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Research article

Physio-cognitive decline syndrome among middle-aged diabetes patients: Handgrip strength significantly correlates with glycaemic control and cognitive score

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ABSTRACT

Aims: To investigate the correlation between glycaemic control with component of Physio-Cognitive Decline Syndrome (PCDS) and among each component of PCDS itself.
Methods: A cross sectional study was conducted (January 2021–November 2022) at Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia on consecutively recruited T2DM outpatients aged 40–59 years old. Data on the latest three months HbA1c, hand grip strength (HGS), usual gait speed (GS), and Indonesian Montreal Cognitive Assessment (MoCA-Ina) were evaluated. Pearson or Spearman's test was used to analyse the correlations.
Results: There were 133 subjects with median age 53 (40–59) years. The PCDS was found in 48.1 % subjects, of which 64.1 % with uncontrolled glycaemia. Significant correlations were found between HGS and HbA1c ($r = -0.24$, $R^2 = 0.06$, $p < 0.01$) and MoCA-Ina score ($r = 0.21$, $R^2 = 0.04$, $p < 0.05$).
Conclusion: The higher HbA1c and the lower MoCA-Ina score, the weaker handgrip strength was.

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1. Introduction

Type 2 diabetes mellitus (T2DM) is one of the chronic diseases with increasing prevalence worldwide. Diabetes complications may occur independently and could be detected in as young as 25-year-old patient [1,2].

Glucose variability, as another form of non-mobility frailty process, may worsen atherosclerosis and endothelial dysfunction [3,4]. Previous studies have shown that glycaemic dysregulation may contribute to both cognitive and physical dysfunction, and vice versa. Low cognitive function may cause difficulties to manage medical instructions, comprehend doctor's advice, and evaluate food intake [5,6]. On the other hand, physical capacity has an important role to maintain diabetic patients' daily activities and to visit the health care service [7]. Nevertheless, those problems are rarely managed as one entity.

Extremity strength as one of the objective parameters to determine physical capacity, has close relationship with cognitive decline. Deceleration of gait speed (GS) had happened 12 years earlier before the onset of mild cognitive impairment (MCI). Moreover, non-memory cognitive domain, particularly executive and linguistic ability, may appear in middle-aged, with hand grip strength (HGS) decline concurrently [7]. Generally, the decline in HGS precede the GS. Therefore, it is proposed that cognitive decline and physical dysfunction have significant association. The terminology of this association has changed from time to time based on the studies during 2015–2019, from cognitive frailty, motor cognitive risk syndrome, to physio-cognitive decline syndrome (PCDS) as the last and proven reversibility term of this condition, in 2020. The PCDS has different pathophysiologies, namely cerebellum dysfunction. An individual may be diagnosed as PCDS when there are mobility-type physical frailty (weakness and/or slowness) and reversible cognitive decline in any domains (not dementia), concurrently, so that early screening and reversiblity is possible [7–9]. However, glycaemic control for T2DM patient has not been addressed in the PCDS management.

Delay in PCDS risk factor control, especially diabetes, may accelerate those declines and may be too late to be prevented. Liang et al. (2021) reported that among elderly with PCDS, 25.4 % were T2DM patients, as it may impair daily activities in the society [9]. Thus, it is important to identify PCDS among middle-aged T2DM patients. This study aimed to investigate the correlation between glycaemic control with component of PCDS and among each component of PCDS itself in the middle-aged T2DM patients. We hypothesized that there were inverse correlations between glycaemic control (HbA1c) with PCDS components (namely HGS, usual GS and cognitive/the Indonesian version of Montreal Cognitive Assessment [MoCA-Ina] score), whereas there were positive correlations between HGS, GS and the MoCA-Ina score. The better the glycaemic control (the lower HbA1c), the higher HGS, GS and MoCA-Ina score were. The higher HGS, the higher GS as well as the MoCA-Ina score were.

2. Subjects, materials, and methods

2.1. Subjects

This was a cross sectional study on consecutively recruited T2DM outpatients aged 40–59 years old (middle-aged) at Diabetes clinic and Integrated Cardiac Centre of Dr. Cipto Mangunkusumo National Referral Hospital, Jakarta, Indonesia from January 2021 until November 2022. All subjects had given their written informed consents.

Criteria to diagnose T2DM was based on the American Diabetes Association (ADA) published guideline [10]. We excluded those who refused to participate in this study. Other exclusion criteria were several other inflammatory conditions, such as autoimmune diseases, liver cirrhosis, end stage renal disease and post-acute care in the past one month, those with acute medical condition or acute exacerbation of previously known chronic disease, pregnant, steroid user over the past two weeks, anaemia with haemoglobin (Hb) level of <11 g/dl and immobility or apparent difficulties in walking. Furthermore, as the PCDS definition not to include dementia and to avoid possible bias in cognitive assessment, we exclude those with symptoms of depression, previously known diagnosis of cognitive impairment and dementia. We defined dementia as those with Indonesian version of Montreal Cognitive Assessment (MoCA-Ina) score of <22 along with Instrumental Activity Daily Living (IADL) score of <6.

Data collection consisted of subjects' age, sex, comorbidities, Charlson Comorbidity Index (CCI), duration of T2DM, body mass index (BMI), functional and cognitive status, appendicular skeletal muscle mass (ASMM), HGS and usual GS. We also documented data on Hb level and the latest three months of HbA1c.

2.2. Physical and cognitive examination

We evaluate functional status based on the Barthel index Activity of Daily Living (ADL) on a 0–20 scale and Lawton IADL on a 1–8 scale [11–13]. For male subjects, we made adjustment for IADL assessment with maximal score of 5, since certain IADL items were not applicable due to socio-cultural aspects. The ASMM index, HGS and GS were categorized based on the Asian Working Group of Sarcopenia (AWGS) 2019 criteria [14].

The body weight and height were measured with standard protocol. The ASMM was measured using BIA Tanita MC-780MA (Tokyo, Japan) at the Human Nutrition Research Centre, Indonesia Medical Education and Research Institute (IMERI), Faculty of Medicine Universitas Indonesia (FMUI). The ASMM index was calculated by dividing the ASMM value by the body height squared in meter.

The HGS was measured in sitting position on dominant hand with the elbow flexed at 90°, while the wrist and forearm in a neutral position and the shoulder in adducted and neutrally rotated using a hydraulic handheld dynamometer Jamar J00105 (Jamar, IA, USA). The highest HGS out of three trials was documented as the subject's HGS. The GS was evaluated using a stopwatch by recording the time to finish a 6-meter flat straight line with subject's usual walking pace. The average of GS out of three trials was documented as subject's usual GS.

Cognitive assessment was done using validated MoCA-Ina based on the official instructions published by Husein N (2010) [15]. The subjects were examined by the same person. The MoCA-Ina score was adjusted to the subject's education level, by adding 1 point for those with less than 12 years of education. The MCI was defined if the MoCA-Ina score ≤26. We decided the MoCA-Ina cut-off point after a thoughtful discussion among experts and our study researchers with the consideration of cognitive score of <1.5 standard deviation (SD) in the middle-aged adults and Borland et al. (2017) study [16]. Finally, we defined PCDS as those with cognitive decline as documented by MoCA-Ina score of ≤26 along with physical decline of either slow GS and/or low HGS.

2.3. Laboratory

HbA1c was assessed with standardised method of National Glycohemoglobin Standardization Program (NGSP) and Diabetes Control and Complications Trial Assay (DCCT) at the central laboratory of Dr. Cipto Mangunkusumo Hospital. The haemoglobin level was measured with the same blood sample. If the subject already had Hb and HbA1c data within the past 3 months, we documented it as the subject's data and the blood test was not performed.

2.4. Statistical analysis

We used the IBM SPSS Statistics for Windows version 20.0 (IBM Corp., Armonk, NY, USA) to analyse the data. This study set the statistical power at 80 % and α value at 5 %. The minimum sample size was 133 based on the correlation coefficient formula and the value of *r* in the previous studies [17–19].

Numeric data was described as mean (SD) for data with normal distribution or median (minimal–maximal) for data without normal distribution based on the Kolmogorov-Smirnov test. Categorical data was described as percentage. To determine the correlation between variables, the Pearson or its alternative the Spearman correlation test was used depending on the data distribution.

2.5. Ethics

This study has been approved by the Ethics Committee of FMUI/Dr. Cipto Mangunkusumo Hospital with registration no: KET-1101/UN2.F1/ETIK/PPM.00.02/2020, which had been extended twice.

3. Results

Out of 765 middle-aged T2DM patients visiting the clinics, there were 267 patients without exclusion criteria, yet 134 patients refused to participate in this study. Ultimately, there were 133 subjects included in our study (Fig. 1).

The subjects' characteristics were described in Table 1. The male and female subjects were approximately in similar proportion (49.6 vs. 50.4 %). The median age was 53 (40–59) years, with most subjects (87.2%) in the age range of 45–59 years. Almost half of the subjects (43.6 %) had ≥12 years of education (high school or college graduates). Higher proportion of subjects had duration of T2DM for >5 years, uncontrolled glycaemia, CCI index of 1–2, independent in basic daily activities, IADL score of >6 and being overweight. Yet, more female subjects had uncontrolled glycaemia (73.1 vs. 63.6 %) and being obese (49.3 vs. 31.8 %) compared to their counterparts. These characteristics were similar with subjects who refused to be enrolled whose median age of 53 (40–59) years old, CCI score of 1 (0–5), and duration of DM for 7 (0–30) years.

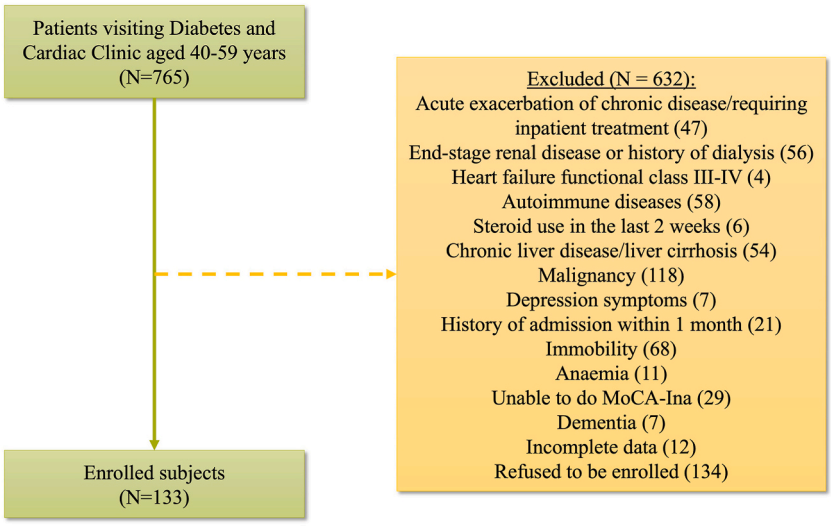

Fig. 1. Subject selection flow chart.

Table 1
Subjects characteristics.

Variables	All Subjects (N = 133)	Male (n = 66)	Female (n = 67)
Age (years), median (min–max)	53 (40–59)	53 (40–59)	53 (41–59)
40–44 years-old, n (%)	17 (12.8)	8 (12.1)	9 (13.4)
45–59 years-old, n (%)	116 (87.2)	58 (87.9)	58 (86.6)
Duration of diabetes (years), median (min–max)[a]	7 (0–30)	7 (0–30)	8 (0–26)
<5 years, n (%)	42 (31.6)	22 (33.3)	20 (29.9)
>5 years, n (%)	91 (68.4)	44 (66.7)	47 (70.1)
HbA1c (%), median (min–max)	7.6 (5.0–15.5)	7.6 (5.0–13.1)	7.6 (5.6–15.5)
HbA1c (mmol/mol), median (min–max)	60 (31–146)	59 (31–120)	60 (38–146)
Controlled, n (%)	42 (31.6)	24 (36.4)	18 (26.9)
Uncontrolled, n (%)	91 (68.4)	42 (63.6)	49 (73.1)
Charlson Comorbidity Index (CCI), mean (SD)	1.5 (0–6)[b]	1.64 (1.4)	1.4 (1.4)
0,[e] n (%)	43 (32.3)	19 (28.8)	24 (35.8)
1–2,[e] n (%)	62 (46.6)	32 (48.5)	30 (44.8)
>2,[e] n (%)	28 (21.1)	15 (22.7)	13 (19.4)
Barthel ADL, median (min–max)	20 (13–20)	20 (15–20)	20 (13–20)
20 (Independent), n (%)	95 (71.4)	45 (68.2)	50 (74.6)
12–19 (Mildly Dependent), n (%)	38 (28.6)	21 (31.8)	17 (25.4)
Lawton IADL, median (min–max)	7 (2–8)	7 (2–8)	8 (5–8)
Adjusted[b]	–	5 (2–5)	–
≥6, n (%)	119 (89.5)	54 (81.8)	65 (97.0)
<6, n (%)	14 (10.5)	12 (18.2)	2 (3.0)
BMI (kg/m^2)[f], mean (SD)	27.4 (12.29–49)[d]	26.51 (4.79)	28.97 (5.67)
Underweight, n (%)	3 (2.3)	3 (4.5)	0 (0.0)
Normoweight, n (%)	18 (13.5)	9 (13.6)	9 (13.4)
Overweight, n (%)	58 (43.6)	33 (50.0)	25 (37.3)
Obese, n (%)	54 (40.6)	21 (31.8)	33 (49.3)
ASMM (kg), median (min–max)	20.1 (12.3–34.20)	24.28 (4.07)[c]	17.5 (12.3–25.9)
ASMM Index (kg/m^2), mean (SD)	8.22 (5.49–12.68)[d]	8.93 (1.35)	7.46 (0.98)
Hand Grip Strength (kg), mean (SD)	24 (6–44)[d]	30.30 (6.31)	19.12 (6.17)
Normal, n (%)	83 (62.4)	46 (69.7)	37 (55.2)
Low, n (%)	50 (37.6)	20 (30.3)	30 (44.8)
Usual Gait Speed (m/s), mean (SD)	1.02 (0.23)	1.07 (0.25)	0.98 (0.20)
Normal, n (%)	72 (54.1)	39 (59.1)	33 (49.3)
Slow, n (%)	61 (45.9)	27 (40.9)	34 (50.7)
Cognitive Status (MoCA-Ina), mean (SD)	24 (13–30)[d]	24.02 (0.47)	23.18 (0.46)
>26 (Normal), n (%)	34 (25.6)	19 (28.8)	15 (22.4)
≤26 (Cognitive Impairment), n (%)	99 (74.4)	47 (71.2)	52 (77.6)
PCDS			
Yes, n (%)	64 (48.1)	30 (45.5)	34 (50.7)
Low Hand Grip Strength, n (%)	19 (29.7)	11 (36.7)	8 (23.5)
Slow Gait Speed, n (%)	21 (32.8)	13 (43.3)	8 (23.5)
Combination, n (%)	24 (37.5)	6 (20.0)	18 (53.0)
No, n (%)	69 (51.9)	36 (54.5)	33 (49.3)

min–max: minimal–maximal; SD: standard deviation; ADL: activity of daily living; IADL: instrumental activity of daily living; BMI: body mass index; kg: kilogram; ASMM: appendicular skeletal muscle mass; m: meter; m/s: meter/second; MoCA-Ina: Indonesian Montreal Cognitive Assessment; PCDS: Physio-Cognitive Decline Syndrome.

[a] 0 year defined as newly diagnosed T2DM and/or being treated as T2DM patient in less than 1 year.
[b] For male subjects, certain IADL items were not applicable due to socio-cultural aspects.
[c] mean (SD).
[d] median (min–max).
[e] excluding DM itself.
[f] based on the Asia-Pacific classification [20].

There were 112 subjects (84.2 %) who used oral antidiabetic medication(s) and 50 subjects (37.6 %) who used combination therapy of insulin and oral antidiabetic medication(s). The most comorbidity reported was dyslipidaemia (72.2 %), with approximately similar proportion of comorbidities between those with or without controlled glycaemia.

The mean usual GS of all subjects was 1.02 (0.23) m/s, whereas the median ASMM index and HGS were 8.22 (5.49–12.68) kg/m^2 and 24 (6–44) kg, respectively. According to AWGS 2019, the mean ASMM index and HGS for both sex groups were normal, whereas the mean usual GS in male subjects was normal, but low in female subjects. Compared to male, there were more female subjects who had low HGS and GS. The median MoCA-INA score was 24 (13–30).

There were 48.1 % subjects with PCDS, which slightly higher among female than male subjects (50.7 vs. 45.5 %), yet more female than male PCDS subjects who had combination of low HGS and usual GS (53 vs. 20 %). The PCDS compared to non-PCDS subjects tended to have higher median age (54 [41–59] vs. 50.4 [5.22] years), T2DM duration (10 [0–30] vs. 6 [0–26] years), and CCI (2 [0–6] vs. 1 [0–5]), yet lower BMI (26.9 [4.76] vs. 29.1 [5.95] kg/m^2), ASMM index (7.7 [1.06] vs. 8.1 [1.46] kg/m^2), HGS (18 [6–36] vs. 24 [12–44] kg), usual GS (0.9 [0.61–1.43] vs. 1.07 [0.56–1.46] m/s), and MoCA-Ina score (23 [13–26] vs. 27 [15–30]). Moreover, there

were 64.1 % PCDS subjects with uncontrolled glycaemia, while among uncontrolled glycaemia subjects there were 45.1 % subjects with PCDS.

There was a significant negative weak correlation between HbA1C and HGS ($r = -0.24$, $R^2 = 0.06$, $p < 0.01$) (Fig. 2A), whereas there was no significant correlation with usual GS and MoCA-Ina score. Further analysis also indicated a significant negative weak correlation between HbA1C and HGS among female subjects ($r = -0.26$, $R^2 = 0.07$; $p < 0.05$). Furthermore, there was a significant positive weak correlation between HGS and MoCA-Ina score ($r = 0.21$, $R^2 = 0.04$, $p < 0.05$) (Fig. 2B). However, there were no significant correlation between usual GS with MoCA-Ina score and HGS.

4. Discussion

In contrast to other studies in which the male subjects were ranged between 42.9 and 65.0 % [21–23], the proportion of male and female subjects in our study was relatively similar (49.6 vs. 50.4 %) with the median age, duration of T2DM, and HbA1c were 53 (40–59) years, 7 (0–30) years and 7.6 (5.0–15.5)%, respectively. Our findings were quite similar to that of Dyer et al. (2022) [23] with mean HbA1c of 7.7 %, but higher than what was reported by Cetinus et al. (2005) [24] with mean HbA1c of 7.14 (1.64)%. However, higher proportion of subjects in our study was still with uncontrolled glycaemia (68.4 %), especially among female (73.1 %). Duarte et al. (2019) [25] proposed some possible reasons, including increased in androgen and decreased in testosterone levels which have essential role for lipid regulation, in addition to social economic disadvantages. In this study, we did not analyse further on the detailed daily activities and occupations which might contribute to their glycaemic control. Moreover, high proportion of female subjects was obese (49.3 %) which may imply the possibility of noncompliance to diet and physical activity recommendation.

The median HGS of all subjects were 24 (6–44) kg, while the mean HGS in males and females were 30.30 (6.31) and 19.12 (6.17) kg, respectively. The mean usual GS was 1.02 (0.23) m/s, whereas the mean GS in males and females were 1.07 (0.25) and 0.98 (0.20) m/s, respectively. The proportion of subjects with low HGS was lower than slow GS subjects (37.6 vs. 45.9 %). This finding contradicted previous studies that generally the decline in HGS precede the GS [9]. Nevertheless, the mean usual GS in female subjects has been already low according to AWGS 2019 criteria [14]. It may be due to more female subjects with uncontrolled glycaemia which increase the risk for DM complications including diabetic neuropathy.

The values of HGS in our study were relatively lower than other studies. Population-based study done by Amaral et al. (2019) [26] on apparently healthy subjects in Brazil indicated that the mean value of HGS in the age group of 40–49 and 50–59 years were 35.1 (10.05) and 32.7 (10.97) kg, respectively. Cetinus et al. (2005) [24] reported that among non-geriatric diabetic subjects, the HGS was as high as 32.49 (12.65) and 30.79 (11.24) kg among those aged 30–49 and > 50 years old, respectively. Li et al. (2016) [27] found even much higher mean HGS among male T2DM subjects in Adelaide, Australia (44.6 [9.4] kg). Nevertheless, among T2DM older adult male and female subjects, Liang et al. (2020) [28] found that the mean HGS were 31.54 (95%CI 30.44–32.64) and 20.33 (95%CI 19.87–20.78) kg, respectively, while the overall mean HGS of all subjects was 23.17 (95%CI 22.81–23.53) kg.

There were 74.4 % subjects with MoCA-Ina score of ≤26. Subjects with PCDS in our study were surprisingly quite high (48.1 %), of which 64.1 % with uncontrolled glycaemia, while among uncontrolled glycaemia subjects there were 45.1 % subjects with PCDS. It may be the reason why the proportion of PCDS subjects was slightly higher among female than male subjects (50.7 vs. 45.5 %), as similar female dominance in other studies [9,11,29]. In contrast, Liang et al. (2021) [9] reported 18.9 % PCDS among community-dwelling older adults with mean age of 74 (5.7) years. The lower cut-off points for MoCA score which was set at ≤18 and only 25.4 % subjects were T2DM patients in Liang et al. (2021) [9] study may cause this different result. On the other hand, study by Lalithambika et al. (2019) [19] found that among seventy T2DM adult patients with mean age of 53.30 (7.69) years, 54.29 % had mild cognitive impairment (MoCA score <26).

Our study set the cut-off point of MoCA-Ina score to define cognitive impairment at ≤26. Normal value of MoCA was still inconsistent in many literatures. Kessels et al. (2022) [30] reported that normal cognitive capacity could be found in 35–75 % of 40–59 years age group with MoCA score of ≤26. However, those with MoCA score of <18 undoubtedly have no normal variant [30]. It means that subjects with MoCA-Ina score of ≤26 in our study, were still possibly a normal variant of normal cognitive function. Moreover, the subjects in our study were still in their productive age with 43.6 % of them had ≥12 years of education. Their occupations or activities need complex cognitive function. In this age group, the cognitive status may still at its peak so that there might be not many changes have happened before reaching 60 years of age [31,32].

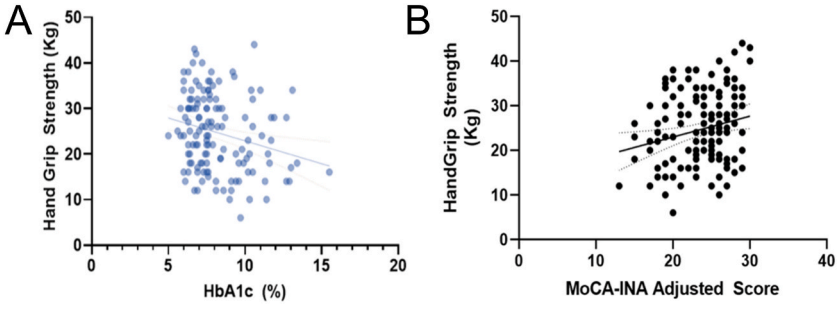

Fig. 2. Correlation between hand grip strength and HbA1c (A), MoCA-Ina score (B).

4.1. Correlation between glycaemic control and usual gait speed

Gait speed is an essential component of physical capacity assessment across studies, namely, to evaluate one's fitness to do daily activities, deterioration or improvement of disease/medical condition and analysis in neurodegenerative disease. Diabetic neuropathy may present as decreased muscle strength of distal extremities, which usually mild when it was detected. Decline in GS may be due to biomechanical degeneration and low aerobic capacity [24]. It is also accelerated by chronic inflammation and mitochondrial dysfunction which are common in chronic diseases, including DM [33]. Moreover, GS represents the patency and distribution of peripheral circulation [21]. Brach et al. (2008) [21] highlighted the role of health status, cognitive, mood, lower extremity circulation, BMI, physical activities, neuropathy, ulcer and extremity muscle strength. Furthermore, insulin resistance may alter white matters in the brain (white matters hyperintensity) which impairs the GS, even since middle-aged [34].

Our study found no significant correlation between glycaemic control and GS. In contrast, Azmon et al. (2018) [18] reported significant negative weak correlation between HbA1c and GS among T2DM elderly patients ($r = -0.208$; $p = 0.007$). It may be because the mean age in Azmon et al. (2018) [18] study was much older (70.7 vs 53 [40–59] years) and the duration of T2DM was much longer (17.09 vs. 7 [0–30] years) than our study. Furthermore, the GS was measured with different method, using a 10-m walk test with an addition of 2 m for acceleration at the beginning and 2 m for deceleration at the end [18]. The mean usual GS of all subjects in our study was also still normal based on AWGS 2019 criteria (1.02 [0.23] m/s). Younger age may lead to fewer change of the white matters, while shorter duration of T2DM may lead to milder complication on lower extremities [35]. Thus, both conditions may still maintain normal GS among our subjects, though it should be aware of that the mean usual GS has already been in low normal range.

4.2. Correlation between glycaemic control and hand grip strength

Hand grip strength is a basic indicator for several things: (1) musculoskeletal status, (2) determinant of weakness, disability, and frailty, (3) predictors of the risks and prognosis of clinical outcomes after treatment and surgery procedure [36].

Our study found a significant negative weak correlation between glycaemic control and HGS ($r = -0.24$, $R^2 = 0.06$, $p < 0.01$). Further analysis also indicated a significant negative weak correlation between HbA1C and HGS among female subjects ($r = -0.26$; $R^2 = 0.07$; $p < 0.05$). The higher the HbA1c, the weaker HGS was. Nevertheless, the coefficient of determination (R^2) only indicated that 6 % of the total variation in HGS can be explained by the linear association between HGS and HbA1c. In other words, there are several other factors that contribute to the HGS.

Manoharan et al. (2015) [36] in their systematic review reported that age, sex, dominant hand, arm circumference, nutritional status, food intake, fatigue, psychological factors, altitude, temperature, oxygenation, smoking and alcohol affect HGS. Moreover, different sex may cause different impact on glucose metabolism in muscle due to higher body fat and physiologically lower muscle mass of upper extremities in female than male [37]. Skeletal muscle has an important role as glycogen storage. Insulin resistance may cause muscle atrophy through protein metabolism changes [38]. Caspase-3, ubiquitin-proteasome, *krüppel-like factor 15 protein* and other pro-inflammatory cytokines have significant contribution to muscle insulin resistance, causing glycogenolysis and impaired mitochondrial function, which lead to muscle strength decline [28]. Therefore, change in glycaemic control may affect muscle strength.

In line with our study, Loprinzi et al. (2016) [38] found that a 5 kg greater HGS was associated with lower odds of having diabetes for both sex groups. Interestingly, there was also no significant association between diabetes severity (HbA1c) and HGS among males, but significant association among females [38]. In contrast, Tanaka et al. (2020) [39] study revealed no significant negative correlation between HbA1c and HGS, whereas meta-analysis done by Gundmi et al. (2018) [40] also reported no significant association between T2DM and HGS. Although Cetinus et al. (2005) [24] found that HGS was significantly lower among diabetic compared to non-diabetic subjects, there was no significant correlation between HbA1c and HGS in both groups. The small sample size in those studies may contribute to this difference. Furthermore, Liang et al. (2020) [28] study revealed that after adjusting for several important factors (e.g., age, alcohol use, smoking status, health status, physical activity, body fat percentage and waist circumference) glycaemic status was inversely associated with HGS among male, but not in female older adult subjects.

4.3. Correlations between glycaemic control and cognitive assessment using MoCA-Ina

Cognitive assessment has been an important issue in the diabetes management. Standards of Care Diabetes 2022 has highlighted decremental effect of high blood glucose to cognitive capacity, and vice versa [5]. Cognitive decline could have been found even in prediabetes state as evidenced by changes in hippocampal and white matters volume [35]. Diabetic patients have a higher risk of MCI, especially the non-amnestic type in males (OR 2.61; 95%CI 1.14–5.98), whereas females were more vulnerable to amnestic MCI (OR 3.02; 95%CI 1.27–7.17) [22]. Hyperinsulinemia and complete pathway of signal transduction in hippocampus were associated with insulin receptors density at that region which may affect learning and memory capacity, especially in long standing insulin resistance condition [22].

Our study indicated that there was no significant correlation between glycaemic control which represented as HbA1c level and cognitive status which represented by MoCA-Ina score. Our median HbA1c was as high as 7.6 (5.0–15.5 %), with much higher median of HbA1c between uncontrolled and controlled glycaemia (8.3 [7–15.5] vs. 6.5 [5–6.9] %), yet relatively similar between PCDS and non-PCDS subjects (7.6 [5.6–13.4] vs. 7.6 [6.1–15.5] %). The duration of T2DM among our subjects vary from newly diagnosed T2DM to as long as 30 years, which may contribute to this insignificant result.

There were limited previous studies that have explored on the association between HbA1c and MoCA score as cognitive assessment

in the middle-aged adults. However, in larger study of geriatric population in Japan, Machii et al. (2020) [41] found similar result that there was no significant difference of HbA1c between those with or without cognitive impairment (7.0 [95%CI 6.5–7.5] vs 6.8 [95%CI 6.4–7.4]%). Fasting plasma glucose variability may better influence cognitive performance rather than HbA1c [41].

Our finding was in contrast with cohort study conducted by Rawlings et al. (2014) [42] which reported that cognitive function may significantly decline after 20 years among middle-aged T2DM patients, especially in those with longer duration of T2DM and poorly controlled glycaemia based on single HbA1c measurement at baseline. However, their study used only one cognitive test per cognitive domain.

Moreover, Lalithambika et al. (2019) [19] found that the mean HbA1c in MCI was significantly higher compared to normal cognitive group (8.79 [1.85] vs. 7.78 [1.60]%, respectively). There was also significant inverse weak correlation between HbA1c and MoCA score ($r = -0.287$; $p = 0.016$) [19]. Longer duration of T2DM (12.04 [6.04] vs. 7 [0–30] years) and higher mean of HbA1c (8.33 [1.8] vs. 7.6 [5.0–15.5]%) in Lalithambika et al. (2019) [19] study may contribute to this different result.

4.4. Correlation among physio-cognitive decline syndrome components

It is a new important issue that PCDS in aging population is a different entity due to muscle-brain axis and its reversibility state. Neuroanatomic functioning has been changed, possibly with the myokines involvement. It is manifested as cognitive dysfunction that may affect the ability to comprehend medical treatment. Neuroanatomic functional changes through microRNA, miR-29b-3p, will further cause muscle atrophy and implicate daily life activities of individuals in long-term period, including the ability to visit the health care service and self-care. Early intervention and further prevention of PCDS development may prevent frailty and disability, even in the middle-aged adult [43].

As the cognitive and physical capacities are integrated in such a way through cerebellum in PCDS, we further analysed the correlation between muscle functions and cognitive status as well as between muscle function itself (between HGS and usual GS). Our study found significant positive weak correlation between HGS and cognitive status ($r = 0.21$; $R^2 = 0.04$; $p < 0.05$), whereas no significant correlation between other variables.

Other studies also reported significant association between HGS and cognitive status. However, those studies used 15-minute Performance Battery, Trail Making Test, Symbol Digit Modalities Test, etc. which were not quite sensitive to screen MCI [32,43]. Adamo et al. (2020) [44] found that working memory and attention did not correlate with HGS among middle-aged adults. However, their glycaemic status was unknown [44]. On the other hand, Herold et al. (2022) [45] found that HGS may be associated with executive functioning, especially in amnestic type MCI, possibly due to neural connectivity in addition to differences in prefrontal cortex hemodynamic and frontal cortical thinning [45].

To the best of our knowledge, this was the first study to assess PCDS among the middle-aged T2DM patients, in addition to analysis on the correlation between PCDS components and glycaemic control (HbA1c) as well as between each component of PCDS. Most previous studies investigated those variables in geriatrics, and compared only against normal subjects [21,46–49]. Generally, they did not assess cognitive status using MoCA, which is better in assessing MCI as an essential component of PCDS. Moreover, cognitive assessment mostly done in older people [19,50]. Thus, this study has become an important pilot study to examine the basic of aging process and frailty of T2DM patients in productive age.

Our study has proved significant correlation between HGS with glycaemic control (HbA1c) and cognitive status (MoCA-Ina score) among middle-aged T2DM patients. However, there was no correlation between cognitive status and glycaemic control. This result imply that HbA1c may have significant association with cognitive status as documented in previous studies [51], yet other factors contribute to this association which need further studies.

The proportion of PCDS, low score on MoCA Ina, low HGS and slow GS among middle-aged T2DM patients in our study was quite high (48.1 %, 74.4 %, 37.6 % and 45.9 %, respectively). Therefore, PCDS is really important and should be considered as one of diabetes complications. Early detection is essential which necessitate screening of physical capacity and cognitive function in all T2DM patients with regular follow up/evaluation in every certain period. Besides HGS which needs a handheld dynamometer to measure, MoCA-Ina and 6-meter walk test [9,15,48], have been well validated and practical so that they may be used in any health care service. Once this condition is detected, early appropriate management should be given before it becomes irreversible.

Among those with PCDS, 64.1 % have not reached the target of glycaemic control, while among those with uncontrolled glycaemia there were 45.1 % subjects with PCDS. These findings suggest that glycaemic control may be essential to prevent and improve PCDS.

Nevertheless, there are several limitations of our study. Indonesian normative parameter of each component of PCDS for middle-aged adults has not available yet, especially for diabetes patients. Therefore, it may underestimate the prevalence of PCDS in our study. Although we have excluded many conditions which may contribute to the correlation among variables, there might still be other cofounders (e.g, micro- and macrovascular DM complications [52]). On the other hand, exclusion a lot of conditions may make the study results difficult to be applied in daily clinical practice. The blood glucose and HbA1c variability were also not investigated in our study. Our study cannot conclude causal relationship between variables as it was a cross sectional study.

There were a lot of chronic inflammation conditions causing endothelial dysfunction that occur in other chronic diseases. The CCI could be used to summarize most of them and assess the prognosis. Although our study was conducted at national tertiary referral hospital, we believe that this study might still be applied in other health care/study setting with less comorbidities other than cerebrocardiovascular problems.

Further large studies on PCDS contributing factors and normative data, especially among middle-aged T2DM patients are necessary. A cohort study is anticipated to reveal causal relationship between variables and to further assess its association with morbidity and mortality. Moreover, PCDS should also be investigated in other chronic diseases.

In summary, our study found quite high proportion of PCDS with uncontrolled glycaemia among middle-aged T2DM patients. The higher HbA1c and the lower MoCA-Ina score, the weaker handgrip strength was. However, there were no significant correlation between glycaemic control and other PCDS components as well as between other PCDS component.

Authors' contributions

Conceptualization: NS, PWL, and DP, Methodology: PWL, NKS, Resources: NS, DP, Data curation: NS, PWL, DP, NKS Writing—original draft preparation: NS, PWL, Writing—review and editing: PWL, NS, DP, NKS, MK, LS, DLT, ND, IR, Supervision: PWL, DP, NKS, DLT, Validation: PWL, DP, Formal analysis: PWL, NS, Funding acquisition: DP.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Purwita Wijaya Laksmi: Conceptualization, Data curation, Methodology, Supervision, Writing – original draft, Writing – review & editing, Validation, Formal analysis. **Dyah Purnamasari:** Conceptualization, Data curation, Resources, Supervision, Validation, Writing – review & editing, Funding acquisition. **Naldo Sofian:** Conceptualization, Data curation, Resources, Visualization, Writing – original draft, Writing – review & editing, Formal analysis. **Nina Kemala Sari:** Data curation, Methodology, Supervision, Writing – review & editing. **Mohammad Kurniawan:** Writing – review & editing. **Lugyanti Sukrisman:** Writing – review & editing. **Dicky Levenus Tahapary:** Supervision, Writing – review & editing. **Noto Dwimartutie:** Writing – review & editing. **Ikhwan Rinaldi:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] A. Chawla, R. Chawla, S. Jaggi, Microvasular and macrovascular complications in diabetes mellitus: Distinct or continuum? Indian J. Endocrinol. Metab. 20 (4) (2016) 546–553.
[2] J.B. Halter, G Oj, S. Studenski, K.P. High, S. Asthana, C.S. Ritchie, et al., in: W.R. Hazzard (Ed.), Hazzard's Geriatric Medicine and Gerontology, Seventh., McGraw Hill, 2017.
[3] L.P. Fried, C.M. Tangen, J. Walston, A.B. Newman, C. Hirsch, J. Gottdiener, et al., Frailty in older adults : evidence for a phenotype, J. Gerontol. A Biol. Sci.Med. Sci. 56 (3) (2001) 146–157.
[4] H.M. González, W. Tarraf, P. Vásquez, A.H. Sanderlin, N.I. Rosenberg, S. Davis, et al., Metabolic syndrome and neurocognition among diverse middle-aged and older hispanics/latinos: HCHS/SOL results, Diabetes Care 41 (7) (2018) 1501–1509.
[5] American Diabetes Association. Standards of Medical Care in Diabetes, 2021.
[6] A. Fink, N. Buchmann, C. Tegeler, E. Steinhagen-Thiessen, I. Demuth, G. Doblhammer, Physical activity and cohabitation status moderate the link between diabetes mellitus and cognitive performance in a community-dwelling elderly population in Germany, PLoS One 12 (10) (2017) e0187119.
[7] L.K. Chen, H. Arai, Physio-cognitive decline as the accelerated aging phenotype, Arch. Gerontol. Geriatr. 88 (2020) 104051.
[8] R.A. Merchant, Y.H. Chan, R.J.Y. Hui, C.T. Tsoi, S.C. Kwek, W.M. Tan, et al., Motoric cognitive risk syndrome, physio-cognitive decline syndrome, cognitive frailty and reversibility with dual-task exercise, Exp. Gerontol. 150 (2021) 111362, https://doi.org/10.1016/j.exger.2021.111362.
[9] C.K. Liang, W.J. Lee, A.C. Hwang, C.S. Lin, M.Y. Chou, L.N. Peng, et al., Efficacy of multidomain intervention against physio-cognitive decline syndrome: a cluster-randomized trial, Arch. Gerontol. Geriatr. 95 (2021) 104392, https://doi.org/10.1016/j.archger.2021.104392.
[10] American Diabetes Association, Standards of Medical Care in Diabetes (2022).
[11] E.I. Isik, S. Yilmaz, I. Uysal, S. Basar, Adaptation of the lawton instrumental activities of daily living scale to Turkish: validity and reliability study, Ann. Geriatr. Med. Res. 24 (1) (2020) 35–40.
[12] M. Pashmdarfard, A. Azad, Assessment tools to evaluate activities of daily living (ADL) and instrumental activities of daily living (IADL) in older adults: a systematic review, Med. J. Islam. Repub. Iran (2020) 2020.
[13] S.A.M. Sikkes, E.S.M. De Lange-De Klerk, Y.A.L. Pijnenburg, P. Scheltens, B.M.J. Uitdehaag, A systematic review of Instrumental Activities of Daily Living scales in dementia: room for improvement, J. Neurol. Neurosurg. Psychiatry 80 (1) (2009) 7–12.
[14] L.K. Chen, J. Woo, P. Assantachai, T.W. Auyeung, M.Y. Chou, K. Iijima, et al., Asian working group for sarcopenia: 2019 consensus update on sarcopenia diagnosis and treatment, J. Am. Med. Dir. Assoc. 21 (3) (2020) 300–307, https://doi.org/10.1016/j.jamda.2019.12.012.
[15] N. Husein, S. Lumempouw, Y. Ramli, Montreal Cognitive Assessment versi Indonesia (MoCA-Ina) untuk skrining gangguan kognitif [Indonesian version of Montreal Cognitive Assessment (MoCA-Ina) for cognitive imparment screening], Neurona 27 (4) (2010).

[16] E. Borland, K. Nägga, P.M. Nilsson, L. Minthon, E.D. Nilsson, S. Palmqvist, The Montreal Cognitive Assessment: normative data from a large Swedish population-based cohort, J. Alzheim. Dis. 59 (3) (2017) 893–901.
[17] M.E. Wallymahmed, C. Morgan, G.V. Gill, I.A. MacFarlane, Aerobic fitness and hand grip strength in type 1 diabetes: relationship to glycaemic control and body composition, Diabet. Med. 24 (11) (2007) 1296–1299.
[18] M. Azmon, N. Gayus, H. Michal, L. Olmer, T. Cukierman-Yaffe, The association between glucose control and functional indices in older people with diabetes, Int. J. Endocrinol. 2018 (2018).
[19] C.V. Lalithambika, C.S. Arun, L.A. Saraswathy, R. Bhaskaran, Cognitive impairment and its association with glycemic control in type 2 diabetes mellitus patients, Indian J. Endocrinol. Metab. 23 (3) (2019) 353–356.
[20] S. Inoue, P. Zimmet, I. Caterson, C. Chunming, Y. Ikeda, A. Khalid, et al., Obesity Task Force. The Asia – Pacific Perspective: Redefining Obesity and its Treatment, vol. 56, 2000.
[21] J.S. Brach, J.B. Talkowski, E.S. Strotmeyer, A.B. Newman, Diabetes mellitus and gait dysfunction: possible explanatory factors, Phys. Ther. 88 (11) (2008) 1365–1374.
[22] A. Winkler, M. Dlugaj, C. Weimar, K.H. Jöckel, R. Erbel, N. Dragano, et al., Association of diabetes mellitus and mild cognitive impairment in middle-aged men and women, J. Alzheim. Dis. 42 (4) (2014) 1269–1277.
[23] A.H. Dyer, I. Batten, C. Reddy, L. Townsend, C.P. Woods, D. O'Neill, et al., Neuropsychological decrements in midlife type-2 diabetes are not associated with peripheral NLRP3 inflammasome responsiveness, Front. Immunol. 13 (2022) 1021351.
[24] E. Cetinus, M.A. Buyukbese, M. Uzel, H. Ekerbicer, A. Karaoguz, Hand grip strength in patients with type 2 diabetes mellitus, Diabetes Res. Clin. Pract. 70 (3) (2005) 278–286.
[25] F.G. Duarte, S. Da Silva Moreira, M.D.C.C. Almeida, C.A. De Souza Teles, C.S. Andrade, A.L. Reingold, et al., Sex differences and correlates of poor glycaemic control in type 2 diabetes: a cross-sectional study in Brazil and Venezuela, BMJ Open 9 (3) (2019).
[26] C.A. Amaral, T.L.M. Amaral, G.T.R. Monteiro, M.T.L. Vasconcellos, M.C. Portela, Hand grip strength: reference values for adults and elderly people of Rio Branco, Acre, Brazil, PLoS One 14 (1) (2019) e0211452.
[27] J.J. Li, G.A. Wittert, A. Vincent, E. Atlantis, Z. Shi, S.L. Appleton, et al., Muscle grip strength predicts incident type 2 diabetes: population-based cohort study, Metabolism 65 (6) (2016) 883–892, https://doi.org/10.1016/j.metabol.2016.03.011.
[28] X. Liang, C.Q. Jiang, W. Zhang, Sen, F. Zhu, Y.L. Jin, K.K. Cheng, et al., Glycaemia and hand grip strength in aging people: guangzhou biobank cohort study, BMC Geriatr. 20 (1) (2020) 399.
[29] Y.C. Lin, C.P. Chung, P.L. Lee, K.H. Chou, L.H. Chang, S.Y. Lin, et al., The flexibility of Physio-Cognitive Decline Syndrome: a longitudinal cohort study, Front. Public Health 10 (2022) 820383.
[30] R.P.C. Kessels, N.R. de Vent, C.J.W.H. Bruijnen, M.G. Jansen, J.F.M. de Jonghe, B.A.G. Dijkstra, et al., Regression-based normative data for the Montreal cognitive assessment (MoCA) and its memory index score (MoCA-MIS) for individuals aged 18–91, J. Clin. Med. 11 (14) (2022) 4059.
[31] K.N. Williams, S. Kemper, Interventions to reduce cognitive dfecline in aging, J. Psychosoc. Nurs. Ment. Health Serv. 48 (5) (2010) 42–51.
[32] T. Salthouse, Consequences of age-related cognitive declines, Annu. Rev. Psychol. 63 (2012) 201–226.
[33] J. Verghese, R. Holtzer, M. Oh-Park, C.A. Derby, R.B. Lipton, C. Wang, Inflammatory markers and gait speed decline in older adults, J. Gerontol. A Biol. Sci. Med. Sci. 66 (10) (2011) 1083–1089.
[34] T. Katsumata, T. Otori, Y. Nishiyama, S. Okubo, Y. Nishiyama, H. Nagayama, et al., Correlation between insulin resistance and white matter lesions among non-diabetic patients with ischemic stroke, Neurol. Res. 32 (7) (2010) 743–747.
[35] V. Garfield, A.E. Farmaki, S.V. Eastwood, R. Mathur, C.T. Rentsch, K. Bhaskaran, et al., HbA1c and brain health across the entire glycaemic spectrum, Diabetes Obes. Metab. 23 (5) (2021) 1140–1149.
[36] V.S. Manoharan, S.G. Sundaram, J.I. Jason, Factors affecting hand grip strength and its evaluation: a Systemic Review, Int. J. Physiother. Res. 3 (6) (2015) 1288–1293.
[37] H. Choe, H. Sung, G.H. Kim, O. Lee, H.Y. Moon, Y.S. Kim, Associations between grip strength and glycemic control in type 2 diabetes mellitus: an analysis of data from the 2014-2019 Korea National Health and Nutrition Examination Survey, Epidemiol. Health 43 (2021) e2021080.
[38] P.D. Loprinzi, J.P. Loenneke, Evidence of a link between grip strength and type 2 diabetes prevalence and severity among a national sample of U.S. adults, J. Phys. Act. Health 13 (5) (2016) 558–561.
[39] S. Tanaka, M. Takubo, G. Kohno, M. Kushimoto, J. Ikeda, K. Ogawa, et al., Inverse correlation between grip strength and serum phosphorus: a retrospective observational study in Japanese elderly with poorly controlled type 2 diabetes, Geriatrics (Basel) 5 (2) (2020) 33.
[40] S. Gundmi, A.G. Maiya, A.K. Bhat, N. Ravishankar, M.H. Hande, K.V. Rajagopal, Hand dysfunction in type 2 diabetes mellitus: systematic review with meta-analysis, Ann. Phys. Rehabil. Med. 61 (2018) 99–104.
[41] N. Machii, A. Kudo, H. Saito, H. Tanabe, M. Iwasaki, H. Hirai, et al., Walking speed is the sole determinant criterion of sarcopenia of mild cognitive impairment in Japanese elderly patients with type 2 diabetes mellitus, J. Clin. Med. 9 (7) (2020) 2133.
[42] A.M. Rawlings, A.R. Sharret, A.L.C. Schneider, J. Coresh, M. Albert, D. Couper, et al., Diabetes in midlife and cognitive change over 20 years: the atherosclerosis risk in communities neurocognitive study, Ann. Intern. Med. 161 (11) (2014) 785–793.
[43] I. Feinkohl, J.F. Price, M.W.J. Strachan, B.M. Frier, The impact of diabetes on cognitive decline: potential vascular, metabolic, and psychosocial risk factors, Alzheimers Res. Ther. 7 (1) (2015), https://doi.org/10.1186/s13195-015-0130-5.
[44] D.E. Adamo, T. Anderson, M. Koochaki, N.E. Fritz, Declines in grip strength may indicate early changes in cognition in healthy middle-aged adults, PLoS One 15 (4) (2020) e0232021, https://doi.org/10.1371/journal.pone.0232021.
[45] F. Herold, B.K. Labott, B. Grässler, N. Halfpaap, C. Langhans, P. Müller, et al., A link between handgrip strength and executive functioning: a cross-sectional study in older adults with mild cognitive impairment and healthy controls, Healthcare (Basel) 10 (2) (2022).
[46] M.C. Masters, J. Perez, K. Tassiopoulos, A. Andrade, R. Ellis, J. Yang, et al., Gait speed decline is associated with hemoglobin A1c, neurocognitive impairment, and black race in persons with HIV, AIDS Res. Hum. Retroviruses 35 (11–12) (2019) 1065–1073.
[47] K. Sugimoto, H. Ikegami, Y. Takata, T. Katsuya, M. Fukuda, H. Akasaka, et al., Glycemic control and insulin improve muscle mass and gait speed in type 2 diabetes: the MUSCLES-DM study, J. Am. Med. Dir. Assoc. 22 (2021) 834–838.
[48] H.S.P. Lam, F.W.K. Lau, G.K.L. Chan, K. Sykes, The validity and reliability of a 6-Metre Timed Walk for the functional assessment of patients with stroke, Physiother. Theory Pract. 26 (4) (2010) 251–255.
[49] F. Pamoukdjian, E. Paillaud, L. Zelek, M. Laurent, V. Lévy, T. Landre, et al., Measurement of gait speed in older adults to identify complications associated with frailty: a systematic review, J. Geriatr. Oncol. 6 (6) (2015) 484–496, https://doi.org/10.1016/j.jgo.2015.08.006.
[50] J.C. Dalrymple-Alford, M.R. MacAskill, C.T. Nakas, L. Livingston, C. Graham, G.P. Crucian, et al., The MoCA: well-suited screen for cognitive impairment in Parkinson disease, Neurology 75 (19) (2010) 1717–1725.
[51] E.R. Waclawski, Hyperglycaemia and cognitive function-acute and chronic effects and work, Occup. Med. (Lond.) 62 (4) (2012) 236–237.
[52] E.C. Katoulis, M. Ebdon-Parry, H. Lanshammar, L. Vileikyte, J. Kulkarni, A.J.M. Boulton, Gait abnormalities in diabetic neuropathy, Diabetes Care 20 (12) (1997) 1904–1907.