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Original Research

Gait Speed and Evolution of Verbal Fluencies in Frail or Prefrail Older People with Type 2 Diabetes. A Pilot Study

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Abstract

OBJECTIVES: Type 2 diabetes (T2D) is a risk factor of frailty and cognitive impairment. Impaired gait in older people is associated with incident vascular dementia. We aimed to assess whether in frail or prefrail older subjects with T2D, lower gait speed can be associated with faster cognitive decline.

DESIGN: Case-control study nested in a large randomized control trial (RCT, MID-frail); post hoc analysis.

SETTING AND PARTICIPANTS: Older frail and prefrail subjects (>70y) with T2D and with no history of cognitive problems were enrolled in a single recruiting center. Participants were divided into two groups depending on their walking speed – above (fast walkers) or below (slow walkers) using a cut off of 1 m/sec.

MEASURE: Cognitive function was assessed at baseline and during follow-up with the MMSE, category and letter fluencies at 15 sec (initiation) and 15-60 sec (late).

RESULTS: 48 subjects were included, 22 were fast walkers, 26 were slow walkers. The mean follow-up was 60.9 (SD 17.5) weeks. The baseline 0-15 sec letter fluency was higher in fast walkers (p=0.008). There was no difference at baseline with MMSE scores and category fluency. The MID-Frail intervention did not change the evolution of any cognitive changes. Comparisons were adjusted for age, sex and baseline performance, and showed a steeper decline of category fluency score in slow walkers (fast walkers +0.04 (-1.49 to1.56) compared with -0.89 (-2.15 to 0.38), p=0.049) with a moderate effect size.

CONCLUSION: In frail or prefrail older adults with diabetes, we observed a decline in category fluency in those with low gait speed.

Key words: Type 2 Diabetes, frailty, executive function, gait speed, category and letter (verbal) fluency.

Introduction

Type 2 diabetes (T2D) is a risk factor of functional and cognitive decline. Previous studies have shown that T2D increases the risk of developing frailty, sarcopenia and cognitive executive impairment (1-5). Also, frailty or T2D may now be considered risk factors of vascular dementia (6-8). An association of muscle mass decline, cerebral white matter hyperdensities and lower cognitive scores have also been demonstrated (9). Executive function and motor networks stem from the same brain zones, particularly in subcortical frontal white matter, frontal and temporal cortex and central grey matter. In older frail people with T2D, executive functions decline may be faster in case of motor skills impairment as compared with no impairment.

Clinicians need simple and reliable measurements with easy to remember cut-offs to identify high risk patients who demonstrate steeper cognitive decline in daily practice. A prospective cohort (10) with community older dwellers has shown an association between gait speed and incident dementia. Gait speed was used as continuous and dichotomous variable: One-SD lower gait speed (GS) increased by 59% the hazard of dementia. The log-likelihood of models with GS dichotomized using increasing thresholds suggests 1.0 m/s to be the optimal cut-off. Fluencies are used in daily practice for executive function evaluation in association with testing of attention, inhibition and flexibility. They also test lexical access ability. Two types or verbal fluency exist; semantic or category fluency and letter or phonemic fluency. In category fluency the subject is asked to retrieve as much as possible words belonging two one category. The most frequently used category is animals because it is the most straightforward. Letter fluency involves generation of words beginning with a given letter (F, A or S in English, P, Q or R in French). To retrieve the highest number of words the subject uses lexical memory and strategies such as clustering (animals of the farm, of the zoo, insects, etc…) and switching (changing from one subcategory to one other). Other executive abilities are also involved such as attention / inhibition to avoid duplicate or intrusion and speed processing influence the final result. Early (first 15 seconds of word retrieval) and late (up to 60 second) scores of fluencies are important to consider separately because the executive processes involved are different and correspond with different grey matter atrophy localizations (11, 12). Lower early scores (executive networks) are associated with smaller volumes in bilateral inferior frontal gyri and in the right thalamus. Lower late scores (memory networks) are associated with a smaller left inferior parietal gyrus and the left anterior hippocampus. Cross-sectional studies bring varying results in people with T2D compared with others: no difference (13) or lower animal fluency score (14). Longitudinal studies showed a faster

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decline in verbal letter or animals fluencies in older people with T2D when compared with those without (15-17). In a large community-based cohort of older people, low GS was the most frequent criterion out of the five frailty phenotype criteria but is not present in all prefrail or even in all frail subjects (18). The evolution in executive functions may display different patterns according to the baseline GS.

Our objective in this pilot study was to test whether in frail or prefrail older people with T2D, a baseline low GS is associated with faster executive cognitive decline.

Methods

The primary outcome is the difference in the number of words retrieved in each of the fluencies at baseline and during the follow-up.

Design

The MIDFRAIL study (19, 20) was an European multi-centric open-label randomized control trial testing a multimodal intervention to prevent functional decline in frail or pre-frail non-dependent subjects with T2D versus a control group of usual care. The MID-Frail intervention consisted of: optimization of blood glucose and pressure control, therapeutic nutritional diabetes education and a resistance exercise training exercise program. The main outcome was the change in Short Physical Performance Battery (SPPB) score. The substudy SARTRAIN (4) aimed to provide a comprehensive assessment of muscle function. The follow-up visits were performed at the same schedule as the MID-frail main study but cognitive assessments were performed three times for each subject: at baseline, on the 18th or 26th week's visits (intermediate visit) and not twice to avoid a test retest effect and on the 68th week (end of study visit). The follow-up visits could either be performed 2 weeks before to 2 weeks later. The MID-Frail study (ClinicalTrials.gov Identifier: NCT01654341) and the present sub-study protocols were approved in France by the Comité de Protection des Personnes (CPP) "SUD-Ouest et Outre Mer III".

Population

This substudy of SARTRAIN involved subjects from a Bordeaux recruiting center. No sample size calculation was performed in relation to the present study as this was a pilot initiative. Subjects were included in the MID-frail study if age was over 70 years, T2D was known for over 2 years, and if they demonstrated at least one of the Fried's frailty criteria (18). They were not included if the Barthel score (21) (which assessed independence for basic activities of daily living) was < 60/100, if the SPPB was not possible to score, if the Mini Mental State Examination (MMSE) score (22) was < 20, if they had a previous history of unstable coronary heart disease or myocardial infarction in the last 6 months, or stage NYHA III or IV heart failure and if they suffered from a terminal illness (<6 months life expectancy). Participation in SARTRAIN was considered only in subjects enrolled in MID-frail and this did not add further inclusion/exclusion criteria. They were enrolled after signing two informed consents: one for the MID-Frail study and one for the SARTRAIN substudy.

Assessments

At the baseline visit, weight and height were measured and BMI in kg/m^2 was calculated. Full Mini Nutritional Assessment (MNA, 0-30, normal nutritional status if >23.5) measures were scored. Independence for daily living activities were assessed with the Barthel index (21), with 100/100 indicating full basic activities independence, and with the Lawton instrumental activities of daily living score (0-8, 8 indicates full independence) (23). Glycosylated hemoglobin (HbA1c in mmol/mol) reflected the average blood glucose control over 2-3 months. A history of falls was looked for retrospectively (questioning, medical files). Patients were former fallers if at least one fall was reported in the previous year. Patients were classified as prefrail or frail according to the original Fried's criteria (24). Weight loss criterion was fulfilled if an unintentional weight loss of 4.5 kg was present during the past year; exhaustion criterion was based on the response yes to one from the two first statements on the CES-D depression scale; low physical activity was ascertained if the weekly physical activity of the subject was lower or equal to 383 kcal per week in men and 270 kcal per week in women; slowness was assessed by walk time and stratified by gender and height; finally, weakness was assessed by grip strength and stratified by gender and BMI.

SPPB which assesses lower limb performance consisted of three tasks: balance, 5 chair rises and 4 meter gait, the last two were timed. Each task is scored 0 to 4, 4 is the maximal score. Total SPPB is the sum of the three sub-scores. The 4-meter gait time was also used to define gait speed. Subjects were classed into two groups: slow-walkers if time was 4 seconds or more and fast-walkers if time was lower. This cut-off value was found relevant to predict adverse events (25) including dementia (12).

Cognitive outcomes

Cognitive status was assessed with the MMSE score (22), and verbal fluencies (category and letter fluencies) (26). Subjects were asked to name as many different examples of one category as they could in one minute: The term 'Animals' was used for category fluency and words starting with the letter "P" for letter fluency. The words were recorded by the examiner and grouped by periods of 15 seconds. The normal score for total category fluency in French population (10th percentile) goes from 9 (no diploma) to 14 (secondary degree) for this age category. The normal score for total letter fluency in French population (10th percentile) goes from 4 (no diploma) to 8 (secondary degree). We describe the initial (first 15 sec) and late (15-60 sec) for both fluencies.

Table 1. Characteristics of subjects according to their walking speed and their group of MID Frail intervention at baseline

	All	Fast walkers: gait speed <1m /sec			Slow walkers: gait speed ≥ 1m /sec			P value
		All	Intervention	Control	All	Intervention	Control	Fast / Slow
n	48	22	10	12	26	9	17	
Follow-up, weeks								
mean (SD)	60.9 (17.5)	60.0 (18.9)	63.0 (2)	57.6 (6.0)	61.6 (16.5)	68.0 (0.0)	58.2 (19.8)	0.389
Age, mean (SD)	78.0 (4.9)	75.9 (4.0)	75.5 (3.8)	77.4 (4.0)	80.3 (4.7)	82.0 (7.0)	79.4 (4.5)	0.004
Gender (%F)	35.0	13.6	0	25.0	53.8	66.7	47.1	0.004
Frail phenotype, %	17 (35.0)	1 (4.5)	0	1 (8.3)	16 (61.5)	7 (77.8)	9 (52.9)	<0.001
Previous fallers (%)	5 (10.4)	0	0	0	5 (19.2)	3 (33.3)	2 (11.8)	0.03
Fallers during follow-up (%)	21 (43.8)	6 (27.3)	2 (20.0)	4 (33.3)	15 (57.7)	5 (55.6)	10 (58.8)	0.044
BMI, kg/m², mean (SD)	29.8 (6.6)	30.7 (4.7)	29.7 (4.3)	32.0 (5.3)	31.1 (6.1)	35.8 (6.6)	28.9 (4.6)	0.944
MNA, median (IQR)	26.0 (2.5)	27.0 (9.5)	28.0 (1.8)	26.0 (2.5)	24.9 (4.5)	23.0 (4.3)	26.0 (2.5)	0.013
HbA1c, mmol/mol median (IQR)	56.8 (11.7)	57.7 (10.6)	54.1 (15.8)	56.3 (10.1)	62.2 (23.7)	62.2 (38.3)	61.2 (11.4)	0.021
Barthel index (0-100), median (IQR)	100 (5)	100 (0)	100 (1)	100 (0)	95 (15)	95 (13)	95 (10)	0.003
IADL (0-8), median (IQR)	7.5 (1)	8 (4)	8 (1)	8 (1)	4 (4)	7 (3)	7 (2)	0.061
SPPB, median (IQR)	10 (6)	12 (2)	12 (2)	11 (2)	7 (5)	7 (4)	7.5 (4)	
Verbal fluencies								
mean (SD)								
Category fluency, total, 60s	15.8 (4.9)	17.4 (6.6)	19.5 (7.2)	15.2 (4.9)	15.8 (4.9)	13.9 (5.4)	16.9 (4.2)	0.332
Category fluency, initial, 15s	6.8 (2.0)	7.5 (2.5)	7.8 (2.8)	7.1 (1.1)	6.5 (1.8)	5.9 (1.6)	6.9 (1.8)	0.151
Category fluency, late, 15-60s	9.0 (4.3)	9.9 (5.8)	11.7 (5.4)	8.5 (5.4)	9.2 (3.9)	8.0 (4.6)	10.0 (3.3)	0.689
Letter fluency, total, 60s	9.6 (4.8)	11.7 (5.9)	13.1 (6.4)	10.9 (4.9)	8.6 (3.8)	8.1 (2.9)	8.9 (4.2)	0.055
Letter fluency, initial, 15s	3.9 (1.7)	4.8 (1.8)	4.7 (2.1)	5.0 (1.4)	3.4 (1.8)	3.3 (1.8)	3.4 (1.8)	0.008
Letter fluency, late, 15-60s,	5.7 (3.8)	6.9 (4.8)	8.4 (5.1)	5.3 (3.7)	5.2 (2.7)	4.8 (1.8)	5.6 (3.1)	0.272
MMSe, mean (SD)	27.0 (2.4)	27.6 (1.6)	27.4 (1.6)	28.4 (1.0)	26.6 (2.7)	26.9 (3.0)	26.5 (3.0)	0.113

Comparisons according to gait speed were done with Fisher exact test and Chi-squared test for category variables and with Student's test or Mann-Whitney's test for continuous variables according to their distribution.

Statistical analysis

First, we studied whether the distribution of the quantitative parameters was normal using a Shapiro-Wilk's test. Median and interquartile range (IQR) describe non normal quantitative variables and mean and standard deviation (SD) were used for normal (Gaussian) variables.

We compared the subjects for baseline assessment with Fisher exact tests and Chi-squared tests for category variables and with Student's test or Mann-Whitney's test for continuous variables according to their distribution. A P-value<0.05 was considered as statistically significant.

We performed an analysis using unadjusted and adjusted age and, gender and baseline performance linear models for repeated measures to explore the effects of MID-Frail intervention and the effects of baseline gait speed categories. We aggregated the 18th-26th week measures as intermediate data. The software SPSS 23 (IBM®) was used for these analyses.

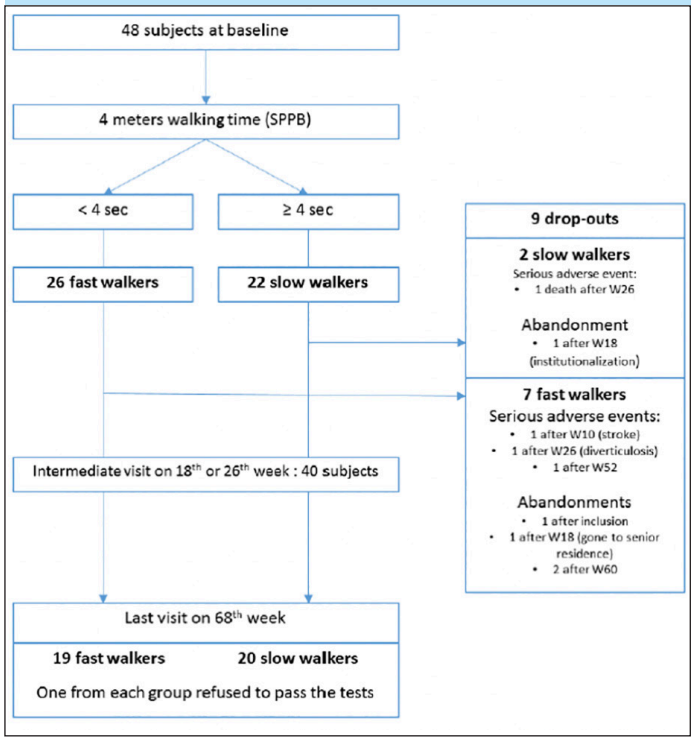
Results

In total, 48 subjects (mean age 78.0y (4.9), 35% women) were included in the study (Figure 1). Frailty was found in 35.4% and the others were prefrail (Table 1). Fast walkers numbered 22 and slow walkers, 26. Fast walkers were younger and more often men compared with slow walkers. Fast walkers were less often frail (4.5 % versus 61.5 %, $p < 0.001$); they had no history of falls in the previous year (0% versus 20.0%, $p = 0.03$); they had higher MNA score (27.0 (9.5) versus 24.9 (4.5), $p = 0.013$), had lower HbA1c values (57.7 mmol/mol (10.6) versus 62.2 (23.7), $p = 0.021$ and higher SPPB scores (12 (2) versus 7 (5), $p < 0.001$). Among frailty criteria exhaustion was the most frequent item in both groups (fast walkers (FW) 86.4% and slow walkers (SW) 92.3%). Low physical activity was assessed in 45.4% of FW and in 57.7% of SW, low hand grip strength in 31.8% of FW and in 73.1% of SW, and weight loss was not frequent: 4.5% in FW and 3.8% in SW. Slow gait speed according to Fried criteria was found in 53.8% of SW.

During follow-up, 5 subjects abandoned the study (Figure 1). Two abandonments were caused by admission into a nursing home. Three dropped out because of serious adverse events. One subject died. Subjects lost for follow-up were not different from others for any of the variables.

At baseline assessment none of the subjects had significant cognitive impairment according to the MMSE test (Table 1). However, 0-15 sec letter fluency scores were lower in the slow walkers' group (3.4 (1.8) compared with 4.8 (1.8), $p = 0.008$) in the fast walkers' group.

Figure 1. Flow of subjects across the study. Subjects were distributed into two groups according to 4-meter gait speed



Subjects were followed on average for 60.9 weeks (17.5). In this sub-sample of MID-Frail population the intervention did not modify the evolution of MMSE or verbal fluencies (table 2). Unadjusted comparisons according to gait speed showed a steeper decline of MMSE in slow walkers (-0.85 (-2.23 to 1.09) compared with +34 (-0.39 to 1.09), p =0.037) in the fast walkers' group. After adjustment for age, gender and baseline MMSE, the difference was not significant (p = 0.625) (Table 2).

Category fluency (0-60 sec) decreased more in slow walkers than in fast in the unadjusted and adjusted analysis: adjusted for age, gender and baseline 0-60 sec category fluency, +0.04 (-1.49 to 1.56) in fast walkers compared with -0.98 (-2.15 to 0.38), p = 0.049. However, the effect size was moderate. It was not possible to determine if the alteration occurred more in the 0-15 sec time or later; the adjusted analysis on both 0-15 sec and 15-60 sec did not show significant differences between groups.

Letter fluency (0-60sec) increased in slow walkers according to the unadjusted analysis (Table2). The improvement observed in slow walkers occurred mainly in the initial 0-15 sec (+0.73 (0.08 to 1.38) compared with -0.16 (-0.92 to 0.60), p = 0.006) in the fast walkers' group. Comparison at end of follow-up between slow and fast walkers did not show a differences between groups in 0.15 sec letter fluency score (4.56 (1.75) words in fast walkers versus 4.05 (2.11) in slow walkers, p = 0.442). There was no more difference in letter fluency count change with follow-up according to gate speed in the adjusted analysis for age, gender and baseline 0-60 letter fluency.

Discussion

In this sample of frail and prefrail subjects with T2D and without initial cognitive problems we found a higher decline in those with a 4-meter gait time higher than 1m/sec for category verbal fluencies. The Mid-Frail intervention did not alter these observations in this sample.

Impaired cognition is recognized to alter gait ability (see (27) for review). In addition, gait speed in the lowest quartile in a community-based cohort was shown associated with a faster MMSE decline over a 7-year period (28). Similar results were found also in a 660-subjects community-based longitudinal study over 3 years (29). Qualitative analysis of gait, such as step length may be more sensitive to predict cognition decline (27).

A prospective cohort study (22) followed up 154 subjects aged 65 y or older, without dementia at baseline. Overall, 14.3% progressed to dementia. The rate of progression to dementia was not different according to T2D diagnosis. Gait speed at baseline did not differ between subjects who progressed to dementia and those who didn't. The important result from this latter study (22) was that the risk of dementia was almost 7 times as great for those whose gait velocity declined. Consequently, some authors (30) defined the Motoric Cognitive Risk (MRC) syndrome as the association of a cognitive complaint and slow gait speed (one standard deviation below age- and sex-matched peers). This syndrome was associated with incident dementia and mortality in several studies (31). Finally, frailty has been shown to be a risk factor of MRC syndrome (32).

We did not find reports specifically studying the relationships between verbal fluencies decline and baseline gait speed and none were identified in non-cognitively impaired subjects. With diagnosed dementia, verbal fluencies decline was related to baseline lower gait speed (33).

Verbal fluency assessed both verbal ability and executive functions (34). We have interpreted the observation of an improvement of letter fluency in those with low gait speed due to a training effect. Letter fluency performance may be more associated with the educational level than category fluency, particularly with the naming animals category (35). Initial poor cognitive performance is a strong predictor of further decline. This is the reason why we adjusted the analysis on baseline performance. With this adjustment the improvement of letter fluency in slow walkers was no longer observable. The higher rate of MMSE decline in slow walkers was not significant in the adjusted analysis, possibly due to the same mechanism although baseline MMSE scores were not significantly different according to the groups studied. Slow walkers were about 5 years older than fast walkers. We have adjusted the general linear model on age. However, relationships between age and decline may be non-linear; consequently the effect of age may be not fully controlled in the present analysis; enrollment in a future dedicated study should be stratified on age.

Finally the subjects were included in a randomized control trial and they were tested several times in a short period. We cannot rule out a training effect. This training effect may explain a part of the improvement of letter fluencies in slow

Table 2. Longitudinal changes of cognitive assessments during the follow-up according to MID-Frail intervention or gait speed categories

	MMSe		Verbal fluency, category, animals		Verbal fluency, letter, P	
	Adjusted Mean difference during follow-up (95% CI)	P (f)	Adjusted Mean difference during follow-up (95% CI)	P (f)	Adjusted Mean difference during follow-up (95% CI)	P (f)
According to intervention (unadjusted)		0.325 (0.030)		0.965 (0.000)		0.362 (0.29)
intervention	-0.33 (-1.62 to 0.96)		-0.69 (-3.48 to 2.09)		-0.92 (-3.73 to 1.88)	
control	-0.31 (-1.32 to 0.69)		-0.89 (-3.67 to 1.89)		-0.95 (-1.44 to 3.33)	
According to intervention (adjusted on age and gender)		0.416 (0.022)		0.825 (0.002)		0.787 (0.003)
intervention	-0.43 (-1.72 to 0.86)		-0.69 (-3.28 to 1.90)		-0.95 (-3.46 to 1.56)	
control	-0.25 (-1.25 to 0.75)		-0.89 (-3.09 to 1.31)		+2.17 (0.03 to 4.30)	
According to gait speed unadjusted		0.037 (0.129)		0.010 (0.207)		0.012 (0.200)
Fast walkers	+0.34 (-0.39 to 1.09)		-0.15 (-2.64 to 2.34)		-0.62 (-2.95 to 1.72)	
Slow walkers	-0.85 (-2.23 to 0.53)		-1.78 (-3.91 to 0.35)		+0.72 (-1.26 to 2.71)	
According to gait speed (adjusted on age and gender)		0.546 (0.012)		0.129 (0.083)		0.098 (0.98)
Fast walkers	+0.23 (-1.05 to 1.51)		-0.15 (-2.89 to 2.60)		-1.47 (-4.12 to 1.17)	
Slow walkers	-0.76 (-1.88 to 0.35)		-1.28 (-3.56 to 0.99)		+1.34 (-0.85 to 3.54)	
According to gait speed (adjusted on age, gender and baseline outcome assessment)		0.625 (0.008)		0.049 (0.141)		0.550 (0.14)
Fast walkers	+0.27 (-0.50 to 1.04)		+0.04 (-1.49 to1.56)		-0.64 (-2.26 to 0.97)	
Slow walkers	-0.79 (-1.46 to -0.12)		-0.89 (-2.15 to 0.38)		+0.74 (-0.58 to 2.07)	

Slow walkers: gait speed < or equal to 1m/sec; fast walkers: gait speed > 1m/sec Linear model for repeated measures: data are based on comparison of repeated adjusted time times treatment groups; f is the Cohen f effect size.

walkers.

The strength of the present study relies on the selection of subjects at high risk of both physical and cognitive declines because they had T2D and were frail or prefrail. This added additional strength to our analyses.

In conclusion, this pilot study, which consisted of a group of frail and prefrail subjects with T2D and no initial cognitive problems, observed a higher decline of category fluency in those with gait speed lower than 1m/sec. However, this result must be confirmed by a dedicated study with the possibility to fully adjust the analysis model. We feel that gait speed may be used as a marker of a risk of cognitive decline, and particularly executive function decline.

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Ethical standards: This article complies with the current laws. The study received approval from «Comité de protection des personnes Sud Ouest et Outre-mer III. Participants gave their written informed consent.

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