

## Special Article - Hemodialysis

# A Clinical Study of Comparison of Frail Diabetes vs Frail Nondiabetes Groups and Correlation with Outcomes in Patients on Maintenance Hemodialysis

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**Aim:** To compare frail diabetes group with frail nondiabetes group and correlation with outcomes in patients on maintenance hemodialysis.

**Patients and Methods:** We assessed frailty in patients on maintenance hemodialysis in our centre over a period of one year. Patients with diabetes kidney disease (frail diabetes group) and the end stage renal disease patients with nondiabetic kidney disease (frail nondiabetes group) were studied for the outcomes like falls, hospitalizations and deaths.

**Results:** A total of 205 patients were on maintenance hemodialysis in our centre. Of this, 167 patients satisfied the inclusion and exclusion criteria and were included in the study. Of 167 patients, 108 patients had diabetic renal disease and 59 patients had non diabetic kidney cause. Factors associated with frailty were identified to be presence of hypertension, presence of peripheral vascular disease, smoking, hepatitis C, low Kt/V, anemia, serum creatinine, higher inter dialytic weight gain and presence of intra dialytic hypotension. Outcomes like falls and hospitalizations were more in frail diabetes compared to frail nondiabetes group.

**Conclusion:** Prevalence of frailty is high in patients with diabetes related end stage renal disease on dialysis than in patients with non diabetes related kidney disease.

Falls and hospitalizations are more in patients of frail diabetes group compared to nonfrail diabetes group though there was no difference in deaths between the two groups.

**Keywords:** Frailty; Diabetes mellitus; Maintenance; Hemodialysis

## Introduction

Frailty is a state of decreased physical reserves causing loss of physical and mental strengths [1]. Frailty is reported to be a state of improper, premature and unsuccessful ageing. Frailty is known to be severe in patients with chronic illnesses like diabetes, chronic kidney disease. It is also understood that with increasing severity of kidney disease, frailty would increase in severity because CKD is a state of chronic inflammation.

Diabetes mellitus is a multisystem disease with progressive loss of structure and function of the organs involved. With the increasing longevity of survival, the ageing population would be on rise in future. The incidence of diabetes is also expected to rise to by 2025. Immunologically, diabetes is state of chronic low grade inflammation. Diabetes is reported to be associated with accelerated ageing which causes sarcopenia and thus increased frailty. Hence diabetes is said to an immunoageing process. Though the pathogenesis of frailty is multifactorial in patients with diabetes, presence of sarcopenia would lead to hyperglycemia due to inadequate metabolism [2]. Presence of hyperglycemia and sarcopenia are interdependent and hence in patients with diabetes, frailty may be severe. It is expected that both the diabetes and end stage renal disease being chronic inflammatory

states associated with sarcopenia, frailty would be severe in both the conditions.

Presence of diabetes may be considered as a risk factor for development of frailty in patients on maintenance hemodialysis. In addition, certain preventive measures may be taken to reduce the morbidities like falls, hospitalizations

### Aim

To determine the impact of diabetes on frailty in patients on maintenance hemodialysis.

### Patients and Methods

The study was carried out at our centre in 210 patients. Under this cashless government scheme, Patients are given thrice weekly hemodialysis using polysulfone membrane with surface area of 1.3 m<sup>2</sup>. Total number of hours of hemodialysis per week was 12 hours per patient. Erythropoietin is given twice weekly depending on the requirement. All the patients had permanent vascular access. Daily clinical assessment and a periodical biochemical assessment is done as per the scheme which is funded by the government for the below poverty line patients.

**Table 1:** Baseline characteristics of the study group.

| Characteristic       | Frail DM (108) | Frail non DM (59) | P value  |
|----------------------|----------------|-------------------|----------|
| Male : Female        | 72:36          | 40:19             | 0.9      |
| Age <40 YRS          | 42[38.88%]     | 27[45.76%]        | 0.3      |
| >40 YRS              | 66[61.11%]     | 32[54.23%]        |          |
| BMI (normal)         | 38[35.18%]     | 30[50.84%]        | 0.07     |
| (abnormal )          | 70[64.81%]     | 29[49.15%]        |          |
| access AVF           | 88[81.48%]     | 54[91.52%]        | 0.1      |
| IJV                  | 20[18.51%]     | 5[8.47%]          |          |
| Vintage <2YR         | 52[48.14%]     | 31[52.54%]        | 0.7      |
| >2YRS                | 56[51.85%]     | 28[47.45%]        |          |
| Hypertension         | 104[96.29%]    | 32[52.23%]        | <0.00001 |
| CVA                  | 49[45.37%]     | 23[38.98%]        | 0.5      |
| PTB                  | 11[10.18%]     | 6[10.16%]         | 0.7      |
| LVD                  | 66[61.11%]     | 33[55.93%]        | 0.6      |
| PVD                  | 94[87.03%]     | 17[28.81%]        | <0.00001 |
| Smoking              | 70[64.81%]     | 12[20.33%]        | <0.00001 |
| Hepatitis B          | 9[8.33%]       | 5[8.47%]          | 0.79     |
| Hepatitis C          | 29[26.85%]     | 7[11.86%]         | 0.03     |
| Kt/V <1.2            | 87[80.55%]     | 24[40.67%]        | <0.00001 |
| Hemoglobin <10gm/dl  | 87[80.55%]     | 37[62.71%]        | 0.01     |
| S.creatinine >5mg/dl | 92[85.18%]     | 27[45.76%]        | <0.00001 |
| IDWG>3KG             | 90[83.33%]     | 20[33.89%]        | <0.00001 |
| IDH                  | 92[85.18%]     | 24[40.67%]        | <0.00001 |

CVA: Cerebrovascular Accident; PTB: Pulmonary Tuberculosis; LVD: Left Ventricular Dysfunction; PVD: Peripheral Vascular Disease; IDWG: Interdialytic Weight Gain; IDH: Intradialytic Hypotension.

**Table 2:** Outcomes like falls, deaths and hospitalizations in frail diabetes and frail nondiabetes groups.

|                  | DM[108]    | NONDM[59]  | P value |
|------------------|------------|------------|---------|
| Falls            | 90[83.33%] | 25[42.37%] | <0.0001 |
| Deaths           | 13[12.03%] | 7[11.86%]  | 0.8     |
| Hospitalizations | 96[88.88%] | 31[52.54%] | <0.0001 |

### Inclusion criteria

Patients who have been on regular dialysis schedule for at least 6 months

Patients of >18 years of age and <65 years

Patients who have given consent to participate in the study

Those who are frail by Fried frailty criteria

### Exclusion criteria

Patients of <18 years and >65 years.

Patients who are bed ridden, had a recent history of hospitalization, psychological illness.

Patients who have not given consent.

Patients are divided into two groups, those with diabetes and frailty –frail diabetes group and those with frailty, but without diabetes –frail nondiabetes group.

Demographic data, details of dialysis, lab parameters and the outcomes like falls, hospitalizations and deaths were assessed.

## Results

A total of 205 patients were on hemodialysis in our centre. 167 patient's satisfied inclusion and exclusion criteria. Of this, 108 patients had diabetes related end stage renal disease and 57 had renal disease due to other causes.

Baseline characteristics of both the groups are shown in Table 1. Prevalence of frailty in our population was 81.46%. Number of patients in frail diabetes group was 108 (64%) and in frail nondiabetes group was 57 (35%). Male to female ratio was 112:55. The number of patients of age >40 years (98) were more than those with age <40 years (69). There was no statistically significant difference in age, gender, BMI, vintage of dialysis, type of vascular access between both the groups. Factors like hypertension, peripheral vascular disease, smoking, lowers Kt/V, anemia, higher inter dialytic weight gain and presence of intradialytic hypotension.

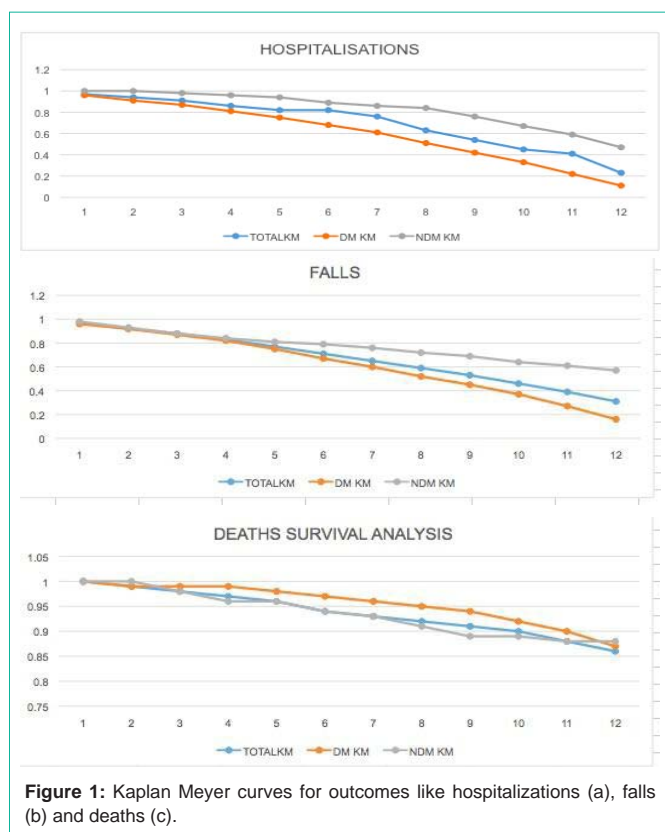
Regarding the Fried frailty criteria, Weight loss, Physical inactivity were severe in patients with frail diabetes group compared to frail nondiabetes group ( $p>0.05$ ). Other criteria like Physical exhaustion, handgrip and walk speed did not differ much between the two groups ( $p<0.05$ ) (Table 2).

Outcomes that were assessed include falls, hospitalizations and deaths. Though deaths did not differ significantly between the frail diabetes and frail nondiabetes group, number of falls and hospitalizations were found to be significant in frail diabetes group ( $p<0.05$ ) (Figure 1) compared to frail nondiabetes group.

## Discussion

Frailty is a constellation of impairment of physical and mental functions. Frailty is commonly observed in old patients and in those with chronic illnesses Frailty is assessed using fried frailty criteria which includes gait speed, hand grip strength, Physical Exhaustion, Physical Inactivity and Weight loss [1]. Patients with chronic kidney disease are known to have increased risk of frailty. CanFIT study determines the prevalence of frailty in CKD population to be 7 times more compared to nonCKD population [3]. An increase in incidence of frailty and other comorbidities was reported in ageing CKD patients [4]. Studies have shown that coexistence of frailty and CKD would lead to worse outcomes [5,6]. It is also reported that frailty is an independent factor for risk of death and hospitalization in patients with CKD and in dialysis patients [5,7,8].

Diabetes and end stage renal disease share similarities in that both are states of chronic inflammation with increased rates of sarcopenia. It was also observed that diabetes can impair physical function in patients with CKD independent of function of overt changes in renal function and other vital organs. Both the entities share common pathophysiology mechanisms like elevation of IL-6, IL-1.TNF- $\alpha$ , decreased levels of GH, IGF-1, testosterone and vitamin D leading to metabolic dysregulation they are also states of malnutrition and enhanced oxidative stress. The up regulation of inflammatory state and the down regulation of metabolic milieu would cause sarcopenia and thus increased degree of frailty. An increased incidence of microvascular and macrovascular complications is also seen in patients with diabetes and frailty. In addition, frailty itself is a state of chronic inflammation with an increase in IL-6 and CRP along with



**Figure 1:** Kaplan Meyer curves for outcomes like hospitalizations (a), falls (b) and deaths (c).

activation of other immunological components.

An increased insulin resistance and thus the hyperglycemic episodes are reported in diabetic frail patients. This implies that appropriate usage of oral hypoglycemic agents may decrease the development of frailty. But it is well known that in the dialysis population, hypoglycemia is common due to prolonged duration of action of endogenous insulin, malnutrition, low muscle mass. Recurrent hypoglycemic events would lead to frailty and cognitive dysfunction.

The effect of diabetes on frailty is also well reported. Increased sarcopenia, decreased muscle synthesis, increased muscle breakdown, increased intramuscular lipid accumulation, decreased muscle quality and strength are some of the factors described in literature.

In a study done by Lee, et al. in CKD patients, it was shown that the presence of comorbidities such as diabetes and hypertension was associated with frailty with an odds ratio of 2.73, 2.57 respectively and combined presence of diabetes and hypertension was associated with an increase of odds ratio of 3.76 [9,10].

In our study, prevalence of frailty was 81.6%. We did not find significant difference in frailty with age (>40 years and <40 years) or the gender. This is in contrast to the findings in CanFIT study where older age, female gender were more likely to be associated with frailty [11] though the age cut off in our study was taken as 40 years instead of 65 years. Factors like BMI, duration of dialysis and type of vascular access did not show statistically significant difference. This is similar to the study reported by Lee, et al. where factors like diabetes, cardiac disease, and cerebrovascular disease had a significant association with

frailty but factors like vintage of dialysis and dialysis modality did not show relation with frailty [12]. The effect of diabetes on frailty is multi factorial. Increased sarcopenia, decreased muscle synthesis, increased muscle breakdown, increased intramuscular lipid accumulation, decreased muscle quality and strength are some of the factors described in literature.

The increased frailty in diabetic dialysis group may be due to hypoglycemia rather than hyperglycemia episodes. Frailty is known to increase insulin resistance and thus cause hyperglycemia. This implies that appropriate usage of oral hypoglycemic agents may decrease the development of frailty. In the dialysis population, hypoglycemia is common due to prolonged duration of action of endogenous insulin, malnutrition, low muscle mass. Recurrent hypoglycemic events would lead to frailty and cognitive dysfunction.

In conclusion, in our study, dialysis patients with diabetes are at high risk of development of frailty compared to nondiabetes dialysis population. Frail diabetes patients are at increased risk of hospitalizations and falls.

In a recent study in elderly, Lifestyle interventions and Independence for Elders (LIFE) showed that measures to curb frailty may decrease the number of deaths, falls and hospitalizations [13]. In a similar way, preventive measures in the form of counseling regarding nutrition, lifestyle, exercise and education may decrease the prevalence of frailty and its complications.

## Limitations

Our study sample is small in number.

The follow up period is only one year.

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