug administration. Goal-directed fluid therapy was implemented to replenish intravascular volume while avoiding fluid overload, which could lead to complications such as heart failure. Continuous monitoring of blood glucose levels post-surgery was also essential to prevent hypoglycemia, particularly in patients with epinephrine-predominant tumors[16].

CONCLUSION

Anesthetic management for adrenal pheochromocytoma resection in adult patients with DCM presents significant risks but is achievable with careful planning. Our multidisciplinary team conducted thorough preoperative assessments and maintained vigilant perioperative monitoring; anesthesia and fluid management were optimized to achieve stable hemodynamics throughout the procedure. The use of robot-assisted laparoscopy further enhanced surgical safety. The challenges inherent in perioperative anesthetic management can be mitigated through invasive monitoring techniques and minimally invasive surgical approaches. This case underscores the importance of personalized management strategies and multidisciplinary collaboration for achieving successful outcomes.

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BRIEF COMMUNICATION

Integrating Early CKD Detection into Primary Care: A Call for Action in South Asia

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ABSTRACT

This article is inspired by and aims to sensitize health care professionals and policymakers in alignment with World Kidney Day 2025, themed "Are Your Kidneys OK? Detect Early, Protect Kidney Health". Chronic kidney disease (CKD) is a growing public health crisis in South Asia, driven by high rates of diabetes, hypertension, and delayed diagnosis. Despite the availability of simple and cost-effective screening tools, early detection remains suboptimal due to gaps in primary care integration, limited awareness, and health care disparities. Primary care physicians (PCPs) play a pivotal role in identifying at-risk individuals through systematic screening using urine albumin-to-creatinine ratio (uACR) and estimated glomerular filtration rate (eGFR) tests. However, barriers such as inadequate training, lack of standardized screening protocols, and resource limitations hinder effective implementation. This review highlights the urgent need to integrate CKD detection into primary health care by leveraging policy-driven guidelines, workforce training, digital health solutions, and community engagement strategies. Strengthening primary care through AI-driven risk prediction models, mobile health (mHealth) interventions, and telemedicine consultations can enhance early diagnosis and timely nephrology referrals. Additionally, public awareness campaigns aligned with World Kidney Day 2025 can empower individuals to take proactive steps in monitoring their kidney health. Addressing these challenges requires a multisectoral approach involving governments, health care organizations, and academic institutions to establish sustainable CKD screening frameworks. By embedding early CKD detection into routine primary care practices, South Asian countries can mitigate disease progression, reduce health care costs, and ultimately improve patient outcomes. This call for action urges health care stakeholders to prioritize early intervention strategies and reinforce kidney health as a fundamental component of primary health care.

Keywords: Chronic kidney disease, early detection, World Kidney Day, primary care, South Asia, health screening

Chronic kidney disease (CKD) has emerged as a silent epidemic in South Asia, affecting millions of individuals and placing a substantial burden on health care systems[1]. CKD is often asymptomatic in its early stages, leading to late diagnoses when irreversible damage has already occurred. The World Kidney Day 2025 theme, "Are Your Kidneys OK? Detect Early, Protect Kidney Health", underscores the critical need for timely identification and management of CKD to prevent its progression to end-stage kidney disease (ESKD)[2]. Despite advancements in nephrology, early detection remains a major challenge due to a combination of factors, including low awareness, inadequate screening protocols, limited access to specialized care, and socioeconomic barriers that prevent timely intervention[3].

In South Asia, the high prevalence of diabetes, hypertension, and obesity- the three leading causes of CKD- exacerbates the problem. According to epidemiological studies, 10%-15% of adults in the region suffer from CKD, but the majority remain undiagnosed until they present with severe complications[4]. Limited nephrology workforce, lack of standardized CKD screening policies, and overburdened health care infrastructure further hinder effective CKD management. This calls for an urgent paradigm shift- one that integrates CKD screening into primary care settings, ensuring that high-risk individuals are identified early and managed appropriately.

Primary care physicians (PCPs) serve as the frontline of health care and are well-positioned to incorporate

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routine kidney function assessments into their practice. However, many PCPs lack formal training in nephrology and are often unaware of simple, cost-effective screening tools like urine albumin-to-creatinine ratio (uACR) and estimated glomerular filtration rate (eGFR). Strengthening the role of primary care in CKD detection requires comprehensive policy interventions, capacity-building initiatives, digital health integration, and public awareness campaigns[5].

This article highlights the pressing need to integrate early CKD detection into primary care as a sustainable and scalable strategy to combat the growing burden of kidney disease in South Asia. By leveraging policy-driven frameworks, technology-assisted screening, and community-driven awareness initiatives, health care stakeholders can work toward reducing CKD-related morbidity and mortality and improving long-term outcomes.

THE ROLE OF PRIMARY CARE IN EARLY CKD DETECTION

Primary care plays a pivotal role in the early detection and management of CKD, as it serves as the first point of contact for individuals at risk. Given the high prevalence of risk factors in South Asia, integrating routine CKD screening into primary care settings can significantly improve early diagnosis and intervention[5]. However, several challenges hinder effective CKD detection as depicted in Table 1[6-8]. Strengthening primary care with structured screening programs, clinical decision tools, and improved referral pathways can bridge these gaps and enhance patient outcomes.

Risk-Based Screening

Primary care serves as the first point of contact for high-risk populations. Systematic screening of individuals with diabetes, hypertension, cardiovascular disease,

Table 1. Challenges in Integrating Early CKD Detection into Primary Care[6-8]

Challenges	Description
Limited Awareness and Low Screening Rates	• Lack of awareness among general population regarding CKD risk factors and early symptoms • Patients seek medical care only when symptoms appear with late diagnosis • Inadequate public health campaigns focusing on kidney health
Insufficient Training of PCPs	• Limited nephrology education in medical curricula for PCPs • Need for CME programs on CKD risk assessment and early management
Absence of Standardized Screening Protocols	• No universal CKD screening guidelines adopted at the national level • Variability in screening recommendations • Lack of consensus on screening frequency and target populations
Financial and Resource Constraints	• High costs of diagnostic tests in some regions • Limited availability of point-of-care diagnostic tools • Budgetary constraints preventing large-scale screening programs
Health Care Disparities Between Urban and Rural Areas	• Unequal access to health care facilities (fewer well-equipped rural centers) • Limited availability of nephrologists and trained PCPs in primary care settings • Inadequate referral networks connecting rural PCPs with nephrology specialists
Fragmented Referral and Follow-Up Mechanisms	• Lack of clear referral guidelines for PCPs • High dropout rates of patients due to lack of structured follow-up
Challenges in Implementing Digital Health Solutions	• Limited access to digital tools, EHRs, or AI-based CKD risk stratification models • Need for reliable internet connectivity and data security measures
Socioeconomic and Cultural Barriers	• Financial constraints preventing individuals from seeking routine check-ups • Lack of emphasis on preventive health care measures in many communities
Need for Policy and Legislative Support	• Inadequate funding for kidney disease awareness campaigns • Limited integration of CKD prevention into existing NCD programs

CKD = Chronic kidney disease; PCPs = Primary care physicians; CME = Continuing Medical Education; EHRs = Electronic health records; AI = Artificial intelligence; NCD = Noncommunicable disease.

obesity, and a family history of CKD can enhance early detection. Simple, cost-effective tests such as urinalysis should be incorporated into routine check-ups to facilitate early identification of kidney dysfunction[5]. Routine screening at primary care centers, particularly for individuals over 40 years of age or those with comorbidities or risk factors, can significantly reduce the burden of late-stage CKD.

EMPOWERING PRIMARY CARE PHYSICIANS

Despite evidence supporting early CKD detection, many PCPs lack adequate training in nephrology. Continuing Medical Education (CME) programs, integration of CKD risk calculators, and point-of-care decision tools can improve diagnostic accuracy and timely referrals to specialists[6,8]. Encouraging routine blood pressure and glucose monitoring in primary care settings can facilitate early risk identification. Additionally, primary care providers should be trained to recognize early CKD symptoms and implement evidence-based interventions, such as lifestyle modifications and pharmacologic management, to slow disease progression[6].

PUBLIC HEALTH AWARENESS AND PATIENT ENGAGEMENT

Community-based screening programs and awareness campaigns can empower patients to recognize CKD risk factors and symptoms. Mobile health (mHealth) interventions and digital platforms can aid in disseminating educational content and facilitating self-monitoring[9,10]. Strengthening patient education on lifestyle modifications, dietary interventions, and medication adherence is essential to slow CKD progression. Engaging community health workers in spreading awareness and conducting screening camps can further enhance early detection efforts, particularly in rural and underserved areas[9,10].

INTEGRATION OF CKD SCREENING INTO ROUTINE PRIMARY CARE CONSULTATIONS

Standardized CKD risk assessment tools should be integrated into electronic health records (EHRs) to streamline detection efforts. PCPs should routinely assess kidney function in high-risk individuals as part of general health check-ups. Ensuring accessibility to affordable diagnostic tests at primary health care centers is critical for large-scale implementation[11]. A structured framework for screening and follow-up care, including predefined intervals for testing based on individual risk factors, can improve early diagnosis rates and timely interventions.

REFERRAL PATHWAYS AND COORDINATION WITH NEPHROLOGY SERVICES

Developing clear guidelines for PCPs on when to refer patients to nephrologists is crucial for optimizing care[6,8]. Strengthening communication between primary care and nephrology services through teleconsultations can enhance specialist input and ensure continuity of care[12]. Implementing a tiered approach where mild-to-moderate CKD cases are managed in primary care, while advanced cases are referred to specialists, can help balance the workload across health care settings. Establishing dedicated referral networks and specialist outreach programs can further facilitate timely access to advanced nephrology care[5].

STRATEGIES FOR INTEGRATING CKD SCREENING INTO PRIMARY CARE

Integrating CKD screening into primary care requires a multifaceted approach that enhances early detection, improves physician awareness, and strengthens health care infrastructure. The following strategies can facilitate the incorporation of CKD screening into routine primary care practices:

- **Incorporating Routine Risk-Based Screening –** Screening for CKD should be incorporated into routine check-ups, particularly for high-risk populations. PCPs should be encouraged to perform simple tests, such as urinalysis, at regular intervals for at-risk patients[5].
- **Enhancing Physician Training and Awareness –** Regular CME programs, workshops, and online modules should be developed to educate PCPs on the latest guidelines for CKD diagnosis and management. Training should emphasize risk assessment, interpretation of laboratory findings, and appropriate referral pathways to nephrologists[5-8].
- **Developing Standardized Screening Guidelines –** A region-specific, evidence-based screening protocol should be established and widely disseminated. This would help ensure that CKD detection efforts are uniform and implemented consistently across health care facilities. National health agencies, nephrology societies, and public health departments should collaborate to integrate CKD screening guidelines into existing noncommunicable disease (NCD) prevention programs.
- **Expanding Access to Affordable Diagnostic Tools –** Governments and health care institutions should work to reduce the costs of essential tests, while ensuring their availability in primary health

care centers. Point-of-care testing and mHealth units can further help bridge the gap in rural and underserved areas.

- **Strengthening Referral and Follow-Up Mechanisms –** PCPs should be equipped with clear guidelines on when to refer patients to nephrologists. Additionally, structured follow-up mechanisms, including digital health records and patient reminders, can ensure continuity of care and reduce attrition rates.
- **Leveraging Digital Health and Telemedicine –** Integrating digital tools can improve CKD screening efficiency in primary care. AI-driven risk prediction models can assist PCPs in identifying at-risk patients and prioritizing early interventions. Teleconsultation services with nephrologists can provide guidance on patient management while reducing unnecessary referrals.

CONCLUSION

Integrating early CKD detection into primary care is a crucial step toward reducing the growing burden of kidney disease, particularly in South Asia, where the prevalence of risk factors is high. A proactive, structured approach that empowers PCPs with the necessary knowledge, tools, and standardized protocols can significantly enhance early diagnosis and intervention. By embedding CKD screening into routine health check-ups, improving physician training, increasing access to affordable diagnostics, and leveraging digital health solutions, primary care can become the frontline defense against CKD progression.

A holistic, patient-centered strategy that prioritizes early detection, timely intervention, and multidisciplinary collaboration will not only help curb the CKD epidemic but also reduce the socioeconomic burden associated with late-stage disease and dialysis dependency. Now is the time for action- primary care must evolve into a robust, prevention-oriented system that safeguards kidney health for future generations.

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Role of Protein Supplements in Diabetes Management

SHEFALI A KARKHANIS

Protein supplements are commonly used by athletes and fitness enthusiasts to support muscle growth and recovery[1]. However, there is growing interest in the potential role of protein supplements in diabetes management. Diabetes is a chronic condition characterized by elevated blood sugar levels, and the use of protein supplements may offer several benefits for diabetes patients.

Protein is an essential macronutrient that takes longer to digest in comparison to sugar and processed carbohydrates. Protein is important for maintaining muscle mass, regulating blood sugar levels, and promoting satiety. Studies have shown that protein supplementation can improve insulin sensitivity and glucose metabolism in individuals with type 2 diabetes[2].

One study found that supplementing with whey protein improved glucose control in patients with type 2 diabetes by increasing insulin secretion and decreasing insulin resistance[3].

Another study found that protein supplementation, when combined with resistance exercise, improved glycemic control and reduced insulin requirements in patients with type 1 diabetes. The findings of the study suggested that protein supplementation can enhance muscle protein synthesis and reduce muscle breakdown, leading to improvements in insulin sensitivity and glucose uptake[4,5].

OTHER ROLES OF PROTEIN IN DIABETES MANAGEMENT[6]

Improve Lipid Profile

Due to long-standing diabetes, dyslipidemia could be certainly possible. Good biological protein intake helps in maintaining a healthy lipid profile.

Supported Development of Lean Body Mass

Protein intake along with healthy carbohydrate intake helps in building more lean body mass, thus reducing overall fat percentage.

Bolsters Overall Immunity

Being building blocks of the body, proteins are essential in upgrading overall immune response. In case of diabetes, in most cases the immune response is sacrificed as diabetes is a metabolic disorder, which can cause strain on almost every human organ.

In overweight diabetes patients, a high on protein diet can help in weight loss due to the following effects[7]:

- Appetite control.
- Metabolic boost – Protein burns more kilojoule and prevents the slowing of metabolism that can help in weight loss.
- Reduce food cravings – As a high-protein meal leaves an individual satiated, it can reduce the night-time craving.
- Improved body composition – Protein diet helps in increasing the rate of fat loss.
- Reduced energy intake – Increasing the amount of protein in meals can have a significant impact on energy intake, which can help in weight loss.

However, it is important to note that not all protein supplements are created equal. Some supplements may contain added sugars, artificial flavors, and other ingredients that may negatively impact blood sugar control[8].

AMERICAN DIABETES ASSOCIATION (ADA) GUIDELINES FOR PROTEIN INTAKE[9,10]

Although, diabetes patients should consume sufficient protein to manage their blood sugar levels, they should also be mindful of their overall protein intake. As high protein intake and hyperglycemia can increase the glomerular filtration rate and the work load of the kidney.

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It has been seen that one-third of the people with insulin-dependent diabetes and one-fifth of people with noninsulin-dependent diabetes develop nephropathy within 15 years of diagnosis.

- According to the recommendations of ADA, diabetes patients aim for a balanced diet that includes 10% to 20% of calories from protein.
- A dietary intake of between 12% and 20% protein provides flexibility in food selection but exceeds actual needs.
- The adult Recommended Dietary Allowance of 0.8 g/kg body weight should provide guidance for determining desired protein intake for individuals with diabetes.

IMPORTANT TIPS TO REMEMBER BEFORE INCLUDING PROTEIN SUPPLEMENT IN DIABETES CARE

- Check with physician to determine the need of a special protein powder or some other supplements.
- Have a look at the key ingredients to avoid including any allergy causing component in the diet.
- Ascertain nutrition preferences of the individual to find the best option for special diabetic needs.
- Protein can help in weight loss only when they are used to replace carbohydrates and fats[10].
- Protein should not replace fresh fruits, vegetables and whole grain foods, as these provide fiber[10].

CONCLUSION

In conclusion, protein supplements may offer potential benefits for diabetes management, such as improving insulin sensitivity and glucose control. However, it is important to choose supplements carefully and consult with a health care provider before adding them to the diet.

Additionally, diabetes patients should be mindful of their overall protein intake and aim for a balanced diet to manage their condition effectively. With the right approach, protein supplements may be a useful tool for diabetes patients to support their overall health and well-being.

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What is the Diagnosis?

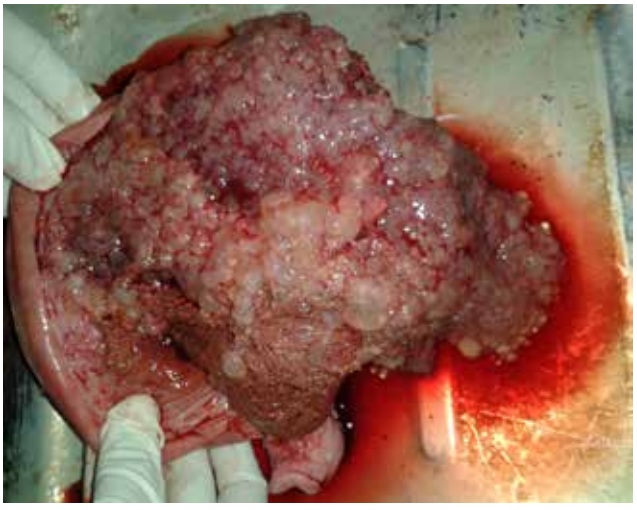
This image is a bisected uterus of 45 years old female presents with negative repeated urine pregnancy test and low serum human chorionic gonadotropin (hCG) level. Ultrasound examination showed an enlarged uterus measuring (18.8 × 9.7 × 15.6 cm) with complex mass in endometrial cavity with multiple small hypoechoic areas, increased vascularity and no fetal parts.

a) Molar pregnancy caused by "high dose hook effect"

b) Partial molar pregnancy

c) Ectopic pregnancy

d) False pregnancy



Answer to the Picture Quiz from the Indian Journal of Clinical Practice, Vol. 35, No. 9, February 2025

Answer: (a) Meckel-Gruber syndrome

See Answer in the Next Month's Issue!

Professional Indemnity Insurance for Medical Professionals

Doctors in India, since Vedic time, have been equated to God. No other profession, whether it is priest, lawyers, judges or politicians, occupies the same status as that of the medical doctors. Medical profession is the noblest profession.

However, doctors are also human beings and "**to err is human**". Medical error or injury has been known since the time of Hippocrates as principle of non-maleficence, derived from the doctrine of "*primum non-cere*", which means "first do no harm" and its natural corollary, beneficence or "do good", which means doing the right thing for the patient.

With the modern advancement in medical profession, the doctor-patient relationship has also changed from "paternalism", where doctors were "parent figures" taking medical decisions on behalf of their patients to the current "patient-centric" where the patient is an "equal partner". Thus, the type of patients has also changed from ignorant to enlightened.

With the advent of Consumer Protection Act, 1986 and various judgments by the Hon'ble Apex Court of the country and other courts and commissions, patients have started questioning the doctors and their treatment. Numerous cases are being filed against the doctors, hospitals, medical staff, etc., under consumer law, criminal law, civil law, etc. Compensation in lakhs and crores of money is being awarded in favor of the patient or his/her relative, which is to be paid by the doctor from his own pocket.

With increasing litigations against the doctors in the country, it has become very important and vital for the doctors to obtain insurance cover against all such litigations and compensation to be paid, if any. Accordingly, in the year 1991, the **Professional Indemnity Insurance** was introduced for the doctors and hospitals in the country.

MEANING OF THE TERM "INDEMNITY"

The term "indemnity" means "to compensate" or reimburse. The principle of indemnity is strictly followed in liability insurances.

Indemnity means a legal obligation to cover the liability of another. "To indemnify" does not merely mean to reimburse in respect of money paid but to save from loss in respect of the liability against which indemnity has been given.

"To indemnify" means to make good a loss suffered by a person in consequence of the act or default of another.

Indemnity is a contract, express or implied, "to keep a person who has entered, or is about to enter, into a contract of liability indemnified against the liability independently of the question whether a third party makes default or not."

PROFESSIONAL INDEMNITY INSURANCE

Professional indemnity insurances are designed to provide the insured person protection against the financial consequences of legal liability. This policy is meant for professionals to cover liability falling on them as a result of errors and omissions committed by them whilst rendering professional service. If the insured is legally liable to pay damages or compensation to others, the policy will indemnify him subject to the terms and conditions and limitations of the contract.

Indemnity is also available in respect of legal costs awarded against the insured as well as legal costs and expenses incurred by the insured with the written consent of the insurers in the defense or settlement of claims.

IMPORTANCE OF PROFESSIONAL INDEMNITY INSURANCE IN MEDICAL PROFESSION

The medical professional is expected to bring a reasonable degree of skill and knowledge and must exercise a reasonable degree of care.

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

The Hon'ble Apex Court in the matter titled as **"Kusum Sharma & Others versus Batra Hospital & Medical Research Centre, 2010 (3) SCC 480** has held that-

> *"94. On scrutiny of the leading cases of medical negligence both in our country and other countries*

specially United Kingdom, some basic principles emerge in dealing with the cases of medical negligence. While deciding whether the medical professional is guilty of medical negligence following well known principles must be kept in view:

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

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

Gross negligence is intentional failure to perform a manifest duty in reckless disregard of the consequences. Ordinary negligence is based on the fact that one ought to have known results of his acts, while gross negligence rests on the assumption that one knew results of his acts, but was recklessly or wantonly indifferent to the results.

If there is gross medical mistake, then the doctor will be liable for the negligene committed by him. In such case, doctor would be liable to pay huge compensation to the patient or his/her relatives.

To protect oneself from such huge compensation to be paid, if any, it is important and vital to obtain professional indemnity insurance.

SALIENT FEATURES OF PROFESSIONAL INDEMNITY INSURANCE

Indemnity

The professional indemnity insurance is meant for professionals to cover liability falling on them as a result of errors and omissions committed by them whilst rendering professional service. The indemnity applies only to the claim arising out of bodily injury and/or death of any patient caused by or alleged to have been caused by error, omission or negligence in professional service rendered or which should have been rendered by the insured or the assistants or the team of people employed by the insured.

Policy Period

Period commencing from the effective date and hour as mentioned in the policy and terminating at the midnight on the expiry date as mentioned in the policy.

Period of Insurance

Period of insurance means period commencing from the retroactive date and terminating on the expiry date as mentioned in the policy.

Commission of Act

The Act (medical negligence by doctor or hospital) has to be committed during the period of insurance commencing from retroactive date.

Retroactive Date

Retroactive date is the date when the risk is just incepted under "claims made" policy and thereafter renewed without any break in the period of insurance.

Limit of Indemnity

Irrespective of the number of persons or entities named in the insurance policy or added by endorsement, the total liability of the insurance company for damages inclusive of defense costs shall not exceed the limit of indemnity as mentioned in the policy.

Defense Cost

The insurance company pays all costs, fees and expenses incurred with their prior consent in the investigation, defense or settlement of any claim made against the doctor or hospital and the costs of representation at any inquest, inquiry or other proceedings in respect of matters which have a direct nexus to any claim made or which might be made against the insured. Such costs, fees and expenses are called defense cost.

Claims Series Clauses

Where series of losses and/or bodily injuries and/or deaths are attributable directly or indirectly to the same cause or error or commission relating to discharge of professional services all such losses and/or bodily injuries and/or deaths claims shall be added together and all such losses and/or bodily injuries and/or deaths shall be treated as one claim and such claim shall be deemed to have been made when the first claim was made in writing.

Registration

- **Doctor:** The doctor should be duly registered with his/her respective medical council.
- **Hospital/Medical establishment:** The Hospital/ Medical establishment should be registered with competent authority as per local law and rules. In territories where there is no registration

facility, then following minimum norms have to be complied with for considering the indemnity insurance policy:

- At least 10 in-patient facility
- Fully equipped operation theater of its own
- Fully qualified nursing staff in its employment round the clock, unless indicated to the contrary and additional premium paid
- Fully qualified doctor/doctors should be in charge round the clock
- The insured shall comply with registration formalities as and when official regulations or laws are enforced.

Short Period Policy

Short period policies are not permitted. However, in case of cancellation of the policy by the insured, short period scale rates as provided for will be applicable.

Compromise/Settlement

In normal course, all claims for compensation have to be legally established in court of law. However, insurers can arrive at compromise or settlement if *prima facie* liability exists under the policy.

Jurisdiction

Jurisdiction applicable will be of Indian courts only.

Exclusions

- Liability assumed under the agreement
- Cosmetic surgery (cosmesis)
- Liability arising out of:
  - Deliberate, willful or intentional non-compliance of statutory provisions
  - Loss of goodwill, libel, slander, false arrest, defamation, etc.
  - Fines, penalties, punitive or exemplary damages
  - Genetic injuries caused by X-ray treatment or diagnosis with radioactive substances
  - Professional services rendered by the insured prior to retroactive date
  - War and warlike perils
  - Nuclear fuel/ionizing radiation/radioactive contamination.

Premium Rate of Insurance

Separate rates of insurance are applicable to doctors, medical establishments, medical professionals, etc. Group discounts are available with the insurance companies for a group of doctors. Additional premium is applicable in case doctors want to cover qualified staff working with them. Whenever multiple specializations are involved, then the rate of insurance shall be of the specialization which attracts higher rate of insurance.

List of Eligible Medical Establishments

- Laboratories and diagnostic centers
- Hospitals
- Mental homes
- Nursing/convalescent homes
- Homes for physically disabled
- Clinics
- Dispensing pharmacies
- Veterinary hospitals and/or clinics and the like.

BENEFITS OF PROFESSIONAL INDEMNITY INSURANCE

- It is beneficial not only to the doctors or hospital but also to the patients and their dependents because the insurance company takes care of the compensation.
- Retroactive benefit: This means that the insured will be covered for any professional act or omission occurring during the period of insurance.
- It would take care of the amount of damages against third party.
- Scheme will also compensate on the principle of "no fault liability" to give some relief in the case of death or permanent disablement of the patient.
- The company will also pay the defense costs, which have a direct relevance to the claim.

LIMITATIONS OF PROFESSIONAL INDEMNITY INSURANCE

The only limitation that this policy has is that the amount of compensation is restricted by the limit of indemnity as mentioned in the policy.

CONCLUSION

Professional indemnity insurance is a tool, which not only meets the claim of compensation awarded against doctor/hospital but also gives a sense of mental security that even if some negligence is proved, the insurance company will take care of it.

Professional indemnity insurance covers all sums, which the insured professional becomes legally liable to pay as damages to third party in respect of any error and/or omission on his/her part committed whilst rendering professional service.

The insurance companies not only pay the compensation to other party but also arrange for the legal help from advocates because they sometimes join hand with other party for monetary gains with an excuse that it's the insurance not the doctor who is to pay the compensation.

However, one must never forget that the security is only monetary. The person's reputation and goodwill is not insured. So, all doctors should use their reasonable standard of care while treating and operating on their patients.

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DRS-WCPD: 11th World Congress on Prevention of Diabetes and Its Complications

METFORMIN IN PREGNANCY: HAAN KI NAA?

Dr Rajeev Chawla, New Delhi; Dr Shalini Jaggi, New Delhi; Dr Mayura Kale, Aurangabad

- Metformin remains the most effective drug for managing hyperglycemia in gestational diabetes mellitus (GDM), although its exact mechanisms are not fully understood.
- Metformin is a standard treatment option for pregnant patients with a history of type 2 diabetes (T2D), GDM, or any degree of hyperglycemia detected during the second or third trimester.
- However, the blood glucose targets for pregnant women are very stringent (fasting blood sugar [FBS]: 90 mg/dL and postprandial blood sugar [PPBS]: 120 mg/dL). If metformin is insufficient for managing glucose levels, insulin may be initiated.
- According to guidelines, insulin is the primary treatment for any dysglycemia in pregnant women who do not achieve target glucose levels with medical nutrition therapy or lifestyle changes alone.
- Adding metformin can be beneficial for pregnant women with T2D on insulin who require higher doses.
- Additionally, metformin should be prescribed if insulin administration is problematic due to availability, cost, or the patient's inability to self-administer or self-monitor.
- The few contraindications to metformin include fetoplacental insufficiency, intrauterine growth restriction, hypertension, and pre-eclampsia. Patients with these conditions should be started on insulin immediately.
- In high-risk pregnancies, such as those involving macrosomia or small-for-gestational-age babies, insulin should not be delayed.
- For women with polycystic ovary syndrome, metformin is the safest drug for managing blood glucose levels. Although the ADA guidelines recommend discontinuing metformin after 12 weeks, studies have shown that continued use can prevent the progression from mild dysglycemia to GDM.
- Clinicians should advocate for early blood sugar testing (postprandial glucose [PPG] >110 mg/dL) during pregnancy rather than waiting for the development of GDM in the second or third trimester before initiating treatment.

Overall, metformin is considered safe for use during pregnancy, and insulin should be added when metformin alone is insufficient for glycemic control. In 30% to 40% of clinical situations, patients may require insulin in addition to metformin to manage their blood glucose levels effectively.

CGM AS A GUIDE FOR DIETARY INTERVENTIONS

Dr Suhas Erande, Pune

The role of food-based dietary strategies in achieving T2D remission has gained significant attention, particularly with the rise of Mediterranean and plant-based diets. Continuous glucose monitoring (CGM) technology has shown promise in refining diet and lifestyle adjustments, but its application has limitations. Recent editorial critiques highlight that promoting CGM for nondiabetics may lack sufficient evidence and could potentially lead to eating disorders. For newly diagnosed patients reluctant to start medication, CGM can offer valuable insights, helping to reduce instances of hypoglycemia and hyperglycemia. It provides a feedback loop that enhances dietary adherence and overall health outcomes. Studies have demonstrated that dietary responses can vary significantly due to factors such as microbiota and food additives in processed foods.

To optimize the use of CGM, integrating it with personalized dietary guidance can be highly effective. Health care providers can use CGM data to offer tailored meal timing and composition advice, thereby stabilizing blood sugar levels. Practical strategies include:

- Focusing on one meal at a time and modifying it if PPG is high, such as substituting rice with more vegetables or lentils.
- Advising patients to keep a food diary to better correlate with glucose spikes from the ambulatory glucose profile.
- Teaching patients to monitor their time-in-range for motivation.

- Explaining the impact of exercise and stress on glucose levels.
- Encouraging experimentation with different diets, such as low-carb or high-protein, or sequencing foods to manage PPG spikes effectively.

FETAL ORIGIN OF TYPE 2 DIABETES

Dr CS Yajnik, Pune

- The fetal origins of T2D emphasize the critical role of early life nutrition and development in determining long-term health outcomes.
- In Indian populations, research has shown that both undernutrition and overnutrition during gestation can increase the risk of T2D in later life.
- This phenomenon, often described as the "thrifty phenotype", suggests that the fetus adapts to a limited supply of nutrients by developing insulin resistance and other metabolic changes.
- Although beneficial in the short-term, it predisposes the individual to diabetes and other chronic diseases in adulthood.
- The Pune Maternal Nutrition Study highlighted the significance of maternal nutrition before and during pregnancy in shaping the metabolic health of offspring.
- Children born to undernourished mothers were found to have lower birth weights and were more prone to developing central obesity and insulin resistance as they aged.
- Overall, early interventions aimed at improving maternal nutrition and fetal growth conditions are essential to break the cycle of diabetes transmission and reduce the burden of T2D in future generations.

NOVEL NONPHARMACOLOGICAL TREATMENT OF DIABETES: *GRYLLUS BIMACULATUS*

Dr Sam-Goo Lee, South Korea

Gryllus bimaculatus, commonly known as two-spotted crickets, has emerged as a promising sustainable protein source. It is rich in essential amino acids and unsaturated fatty acids and offers significant benefits for managing diabetes and other health conditions. Clinical evidence has demonstrated the glucose-lowering effects of cricket powder through the AKT/mTOR pathway, providing a novel approach to diabetes management.

The "D&D" (Diabetes and Dietary) trial, which involved 1,000 patients using a dietary supplement derived from crickets, confirmed the therapeutic effects of this alternative protein in managing diabetes. In the trial, patients were classified into eight groups: Juvenile-T1DM (<17 years), Adult-T1DM (Originated from LADA and T2DM), LADA (latent autoimmune diabetes in adults), etc.

Every 3 months, the patients were more than 20 different parameters such as glycated hemoglobin (HbA1c), microalbumin, fasting blood glucose, post-prandial 2 hours, insulin resistance, homeostasis model assessment of insulin resistance (HOMA-IR), low-density lipoprotein (LDL), high-density lipoprotein (HDL), etc.

Key findings include:

- HbA1c levels reduced from 12% to 6.5% within 3 months.
- Patients with T1D showed recovery in C-peptide levels and insulin secretion.
- Extremely high triglyceride levels (1,400 mg/dL) were normalized in 3 months.
- Improvement in diabetes-related complications, including:
  - Diabetic retinopathy
  - Peripheral neuropathy/numbness in the hands and feet
  - Nighttime urination reduced from 3 times to 1 time
  - Hyperglycemia/hypoglycemia
  - Hypertension
  - Hyperlipidemia
  - Erectile dysfunction, with increased testosterone levels
  - Hemiparalysis and obesity.

HOW TO PREVENT FATTY LIVER IN PEOPLE WITH DIABETES AND PREDIABETES?

Dr Juan Pablo Frias, USA

- The global prevalence of MASLD (metabolic-associated steatotic liver disease) in patients with T2D is approximately 65%.
- Fibrosis is the most significant prognostic factor in MASLD and is correlated with liver-related outcomes and mortality.
- Advanced fibrosis identifies patients requiring in-depth hepatological evaluation, including case-by-case confirmatory biopsy and intensive therapy.
- Primary care physicians, endocrinologists, gastro-enterologists, and obesity specialists should screen

for MASLD with advanced fibrosis using a four-step approach:

- Step 1: Identify patients at risk.
- Step 2: Conduct a thorough history and laboratory tests, including alcohol intake assessment, complete blood count (CBC), and liver function tests.
- Step 3: Perform noninvasive testing for fibrosis.
- Step 4: Measure liver stiffness.

- Approved and emerging pharmacotherapies for MASLD include resmetirom, pegozafermin, semaglutide, survodutide, tirzepatide, and others.

A case of a 64-year-old Latino man with a 14-year history of T2D was discussed. The patient presented with symptoms of hepatic steatosis on abdominal ultrasound.

- Based on the Fib-4 score and liver stiffness measurement, the patient was diagnosed with an intermediate risk for advanced hepatic fibrosis.
- The treatment plan included lifestyle modifications, initiation of glucagon-like peptide-1 (GLP-1) receptor agonist-based therapy, and sodium-glucose cotransporter 2 (SGLT2) inhibitors, along with continued metformin and basal insulin (at a reduced dose).

HOW TO ELABORATE AND/OR VALIDATE RISK SCORES FOR DIABETES AND CARDIOVASCULAR COMPLICATIONS?

Dr Noel Barengo, USA

Two strategies can be used to identify a high-risk population for diabetes and hyperglycemia: a one-step strategy involving diagnostic tests such as oral glucose tolerance test, HbA1c, etc., or a two-step strategy. The two-step strategy includes using diabetes risk scores followed by diagnostic tests.

According to Wilson's criteria for screening, the condition should be an important health problem, and its natural history should be understood. There should be a recognizable latent or early symptomatic stage, and the screening test should be easy to perform, interpret, acceptable, accurate, and sensitive. Additionally, there should be an accepted treatment for the disease, which is more effective if started early. Policies should be established regarding who should be treated, focusing on cost-effective diagnosis and treatment, and case finding should be a continuous process. The objective of developing FINDRISC was to create a simple, economical, and reliable tool that can be easily applied to the general population without requiring blood extraction.

Overall

- Validated screening tests exist.
- These screening tests have been successfully validated and implemented in various countries.
- Key challenges include monitoring attendance, determining short- and long-term benefits, implementing guidelines, and determining the appropriate time interval for screening tests.

MICROBIOTA AND THE PREDICTION OF PREDIABETES AND TYPE 2 DIABETES

Dr Rupjyoti Talukdar, Hyderabad

The gut microbiome, composed of diverse bacteria, fungi, and other microorganisms, regulates digestion, immune function, and overall health. Recent research has highlighted its potential in predicting diabetes and prediabetes. Shifts in the microbiome composition, often influenced by diet and lifestyle, have been linked to metabolic diseases, including diabetes.

- Emerging research suggests that microbiome alterations may precede the onset of diabetes and prediabetes, offering a potential predictive tool. For example, a Finnish study identified bacterial changes during pregnancy that could predict postpartum prediabetes.
- Similarly, a German study recognized microbiome patterns that appeared before developing T2D. These findings suggest that microbiome profiling could aid in the early detection and prevention of diabetes.

However, there are several challenges to overcome, such as:

- While some studies have linked microbiome changes to disease, few have successfully predicted disease onset.
- More large-scale research is needed to validate these findings, particularly in diverse populations like India.
- A multimodal approach incorporating clinical, biochemical, and lifestyle factors.
- Adding metabolomics to studies is crucial for improving prediction accuracy and translating microbiome insights into reliable clinical applications for diabetes management.

News and Views

Impact of Age on Cushing's Disease

A study published recently in the *Journal of Clinical Endocrinology & Metabolism* has found that older patients with Cushing's disease exhibit fewer classical features of the condition compared to younger patients[1].

The study from the US sought to determine the age-related differences in the clinical presentation, tumor characteristics, and surgical outcomes of Cushing's disease using data from the Registry of Adenomas of the Pituitary and Related Disorders (RAPID), which collects data from 11 sites in the United States. A total of 608 patients who underwent transsphenoidal tumor resection for Cushing disease between 2003 and 2023 were evaluated. The age of the participants ranged from 10 to 79 years; nearly 82.0% of the subjects were female. The median age at the time of surgery was 44 years.

Researchers found that older patients presented with larger tumors, more comorbidities such as hypertension, diabetes, hyperlipidemia, coronary artery disease, chronic obstructive pulmonary disease (COPD). They also faced a higher risk of postoperative complications, including thromboembolic events (deep vein thrombosis or venous thromboembolism).

They exhibited greater frailty and showed higher Knosp grades along with increased postoperative cortisol and adrenocorticotropic hormone (ACTH) nadirs. The Knosp classification is used to assess the likelihood of cavernous sinus invasion in pituitary macroadenomas.

Older patients presented with fewer classical features of Cushing's disease. Older age was also associated with lower preoperative 24-hour urinary free cortisol levels, lower Ki-67 proliferation indices (a marker of cell proliferation; high values indicate greater likelihood of tumor growth and spread) and arginine vasopressin deficiency. Conversely, younger patients presented more frequently with hallmark symptoms such as weight gain, abdominal striae, facial rounding, acne, hirsutism, menstrual irregularities, and dorsocervical fat pad, whereas obstructive sleep apnea and infections were more common with advancing age.

These findings suggest an inverse relationship between age and the hallmark symptoms of Cushing's disease. The age-dependent differences in clinical presentation, tumor behavior, and surgical risks, as observed in this study, reinforce the need for increased clinical awareness when assessing and diagnosing Cushing's disease in elderly patients. Furthermore, it underscores the need for tailored diagnostic and management approaches for different age groups.

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Risk Factors for Endometrial Polyps in Asymptomatic Postmenopausal Women

One-third of asymptomatic, postmenopausal women who underwent hysterectomy for uterovaginal prolapse have endometrial polyps, according to a study published in the February 2025 issue of the *American Journal of Obstetrics & Gynecology*[1]. Those using menopausal hormone therapy and women with a higher body mass index (BMI) were particularly at risk for developing these polyps.

This study aimed to determine the prevalence of endometrial polyps in postmenopausal women without symptoms of bleeding and to identify risk factors linked to their occurrence. The study, with a cross-sectional design, examined the prevalence of endometrial polyps in 317 asymptomatic, postmenopausal women who underwent hysterectomy for uterovaginal prolapse. Women who had a hysterectomy for other indications, including postmenopausal bleeding, were not included in the study. Eligible patients received care at a single medical facility in Washington state between 2009 and 2018. The primary outcome was the identification of endometrial polyps through pathology. Risk factors for the presence of polyps were analyzed using both univariate analysis and multivariate regression.

Out of the 317 women included in the study, 106 (33.4%) had endometrial polyps. The average size of the polyps was 13 mm, and the average endometrial thickness was 1.4 mm. The majority (78%) of cases had a single polyp. Two participants (1.89%) were found to have premalignant and malignant lesions; one had endometrial intraepithelial neoplasia and the second had endometrial carcinoma. Baseline clinical and demographic characteristics, such as the

presence of fibroids, endometriosis, and adenomyosis, were comparable between women with and without endometrial polyps.

The likelihood of having polyps was significantly associated with a higher BMI with odds ratio (OR) of 1.06. Similarly, the use of menopausal hormone therapy was associated with greater probability of having endometrial polyps (OR 1.67).

Clinicians should therefore be aware of the possibility of endometrial polyps in postmenopausal women undergoing hysterectomy for uterovaginal prolapse, even in the absence of symptoms. "Although the risk for malignancy seems to be low, more investigation is warranted to truly quantify the lifetime risk" conclude the authors.

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Type 2 Diabetes and Fracture Risk: An Under-recognized Complication

Diabetes duration of ≥10 years, glycated hemoglobin (HbA1c) and/or the presence of at least one microvascular complication such as diabetic retinopathy, nephropathy, or neuropathy increase the risk of any fracture, major osteoporotic fractures and hip fractures. These findings from a recent study were published in the journal *Diabetes, Obesity and Metabolism*[1].

The aim of this study was to find out if duration of diabetes, level of glycemic control, and presence of microvascular complications were associated with an increased risk of fractures at specific anatomical sites in patients with type 2 diabetes.

The study examined data of all patients with type 2 diabetes, aged ≥30 years, from the overall Clinical Practice Research Datalink (CPRD) GOLD cohort between 1987 and 2018. Based on the duration of diabetes, patients were categorized as <2 years, 2 to <5 years, 5 to <8 years, 8 to <10 years, and ≥10 years. Also, based on the most recent HbA1c in the year preceding their enrollment in the present study, patients were grouped as <6%, 6% to <7%, 7% to <8%, 8% to <9%, and ≥9%. The primary outcome was the occurrence of a fracture. Major osteoporotic fractures were defined as a fracture of the hip, vertebrae, humerus or the forearm (radius or ulna).

A total of 121,959 participants formed the study group with male preponderance. Their mean age was 63.0 years, the mean BMI was 31.9 kg/m^2, and mean HbA1c was 8.4%.

The risk of any fracture including major osteoporotic fractures was increased among patients who had diabetes for more than a decade with an adjusted hazard ratio (aHR) of 1.16 and 1.14, respectively. Diabetes duration of >8 years was associated with an increased risk of hip fractures compared to the diabetes duration of <2 years (aHR 1.32). HbA1c level of <6% was associated with a higher risk of any fractures (aHR 1.16), major osteoporotic fractures (aHR 1.21) and hip fractures (aHR 1.35) compared to HbA1c levels in the range of 6% to <7%. The risk of any fracture, major osteoporotic fractures and hip fractures was lower in the group with HbA1c between 7% and <8% with aHRs of 0.91, 0.88, and 0.78, respectively versus HbA1c value between 6% and <7%. In the group with HbA1c ≥8%, the risk of fractures was similar to the group with HbA1c between 6% and <7%.

The study also found that the presence of one or two microvascular complications was significantly associated with an increased risk of any fracture (aHR for one microvascular complication) as well as major osteoporotic fractures (aHR for one microvascular complication 1.13). Only the presence of two microvascular complications notably increased the risk of hip fractures (aHR 1.28) compared to patients without any microvascular complications. When associations with individual microvascular complications were evaluated, specifically retinopathy was associated with a higher risk of any fracture, major osteoporotic fractures, humerus, clavicle, and lower leg fractures.

No such associations were found for ankle, scapula, skull or tibia/fibula fractures. These findings demonstrate increased fracture risk associated with poor glycemic control, microvascular complications, and even stringent HbA1c targets. While stricter glycemic control may help in reducing other diabetes-related complications, on the flip side, it might increase susceptibility to fractures. It also emphasizes that patients should be monitored for microvascular complications.

Hence, implementing fracture-prevention strategies, especially in patients with these risk factors, such as optimizing glycemic control without stringent targets, DEXA scanning to measure bone mineral density and management of neuropathy to prevent fall risks may reduce the burden of fractures.

Reference

1. van Hulten V, et al. The association of type 2 diabetes-related characteristics with fracture risk at different sites. Diabetes Obes Metab. 2024;26(11):4887-96.

Can Self-Monitoring of Urinary Na/K Ratio Improve Salt Reduction Efforts?

Self-monitoring with the urinary sodium/potassium (Na/K) ratio meter, ≥3 times in a day, may be effective in lowering salt intake among patients who find it challenging to reduce their salt consumption, according to findings of a single center, nonrandomized controlled study published in the journal *Hypertension Research*[1].

This study examined the effectiveness and feasibility of a self-monitoring intervention in 160 patients with chronic kidney disease, hypertension, or heart disease who find it hard to reduce their salt consumption. A Na/K ratio meter that measured the urinary Na/K ratio was utilized for this purpose. All the selected participants received follow-up care at the outpatient clinic of Dokkyo Medical University Nikko Medical Center in the city of Nikko in Japan.

The 80 participants in the treatment (T) group received the device to measure their urinary Na/K ratio for a mean duration of 25.1 days. They were instructed to measure it for a minimum of thrice daily and keep it below 2.0, while the control group of 80 subjects was not given the Na/K ratio meter. Both groups received salt reduction education and guidance about home blood pressure measurement.

Almost half (48.8%) of the T group patients could achieve three measurements per day over a mean follow-up period of 13 months. Self-monitoring with the urinary Na/K ratio meter led to a significant reduction in salt intake, which decreased by 1.9 g/day by the second visit ($p < 0.001$). No change was evident in the control group.

The Na-to-K ratio is now increasingly being recognized as a more reliable indicator of the risk of cardiovascular diseases (CVD) and CVD-related mortality than measuring either Na or K intake individually.

Urinary Na-to-K ratio has demonstrated a strong predictive value for hypertension and CVD[2] and thus salt intake. It is easier to measure and also obviates the inconvenience of collecting 24-hour urine samples without any loss of urine.

References

1. Shimoyama M, et al. Effects of salt intake reduction by urinary sodium to potassium ratio self-monitoring method. Hypertens Res. 2024;47(7):1852-60.
2. Mirmiran P, et al. Urinary sodium-to-potassium ratio: a simple and useful indicator of diet quality in population-based studies. Eur J Med Res. 2021;26(1):3.

Prognostic Significance of Silent Mucus Plugs in COPD

Nearly 40% of patients with COPD, who are current or former smokers but who do not have the characteristic mucus-related symptoms such as cough, phlegm, have silent airway mucus plugs detected on computed tomography (CT) scan, according to a study published in the journal *Chest*[1].

This study focused on assessing the risk and protective factors as well as the implications of silent airway mucus plugs in patients with clinically diagnosed COPD. Participants from the multicenter COPDGene cohort formed the study group. Chest CT scans were used to quantify the number of pulmonary segments with mucus plugs and calculate the mucus plug score ranging from 0 to 18. Based on the score, the participants were categorized into three groups (0, 1-2, ≥3). Multivariable linear and logistic regression models were used to assess the risk and protective factors for silent mucus plugs and their associations with disease severity.

The total number of participants in the study was 4,363. A subgroup of 1,739 patients did not have cough or phlegm; of these, 627 (36%) were found to have mucus plugs on CT. Older patients (OR, 1.02) and female patients (OR 1.40) were at higher risk of silent mucus plugs than those who had symptomatic mucus plugs. The risk was also higher among Black patients (OR, 1.93).

After adjusting for potential confounders such as age, BMI, and smoking status, the presence of silent mucus plugs among individuals without cough or phlegm (compared to their absence) was independently associated with worse clinical outcomes, which included a shorter 6-minute walk distance, lower resting arterial oxygen saturation, decreased forced expiratory volume in 1 second (FEV1) % predicted, a greater extent of emphysema, increased airway wall thickness, and greater odds of experiencing a severe exacerbation within the past year.

This study has demonstrated a significant association between mucus plugging and poorer functional, structural, and clinical outcomes, suggesting their potential role in disease severity. Mucus plugging is more a consequence of impaired mucus clearance than hypersecretion. Hence, CT scan for mucus plugs should be a part of routine evaluation of COPD patients.

The authors suggest that "airway mucus plugging may be a distinct phenotype of COPD and could be an imaging biomarker". Detection of mucus plugs

in asymptomatic COPD patients warrants careful evaluation and management, as their presence is indicative of more severe disease and worse prognosis.

Reference

1. Mettler SK, et al. Silent airway mucus plugs in COPD and clinical implications. Chest. 2024;166(5):1010-9.

Association Between Hyperglycemia, Diabetes Duration and Heart Failure

Increased levels of HbA1c, fluctuations in HbA1c, and a history of severe hypoglycemia are all significant risk factors for heart failure in patients with type 2 diabetes, suggests a study published September 13, 2024 in the journal *Diabetes, Obesity and Metabolism*[1].

This study from Australia systematically reviewed longitudinal studies investigating the association of glycemic risk factors such as HbA1c, HbA1c variability, hypoglycemia, and diabetes duration with heart failure in patients with type 2 diabetes. The objective was to explore the link between these factors and the risk of heart failure in these patients.

The final analysis included 40 studies involving 4,102,589 participants. Analysis showed a 15% increased risk of heart failure for each 1% increase in HbA1c, a 2% increased risk for each additional year of diabetes and a 43% increased risk for individuals with a history of severe hypoglycemia. A 20%-26% increased risk of heart failure was observed for each unit increase in the metrics of HbA1c variability (HbA1c standard deviation, coefficient of variation, and average successive variability). All included studies scored high in the risk of bias assessment indicating that issues such as selection bias, confounding factors, and reporting bias might have influenced the results. Results from Egger's test showed the presence of publication bias suggesting that studies reporting strong associations between HbA1c levels and heart failure risk were more likely to be published, while those with negative or weaker findings might have been underreported or not reported. After adjusting for publication bias, a 14% increased risk of heart failure per percentage point increase in HbA1c was observed on trim-and-fill analyses.

This study has highlighted the contribution of glycemic risk factors and duration of diabetes to the increased risk of heart failure in patients with type 2 diabetes. Early intervention and proactive management of these risk factors to achieve stable glycemic levels, reducing HbA1c variability and avoiding severe hypoglycemic episodes may minimize the risk and improve patient outcomes.

Reference

1. Tabesh M, et al. The association of glycaemic risk factors and diabetes duration with risk of heart failure in people with type 2 diabetes: a systematic review and meta-analysis. Diabetes Obes Metab. 2024(12):5690-700.

Factors Influencing Adenomyosis Progression

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*[1].

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 greater than 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.

Reference

1. Borghese G, et al. Progression of adenomyosis: rate and associated factors. Int J Gynaecol Obstet. 2024;167(1):214-22.

Outcomes of Early PPROM

Around 26% of women with very early preterm prelabor rupture of membranes (PPROM) before 23 weeks of gestation, who received expectant management had children who survived to hospital discharge. However, both maternal and neonatal morbidity and mortality rates were high. These findings from a UK study were published in *BMJ Medicine*[1].

The aim of this prospective observational study was to examine the perinatal and maternal outcomes with PPROM occurring before 23 weeks of gestation. The study was conducted using the UK Obstetric Surveillance System (UKOSS), which comprised a national population-based cohort from all 194 obstetric units in the UK. The study period spanned from September 2019 to February 2021.

A total of 326 women with singleton pregnancy and 38 with multiple pregnancies with PPROM between 16 + 0 and 22 + 6 weeks + days of gestation were selected for the study.

The primary outcome measures for the fetus included live birth, survival to hospital discharge, and serious morbidity, which was defined as either requiring supplemental oxygen at 36 weeks postmenstrual age or experiencing an intraventricular hemorrhage grade 3 or 4, or both. For the mother, the outcomes included sepsis, hospitalization to an intensive care unit, surgery to remove the placenta, and death. Pregnancy termination rates for medical reasons were included in the clinical data.

A worst-best range was computed with the assumption that all terminations for medical reasons and those with missing data would have died (minimum value) or all would have been liveborn (highest value). The researchers calculated the perinatal outcomes with all terminations of pregnancy for medical reasons omitted.

The live birth rate was 44% in the group with singleton pregnancies with rates ranging from 30% to 62%. The perinatal survival rate to hospital discharge was 26%, with a range of 17%-53% and the percentage of newborns that lived without serious morbidity was 18%, with a range of 12%-48%. Maternal sepsis developed in 12% of patients with singleton pregnancies, whereas among those with multiple pregnancies, the maternal sepsis rate was 29%, which was statistically significant with p = 0.004. Twenty percent of women with singleton pregnancy and 16% of those with twin pregnancies required surgery to remove the placenta. Five participants developed severe sepsis; of these, 3 required intensive care, while two passed away.

This study highlights the complexities and challenges associated with expectant management of PPROM, particularly before 23 weeks of gestation. The risk of maternal sepsis is a significant concern in these pregnancies. Hence, the critical need for close maternal monitoring, early detection of chorioamnionitis, timely delivery and proper antibiotic therapy in these patients. The authors emphasize the need for careful counseling of families with PPROM, as well as the importance of updating clinical guidelines based on current data. They further advocate the need for further research in maternal sepsis since it poses a significant risk to both the mother and the newborns.

Reference

1. Goodfellow L, et al. Preterm prelabour rupture of membranes before 23 weeks' gestation: prospective observational study. BMJ Med. 2024;3(1):e000729.

Is 2,500 the New 10,000? Revisiting the Step Goal

Walking as little as 2,500 to 3,000 steps per day yields significant health benefits in terms of reduced mortality and incident heart disease, according to a new research published in the *Journal of American College of Cardiology*[1]. Walking faster adds to the beneficial outcomes[1,2].

This study was a meta-analysis of published evidence (up to October 2022) with the objective to investigate the relationship between daily step counts and adverse outcomes. Twelve studies involving 1,11,309 adults, aged 62.5 years (mean) and comprising 60.8% women were selected for analysis. None of the participants had a history of known heart disease. All-cause mortality and incident heart disease were the primary endpoints of the study. There were 4.4% deaths during a median follow-up period of 77.8 months and 1.4% incident heart disease during 72.9 months of follow-up.

Analysis of data revealed a marked decrease in risk for death due to any cause with a daily step count of 2,517 compared to 2,000 steps per day with aHR of 0.92. The risk of new onset of heart disease was also reduced in participants who took a daily step count of 2,735 compared to 2,000 steps per day with aHR of 0.89.

The risk of all-cause mortality was reduced by 36% among participants who took 6,000 (median) steps per day (vs. median of 3,166 steps per day). The highest risk reduction (50%) was observed for those who took 10,000 (median) steps per day compared to the participants who were least active (median of 3,166 steps per day). Compared with the least active participants, the risk of CVD was lower by 42% among the participants with 6,000 (median) steps per day and by 58% among those with 10,000 (median) steps per day[2].

The risk of all-cause mortality and incident heart disease declined further in a nonlinear manner as step count increased to 8,763 steps per day for all-cause mortality (aHR: 0.40) and 7,126 steps per day for incident heart disease (aHR: 0.49). However, an increase in daily step count further than these had no significant impact on the two study endpoints.

A notable finding of the study was a decline in the risk for all-cause mortality as the step count per minute (cadence) increased from low to intermediate or high. Gender had no impact on the dose-response. The risk of all-cause mortality reduced by further 20% with median step per minute count of 63 and 88 compared to 29 steps per minute. The researchers also examined the impact of devices used to measure step count. They found that risk reduction was significant for hip-worn accelerometers compared with pedometers and wrist-worn accelerometers.

This study has demonstrated a dose-response association of steps per day with clinical outcomes. It has identified the minimum step count and the optimum step count to reduce the adverse health outcomes.

The American Heart Association (AHA) as well as the Centers for Disease Control and Prevention (CDC) recommend a daily step count of 10,000 steps per day for a healthy heart and overall health. This study illustrates that this number is not sacrosanct as the benefits were significant even at a step count of ≥2500, which is less than 10,000 steps per day. Failure to achieve the 10,000-step mark may be disheartening for many. For some, for instance, persons with osteoarthritis, reaching this goal may be a daunting task. The take home message from this study is that it is important to be physically active; even some amount of physical activity is better than none. Hence, all patients must be encouraged to be more active for optimum cardiovascular health. Walking, and brisk walking at that, is the simplest, most inexpensive and an effective form of exercise.

"Although step volumes beyond this level were not associated with additional health benefits, there is no reason to discourage individuals from such behavior, as a highly physically active lifestyle may provide other benefits, such as joy, improved quality of life, and better sleep and mental health," write the authors[2].

References

1. Stens NA, et al. Relationship of daily step counts to all-cause mortality and cardiovascular events. J Am Coll Cardiol. 2023;82(15):1483-94.
2. TCTMD News. Available at: https://www.tctmd.com/news/mortality-cvd-benefits-seen-relatively-low-daily-step-counts, dated Sept. 8, 2023. Accessed October 6, 2023.

Predictors of Hemoptysis in Nontuberculous Mycobacterial Pulmonary Disease

Patients with nontuberculous mycobacterial pulmonary disease (NTM-PD), who have a history of tuberculosis (TB), high C-reactive protein (CRP) levels, and reduced % predicted forced vital capacity (FVC) are at a greater risk of developing clinically significant hemoptysis, which is associated with an increased likelihood of all-cause mortality.

This study assessed the incidence of clinically significant hemoptysis, the risk factors contributing to hemoptysis and its association with all-cause mortality in 506 patients with NTM-PD. Data for patients enrolled in a prospective observational cohort study between July 2011 and May 2023 was analyzed in the present study.

Results showed that 43 patients (8.5%) experienced clinically significant hemoptysis, requiring interventions like bronchial artery embolization or surgical resection, with an incidence rate of 2.1 cases per 100 person-years.

The major risk factors identified included a past history of TB (incidence rate ratio [IRR] 1.91), elevated CRP levels (IRR, 1.20 per 1 mg/dL increase), and lower % predicted FVC (IRR, 0.81 per 10% increase). Of note, clinically significant hemoptysis was associated with a higher risk of all-cause mortality (aHR, 2.39).

This study has identified risk factors for clinically significant hemoptysis in patients with NTM-PD. It also suggests clinically significant hemoptysis as a potential risk factor for mortality in these patients underscoring its implications for patient outcomes. These findings highlight the need for early identification and management of at-risk patients to improve survival rates.

Reference

1. Hyung K, et al. Clinically significant hemoptysis and all-cause mortality in patients with nontuberculous mycobacterial pulmonary disease. Respir Med. 2025;237:107946.

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Lighter Side of Medicine

HUMOR

A NICE BOY?

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

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

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

TELL HIM I CAN'T SEE HIM

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

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

COMPUTER POWER

A man dragged himself home and dropped his chair.

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

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

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

HOW DO YOU START A FLOOD?

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

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

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

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

IDENTITY

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

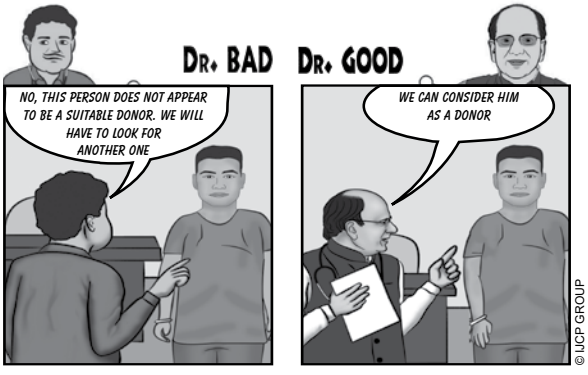
Her mother told her that must say, "I'm Jane Sugarbrown."

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

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

Dr. Good and Dr. Bad

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



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

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

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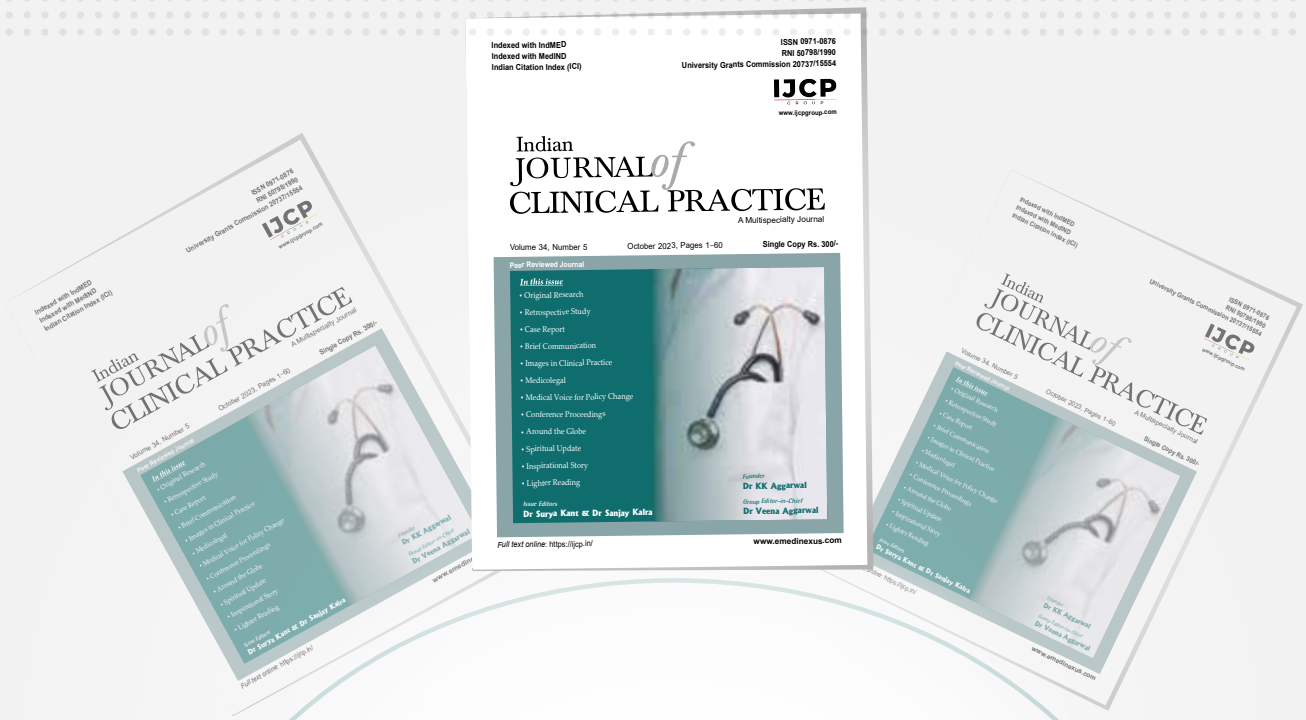

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Examples of common forms of references are:

Articles

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.

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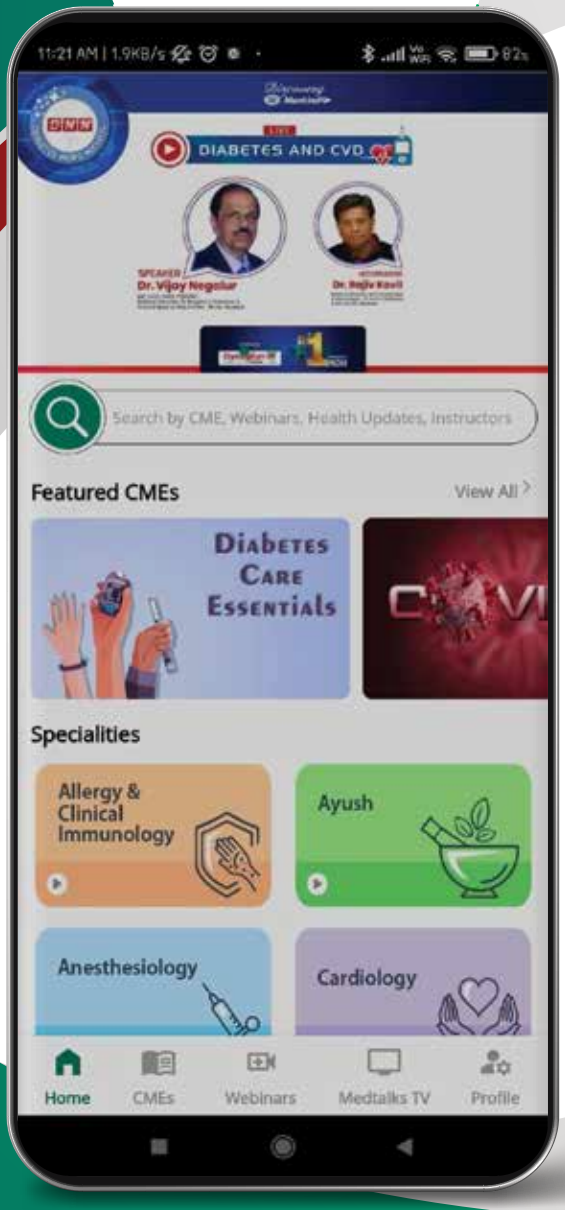

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