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Original research article

Frailty and pre-frailty in elderly type 2 diabetes mellitus: Determinants and adverse outcomes

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Abstract

Background: Frailty is vulnerability to adverse outcomes resulting from an interaction of physical, socio-economic and co-morbidity factors. The study aims to find out the prevalence of Frailty and its association with risk factors and adverse outcomes associated with frailty in elderly Diabetes mellitus study subjects.
Methodology: This descriptive, cross-sectional study was done at a tertiary care centre in Karnataka, India. 224 Elderly diabetics were recruited for the study using systematic random sampling from diabetic Registry. Frailty was assessed by using Multi-dimensional prognostic index by using questionnaire.
Results: Proportion of Frailty and Pre-Frailty in elderly diabetics the were 9.3% and 55.8% respectively. Age, Duration of Diabetes Mellitus, number of Drugs were important determinants of frailty. Frailty associated with adverse health outcomes like hypoglycemic episodes, need for hospitalisation and duration of hospital stay.
Conclusion: Recognizing and understanding frailty is important as it predicts long term outcomes and frailty may be reversible in early stage. Frailty also opens up a new conundrum and challenge for public health, incites research.
Keywords: Adverse outcome, diabetes mellitus, elderly, frailty

Introduction

According to the International Diabetes Foundation, Diabetes currently affects more than 62 million Indians, which is more than 7.2% of the adult population. The average age on onset is 42.5 years. Nearly 1 million Indians die due to diabetes every year. According to Population Census 2011 there are nearly 104 million elderly persons (aged 60 years or above) in India; 53 million females and 51 million males. Both the share and size of elderly population is increasing over time. From 5.6% in 1961 the proportion has increased to 8.6% in 2011. The old-age dependency ratio climbed from 10.9% in 1961 to 14.2% in 2011 for India as a whole. For females and males, the value of the ratio was 14.9% and 13.6% in 2011. (Source: elderly in India 2016. GoI Report).

The concept of frailty was new to India, as India is in the stage of Demographic and epidemiological Transition with steadily rising Life expectancy and more percent of elderly. It has an impact over the quality of life, such as more hospitalizations and disability. Frailty is difficult to diagnose, particularly within primary care settings, due to its coexistence with other age-related conditions and as a result of the lack of a universally accepted clinical definition. It is defined as “A physiologic syndrome characterized

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by decreased reserve and resistance to stressors, resulting from cumulative decline across multiple physiologic systems, and causing vulnerability to adverse outcomes" (Fried *et al*., 2001) or in other words- Vulnerability to adverse outcomes resulting from an interaction of physical, socio-economic and co-morbidity factors.

This definition is in line with some commonly used frailty assessment tools, such as the frailty phenotype, the FRAIL questionnaire, and the Frailty Index. In simplest words, frailty is increased vulnerability to adverse outcomes.[1]Frailty is thought to result from cumulative cellular damage over the life-course, which leads to both malnutrition and sarcopenia. Other factors linked with frailty development include socio demographic influences, such as poverty, living alone, area deprivation and low education level psychological factors, including depression; nutritional issues such as malnutrition and poor oral health, polypharmacy, diseases associated with low physical activity

It is of utmost important to identify and assess Frailty and Pre-Frailty, as it is associated with long term adverse health outcomes and impact on the quality of life of elderly diabetics. If we recognize pre-frailty earlier, we will be able to do interventions at the earliest to address them. The prevalence of frailty in India is not known. Hence this study was done with to find out the proportion of frailty and pre-frailty in elderly type 2 diabetics and to find the risk factors and adverse outcomes among elderly Frail diabetics.

Material and Methods

This Descriptive Cross-Sectional study was conducted in 2019 at Mysore Medical College and Research Institute, a tertiary care center at Mysore, Karnataka, India. Elderly diabetics were chosen for the study from general medicine out-patient from the diabetes registry by using systematic random sampling. All Diabetics who were above 60 years irrespective of duration of Diabetes Mellitus were recruited for the study. Selected participants later may or may not be admitted as in-patient. Various studies on frailty in elderly diabetics showed prevalence of frailty ranging from 15-20% and pre-Frailty ranging from 25-35%. Identifying pre-Frailty was one of the main objective of the study, hence by taking 30% as prevalence of pre-frailty with 6% absolute precision for 95% confidence interval, calculated sample size was 224. Study subjects who were on dialysis or end stage terminal disease like End-stage renal disease and stage III/IV Malignancy were excluded from the study. Patients were labeled as type 2 Diabetes Mellitus by using ADA (American Diabetic Association) guidelines of Fasting plasma Glucose $\geq$ 126 or 2hr plasma glucose $\geq$ 200 or HbA1c $\geq$ 6.5%.

Study instrument

The Multidimensional Prognostic Index. The multidimensional impairment of the patients enrolled in the study was evaluated by the MPI based on a standardized CGA that included information on basal and Instrumental Activities of Daily Living (ADL, IADL), the cognitive status assessed by the Short Portable Mental Status Questionnaire (SPMSQ), the risk of pressure ulcers evaluated by the Exton-Smith scale, and the nutritional status evaluated by the Mini Nutritional Assessment (MNA). Information on co morbidity, evaluated by the Cumulative Illness Rating Scale (CIRS), the number of medications, and the cohabitation status were also collected.

From all these domains, MPI, a multidimensional predictive tool for short- and long-term mortality risk, was calculated according to a validated algorithm. The final score of the MPI ranges from 0 (lowest risk) to 1 (highest risk).

Ethical clearance was taken form in Institutional Ethical committee. Informed consent was taken from the study participants before administering study instrument. The questionnaire was translated to Kannada and back translated to English to ensure reliability. The researcher will explain the instruction to the respondents and will be available for clarifications. The questionnaire will not have any identifying data. Questionnaire contained information on Demographic profile, Multidimensional Prognostic Index, Questions on previous history of diabetes (whether on oral anti hyperglycemic drugs / insulin), Questions on hypoglycemic events, falls and hospitalization, Questions on complications of diabetes like symptoms and history of eye defects, neuropathic symptoms, heart disease, stroke in the 6 months, Measurements including weight, BMI, WHR, Blood Pressure and Laboratory values-HbA1C, Lipid Profile, Serum Creatinine, Urine Microalbumin.

Data was entered into Microsoft Excel (Windows 7; Version 2007) and analyses were done using the Statistical Package for Social Sciences (SPSS) for Windows software (version 22.0; SPSS Inc, Chicago). Descriptive statistics such as mean and standard deviation (SD) for continuous variables, frequencies and percentages were calculated for categorical Variables were determined. Association between Variables was analyzed by using Chi-Square test for categorical Variables and ANOVA (Analysis of Variance)/Kruskal Wallis Test for Quantitative Variables after checking the normality of data by using

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Shapiro-Wilk test. Bar charts and Pie charts were used for visual representation of the analyzed data. Level of significance was set at 0.05.

Results

Overall proportion of elderly diabetic in the present study was 9.3% and proportion of Pre-Frailty was 55.8% (Table 1).

Table 2 depicts that both Frailty and Pre-Frailty were more common among females (60.7% and 11.2 % respectively) compared to males (51.3% & 7.7%) even though the P value is not significant. Proportion of frailty increases as age advances from 60 years. Mean age of non-frail group was 68.21 years, pre-frail group was 70.58 years and frail group was 74.76 years clearly shows that Age is an important determinant of frailty. The association between age and frailty is statistically significant. Duration of type 2 Diabetes Mellitus is directly proportional to Frailty. Proportion of Frailty was 8.3% and 11.5% respectively for diabetics having 6-10 years and more than 10 years. Similar trend is observed in pre-frail subgroup also. The association between duration of DM and frailty is statistically significant.

Smoking, alcohol and patients taking both oral hypoglycemic agents and Insulin were at risk of frailty than their counterparts who were non-smokers, non-alcoholics and patients whose blood sugar was managed only with Oral hypoglycemic agents, which was also statistically significant. Comorbidities like hypothyroidism and hypertension does not seem to be associated with frailty in the present study.

Table 3 shows that all adverse outcomes are more common among frailty and pre-frailty compared to non-frail group. 23.8% of Frailty group study subjects had more than one episode of hypoglycaemia in the last 6 months. Similarly number of falls in the last 6 months was also significantly higher in frail group (i.e. 9.6%) compared to other groups. Around 43% of elderly diabetics had atleast one hospital admission in last one year among frail group compared to only 16.7% in non-frail group. The trend is same even for total admissions in the last one year, which were higher in frail group. All the above associations were statistically significant. Admissions for hyperglycaemia was the one among adverse events which is not statistically significant, even though showing similar pattern.

Table 4 shows that all micro and macro vascular complications of type 2 diabetes mellitus were relatively higher in frail and pre-frail group compared to non-frail group, even though the p values are not showing significance. It is observed from Table 5 that mean urine microalbumin was significantly higher in frail and non-frail group compared to non-frail group. Lipid profile does not seem to be having any association with Frailty.

Table I: Distribution of Study Subjects according to the Frailty Score

Frailty Score	Frequency	Percent
0	78	34.8
1	86	38.4
2	39	17.4
Pre-Frail	**125**	**55.8**
3	18	8.0
4	2	0.9
5	1	0.4
Frail	**21**	**9.3**

Table II: Risk Factors for Frailty in Elderly Diabetes Mellitus Patients

	Not Frail n (%)	Pre-Frail n (%)	Frail n (%)	P Value
Gender				
Female	30 (28.0)	65 (60.7)	12 (11.2)	0.113
Male	48 (41.0)	60 (51.3)	9 (7.7)	
Age (in Years)				
60-70	58 (42.6)	72 (52.9)	6 (4.4)	0.002*
70-80	17 (23.9)	43 (60.0)	11 (15.5)	
>80	3 (17.6)	10 (58.8)	4 (23.5)	
Mean (SD)	68.21 (4.76)	70.58 (6.57)	74.76 (7.37)	<0.001*
Duration of DM (in Years)				
≤ 5	23 (92.0)	2 (8.0)	0	<0.001*
5-10	30 (50.0)	25 (41.7)	5 (8.3)	
>10	21 (15.1)	102 (73.3)	16 (11.5)	

ISSN: 0975 -3583, 0976-2833 VOL12, ISSUE 03, 2021

Medications				
Oral	60 (40.0)	83 (55.3)	7 (4.7)	0.008*
Both OHA & Insulin	18 (24.3)	42 (56.8)	14 (18.9)	
Smoking				
Yes	25 (25.0)	58 (58.0)	17 (17.0)	0.003*
No	53 (42.7)	67 (54.0)	4 (3.2)	
Alcohol				
Yes	5 (14.3)	10 (28.6)	20 (57.1)	<0.001*
No	73 (38.4)	115 (60.5)	1 (0.5)	
Hypothyroidism				
Yes	11 (34.4)	18 (56.3)	3 (9.4)	0.998
No	67 (34.9)	107 (55.7)	18 (9.4)	
Hypertension				
Yes	54 (34.2)	86 (54.4)	18 (11.4)	0.276
No	24 (36.4)	39 (59.1)	3 (4.5)	

Table III: Adverse Outcomes among Frail Elderly Diabetes Mellitus Patients

Adverse Outcome	Not Frail n (%)	Pre-Frail n (%)	Frail n (%)	P Value
Hypoglycemic Events				
0	77 (98.7)	115 (92.0)	13 (61.9)	<0.001*
1	0	7 (5.6)	3 (14.3)	
>1	1 (1.3)	3 (2.4)	5 (23.8)	
Number of Falls				
0	74 (94.9)	112 (89.6)	14 (66.7)	0.003*
1	1 (1.3)	9 (7.2)	5 (23.8)	
>1	3 (3.8)	4 (3.2)	2 (9.6)	
Previous Hospital Admissions				
0	65 (83.3)	79 (63.2)	12 (57.1)	0.001*
1	11 (14.1)	40 (32.0)	5 (23.8)	
>1	2 (2.6)	6 (4.8)	4 (19.0)	
Admissions for Hyperglycaemia				
0	73 (93.6)	119 (95.2)	18 (85.7)	0.224
1	5 (6.4)	5 (4.0)	2 (9.5)	
>1	0	1 (0.8)	1 (4.8)	
Total Admissions in last 1 years				
0	62 (79.5)	79 (63.2)	9 (42.9)	0.002*
1	12 (15.4)	37 (29.6)	7 (33.3)	
>1	4 (5.1)	8 (6.4)	5 (23.8)	
Length of Stay (in Days)				
<3	9 (69.2)	7 (15.2)	0	<0.001*
4-7	4 (30.8)	23 (50.0)	2 (22.2)	
>7	0	16 (34.7)	7 (77.8)	

Table IV: Complications of Type 2 DM and its association with Frailty

Complications	Frailty Group			P Value
	Not Frail n (%)	Pre-Frail n (%)	Frail n (%)	
Retinopathy	24 (30.8)	47 (37.6)	10 (47.6)	0.318
Nephropathy	25 (32.1)	40 (32.0)	8 (38.1)	0.852
Neuropathy	41 (52.6)	81 (64.8)	14 (66.7)	0.186
Diabetic Foot	7 (9.0)	11 (8.8)	5 (23.8)	0.100
IHD	12 (15.4)	30 (24.0)	4 (19.0)	0.330
CVA	3 (3.8)	6 (4.8)	2 (9.5)	0.563

Table V: Comparison of Biochemical Parameters among Frailty Sub Groups

Parameter	Frailty Group			P Value
	Not Frail Mean (SD)	Pre-Frail Mean (SD)	Frail Mean (SD)	

ISSN: 0975 -3583, 0976-2833 VOL12, ISSUE 03, 2021

HbA1c	8.64 (2.66)	8.94 (2.10)	8.60 (1.69)	0.668
Urine Microalbumin	53.61 (117.46)	283.39 (705.2)	451.7 (764.1)	0.327
TC	158.00 (47.39)	148.58 (45.34)	165.0 (56.54)	0.435
HDL	39.41 (13.66)	36.93 (13.27)	36.37 (10.51)	0.576
LDL	104.65 (41.30)	98.03 (31.27)	105.50 (40.71)	0.588
TG	166.56 (102.8)	157.48 (83.07)	116.50 (45.81)	0.345

Discussion

Frailty has many phenotypes including unintentional weight loss, exhaustion (self-reported), weakness (Grip Strength), slow walking speed and reduced physical activity.

Association between Frailty and Diabetes

With advanced ageing, a variety of pathophysiological alterations often lead to frailty, and a vulnerability to adverse health outcomes due to multisystem decline. Frailty is characterized by deterioration in muscle and nerve function, anemia, declining cardiopulmonary reserve, and loss of executive function Diabetic patients tend to have an accelerated ageing process that places them at greater risk of developing frailty at an earlier age [4, 7].

Cardiovascular Health Study (Watson *et al*. 2002) showed 25% frail elderly had diabetes, 18.2% pre-frail had diabetes and 12% non-frail had diabetes. Older diabetics had prevalence and incidence of frailty 19.2% and 12.3% incidence. Older non-diabetics had prevalence and incidence of frailty 11.9% and 7% incidence. Furthermore, frail CHS participants were significantly more likely to have higher glucose and insulin levels at baseline and on oral glucose tolerance testing than those who were not frail. It is clear that diabetes and frailty are closely interrelated, but only minimal evidence suggests the causal relationship between DM and frailty. What is uncertain is whether frailty leads to glucose disorders, glucose disorders lead to frailty, or that both are related to other common factors [4, 8].

Beijing Longitudinal Study of Aging (Chhetri *et al*. 2017) found the prevalence of frailty in pre-diabetics (11.43%) and non-diabetes (11.92%) population was quiet similar. The prevalence of frailty was found to be higher in female compared to male in all 3 groups i.e. non-diabetes, pre-diabetes and diabetes respectively, The prevalence of frailty was found to increase with age and was highest in oldest of old age group ≥85. Prevalence of frailty increased with the number of co-morbidity in all 3 groups; highest in subjects with 3 or more co-morbidity. Similarly, prevalence increased with polypharmacy, subjects with 4 or more medications per day had higher prevalence of frailty in the 3 groups, respectively. The present study has relatively higher pre-frailty group and less prevalence of frailty compared to previous studies. This is probably because India is in stage of demographic and epidemiological transition, prevalence of frailty might rise in near future, indicating a good time for any intervention. Age is a significant determinant of frailty in the present study also. Female Gender was showing higher risk of frailty, even though it was not statistically significant. Smoking, alcohol and duration of DM were associated with frailty in the present study.

Diabetes associated with frailty and incremental association when hypertension or diabetic complications present (Lee *et al*. 2016), increased risk of CVA and Dementia (Fukazawa *et al*. 2013), Diabetics have increased risk of physical disability (Wong *et al*. 2013). History of falls twice that of non-diabetics. Risk increases with presence of cognitive impairment and/or hypoglycemic events. Andrew *et al*. 2012 showed presence of 2 or more chronic diseases and Gender were associated with frailty.

Maggi *et al*., a cohort study done in Italy on health status of diabetes done in Italy. The sample recruited (mean age: 73.3 ± 5.5 years) had a mean duration of diabetes of 11.3 ± 8.2 years. Half were taking sulphonylureas alone or together with other medications, 9.7% were taking insulin in combination with other OADs. Also, 12% of patients reported hypoglycemic events, 90% of whom were taking insulin or sulphonylureas. In addition, 81% of the participants were completely independent in their activities of daily living, while 19% were mildly, moderately or severely disabled. Age, female gender, hypoglycemic events, neuropathy and low diastolic blood pressure were the main variables associated with disability [3].

Liang-kung-Chen *et al*., concluded that, the prevalence and incidence of Diabetes Mellitus is increasing with advancing age. However, elderly diabetic patients with frailty, functional disability, or multiple comorbidities are usually excluded from clinical trials, which make applying current evidence to clinical practice difficult [4].

A study done by Korea by Hak Chul Jang *et al*., revelaed that sarcopenia has been closely related to many clinical consequences, including functional disability, metabolic impairment, increased cardiovascular risk, and mortality, in the older Korean adults.

Analizia Pena de Silva *et al*. the correlation of the frailty syndrome with socio-demographic variable sin

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people with type 2 diabetes mellitus occurred in contexts of low educational level and lack of work [6].

DM, inflammation and frailty

Age-related decline in mitochondrial function can result in lower levels of energy production, impaired utilization of energy and increased production of free oxygen radicals. The resultant increase in inflammatory mediators may influence late-life glucose intolerance and the development of diabetes in frail older adults. Free fatty acid accumulation within tissue leads to abnormalities in phosphorylation of the insulin receptor substrate and dysfunction of the glucose transporter receptor. This accumulation occurs because of abnormalities in mitochondria, increased circulating triglycerides and altered glucose metabolism leads to decreased muscle strength. Stressors precipitate frail individuals into a state of disability [4, 10, 11].

Diabetics develop the conditions necessary for frailty earlier than other aging individuals; therefore, appropriate treatment of DM and frailty precursors can slow the ageing process. As such, the prescription of anti-diabetic treatment in frail diabetic patients must take into consideration not only the standard goal of lowering hyperglycemic levels, but also treating the above-mentioned features. Altogether, frail diabetic patients are a specific group in need of addressing diverse clinical features beyond diabetic control.

Conclusion

Recognizing and understanding frailty is important as it predicts long term outcomes and frailty may be reversible in early stage. Frailty also opens up a new conundrum and challenge for public health, incites research. Studying the depth of Frailty also guides prescribing and decision making for general practitioners. Caring for Frail Elderly Diabetics is important to prevent further functional decline, Optimize Chronic Disease Management Strategies, Early detection of illness and possible adverse drug effect, Identifying and responding to problems such as falls, Immobility, Confusion, Depression, Incontinence, to consider safety of the physical environment, Maximize community and socio-economic supports and for giving Education and Support to Caregivers.

Ethics

Ethical issues are addressed as follows

- The study purpose was explained and informed consent was taken from the students.
- The participation is voluntary.
- Data collected does not contain any identifiers.
- Non-invasive, cause no harm to the participants.
- No cost to the participants.

Budget

No additional budget is required.

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