Original Article

Possible Contribution of Advanced Glycated End Products Level in Motor Dysfunction in The Elderly

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Abstract

Background: Advanced glycated end products (AGEs) are a heterogeneous group of molecules that were initially discovered at the beginning of the 20th century in the classic Maillard reaction. AGEs have generated interest in the biochemical and medical fields because of their biological effects on humans, particularly aging. Several studies have associated a decline in physical functioning with higher concentrations of AGEs.

Objective: This study aimed to investigate the possible contribution of advanced glycated end-products levels in motor dysfunction in the elderly.

Material and methods: The study was carried out on 50 older males aged 65 years old and above who presented to the outpatient clinic of the Main University Alexandria Hospital or were admitted to the Geriatric wards, divided into Group I (control) 20 men with normal handgrip strength and normal walking speed (time to walk 3 meters), Group II (cases) 30 men with poor handgrip strength and slow walking speed.

Results: CML levels in group II (cases) ranged from 45.79 – to 101. with a mean value (S.D) of 62.72 ± 12. CML among group I (control) ranged from 49.35 – to 85.50 with a mean value (S. D) of 62.33 ± 7.92.CML was insignificantly higher among the cases group (p=0.390).

Conclusion: There was no statistically significant difference between the serum levels of CML in group II (cases) and group I (control).

Keywords: Advanced glycated end products (AGEs) ; carboxymethyl lysine (CML) ; motor dysfunction.

Introduction

The World Health Organization has recognized the aging of the population in many countries around the world as one of the most significant challenges of the twenty-first century. In several countries in Asia and Europe, the average life expectancy has already exceeded 80 years, particularly among women. The fastest-growing age group in the United States is the oldest-old (>85 years) group. It has been estimated that by the year 2050, the number of people older than 60 years on the planet will exceed 2 billion. [1,2]

In Egypt, the percentage of older people defined as 60 years of age and more was 5.75% in 1996 and increased to 6.27% in 2006, then to 7.2% in 2013. The percentage is projected to be 8.1% in 2016 and 9.2% in 2021, and it is expected to reach 20.8% in 2050. This means that around 20 million Egyptians will be categorized as elderly by that time. [3]

Over the past couple of decades, advanced glycated end products (AGEs) have received considerable attention as one of the many mechanisms proposed for aging; their progressive accumulation in the organism over time leads to disease and death. [4]

AGEs are a heterogeneous group of molecules that were initially discovered at the beginning of the 20th century in the classic Maillard reaction. With the discovery of glycated hemoglobin in diabetic patients, it became apparent that glycation, a non-enzymatic reaction between reducing sugars such as glucose, and proteins, lipids, or nucleic acids, also occurs under physiological and pathological conditions. [5]

AGEs have generated interest in the biochemical and medical fields because of their biological effects on humans, particularly aging. Most AGEs are detrimental to human health by disrupting our body's hormonal functions and participating in age-related, non-communicable, chronic inflammatory diseases. [6,7]

Advanced glycated end products (AGEs) are considered reliable biomarkers of biological age. [8] A decline in physical functioning has been associated with higher concentrations of AGEs in several studies. [9] Further studies showed the value of AGEs for predicting developing severe walking disability. [10]

Sarcopenia, or loss of muscle strength and muscle mass, is an important factor in underlying mobility difficulties, such as slow walking speed in older adults. [11]

The prevalence of sarcopenia was 4.1–11.5% in the general elderly population and 14.8% in type 2 diabetes according to the Asian Working Group for Sarcopenia criteria. [12,13]

Oxidative stress and inflammatory cytokines are increased by AGEs. [14] In addition, AGEs induce cross-link and breakdown of muscular protein in elderly humans. [15] The expression of AGEs receptors in muscle tissue is increased with aging, [16] suggesting that the intracellular signaling of AGEs–AGEs receptors are accelerated in the muscle of elderly patients. It was reported in a human study that AGEs accumulation in the fast-twitch muscle fibers cross-links with muscle collagen, increases muscle stiffness, and reduces the tonic force of the muscle contraction. Thus, it is suggested that accumulated AGEs levels are associated with muscle mass reduction and sarcopenia in elderly patients. [17]

This study aimed to investigate and assess the possible contribution of advanced glycated end products (AGEs) in motor dysfunction in the elderly.

Subjects

The study was carried out on 50 older males aged 65 years old and above who presented to the outpatient clinic of the Main University Alexandria Hospital or were admitted to the Geriatric wards, divided into 20 men in group I (control) with normal handgrip strength and normal walking speed (time to walk 3 meters), 30 men in the group II (cases) with poor handgrip strength and slow walking speed.
The sample size was decided according to community medicine department advice.
We decided to include males only in the study because of the high difference in cutoff points of Hand Grip Strength between males and females (grip strength <27 kg for men and <16 kg for women) [18] making the comparison between cases and controls is too difficult if both sexes included.
Sarcopenia was diagnosed using the Hand Grip Strength and Timed Up and Go test.

Patients with one or more of the following were excluded:
1. Patients who had a history of accidents or fractures affecting their motor function.
2. Diabetes Mellitus.
3. Chronic liver & kidney disease.
4. Neuropsychiatric illness.
5. Patients who refuse to participate.

METHODS

Informed consent was taken from all participants, and all participants were subjected to:
1. Detailed history taking with an emphasis on:
Age.
Past medical and surgical history (orthopedic surgery).
Drug history (corticosteroids).
2. Full clinical examination.
3. Comprehensive Geriatric Assessment:
MMSE (Mini-mental state examination). [19]
ADL (activities of daily living). [20]
MNA (MINI nutritional assessment). [21]
Get up and Go Test. [22]
4. Routine laboratory investigation: [23]
(CBC, FBS, Urea, Creatinine, SGOT, SGPT, Na, K).
Estimated GFR by Cockroft-Gault method.
5. Assessment of handgrip strength using a dynamometer. [24]
6. Measuring the level of advanced glycated end products; serum carboxy methyl lysine (CML) in a blood sample from the participant using the ELISA technique. [25]
Approval from the Ethical Committee, faculty of medicine, Alexandria University was taken, and the serial number was 0106419 on 18 Jun 2020.

RESULTS

Statistical analysis of the data

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and

maximum), mean, standard deviation, median, and interquartile range (IQR). The significance of the obtained results was judged at the 5% level.
The used tests were:
1 - Mann Whitney test
For abnormally distributed quantitative variables, to compare two studied groups
2 - Student t-test
For normally distributed quantitative variables, to compare two studied groups

Table (1): Comparison between the two studied groups according to age

Age (years)	Group 1 control (n=20)	Group 2 cases (n=30)	p
Young old (65 – <75)	18(90.0%)	27(90.0%)	^{FE}p=1.000
Middle-old (75 – <85)	2(10.0%)	3(10.0%)	
Old (≥85)	0(0.0%)	0(0.0%)	
Min. – Max.	65.0 – 81.0	65.0 – 81.0	
Mean ± SD.	69.75 ± 3.81	69.17 ± 4.17	0.618

t: Student t-test
p: p-value for comparing the two studied groups

Table (2): Comparison between the two studied groups according to functional assessment

Functional assessment	Group1 control (n=20)	Group 2 cases (n=30)	p
TUG test (seconds)			
Min. – Max.	10.0 – 20.0	14.0 – 30.0	
Mean ± SD.	13.68 ± 2.81	21.11 ± 4.79	<0.001*
Hand Grip Strength (kg)			
Min. – Max.	31.0 – 62.0	9.0 – 26.0	
Mean ± SD.	42.21 ± 6.63	17.70 ± 5.55	<0.001*
ADLs (point)			
Min. – Max.	6.0 – 6.0	2.0 – 5.0	
Mean ± SD.	6.0 ± 0.0	3.59 ± 0.89	<0.001*

t: Student t-test **U: Mann Whitney test**
p: p-value for comparing **the two studied groups**
*: Statistically significant at $p \leq 0.05$

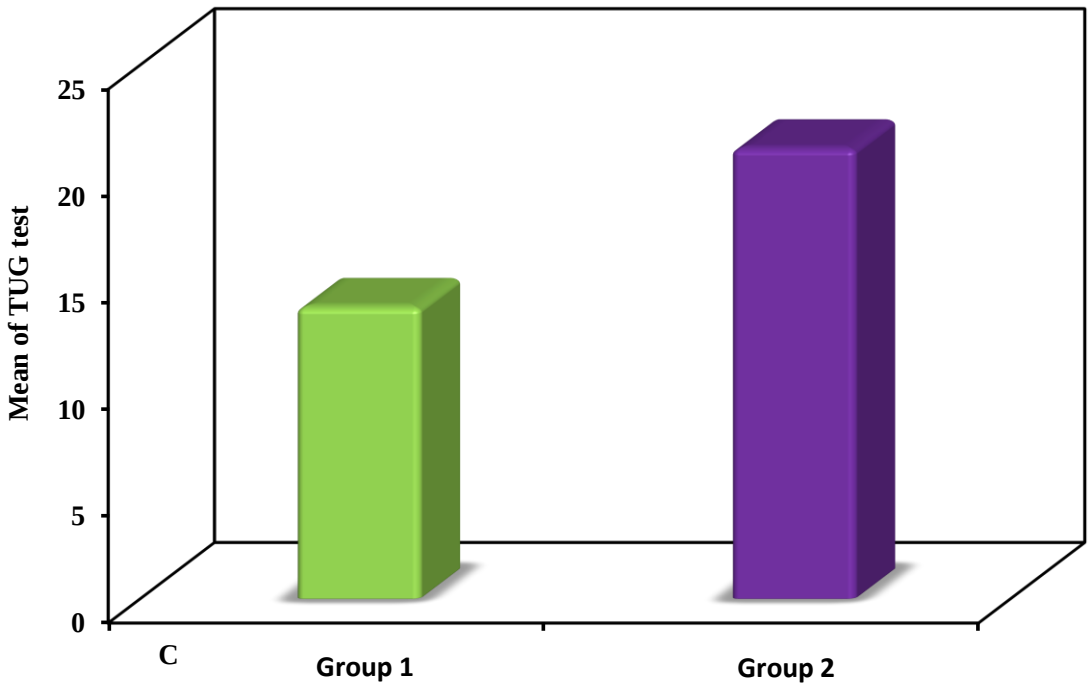

Figure (1): Comparison between the two studied groups according to the TUG test

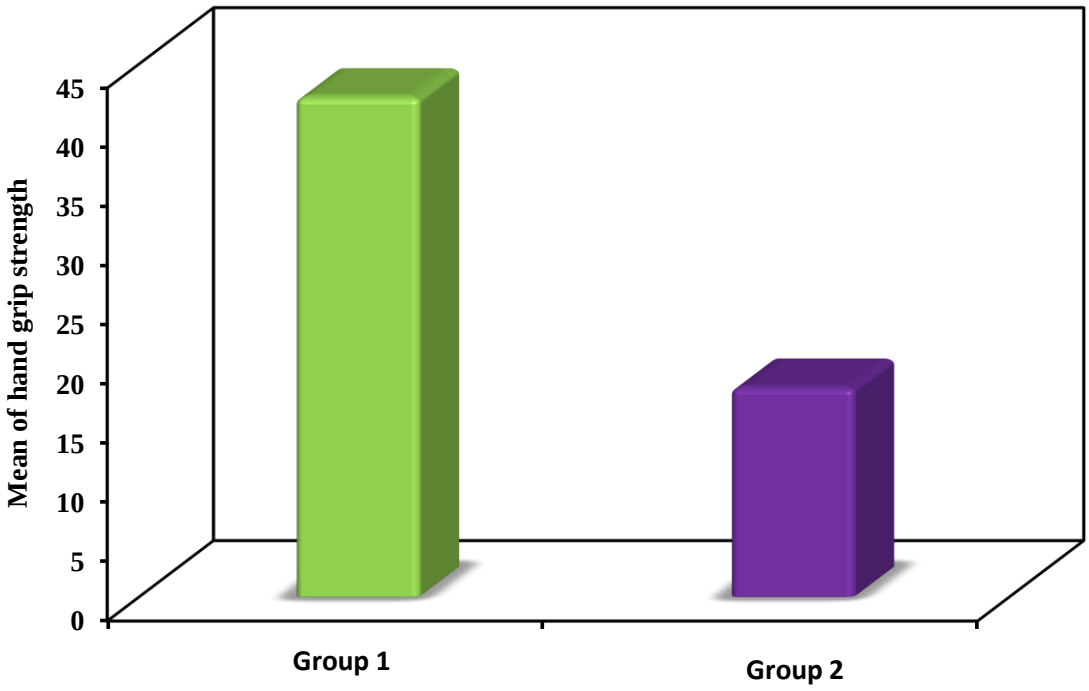

Figure (2): Comparison between the two studied groups according to Hand Grip Strength

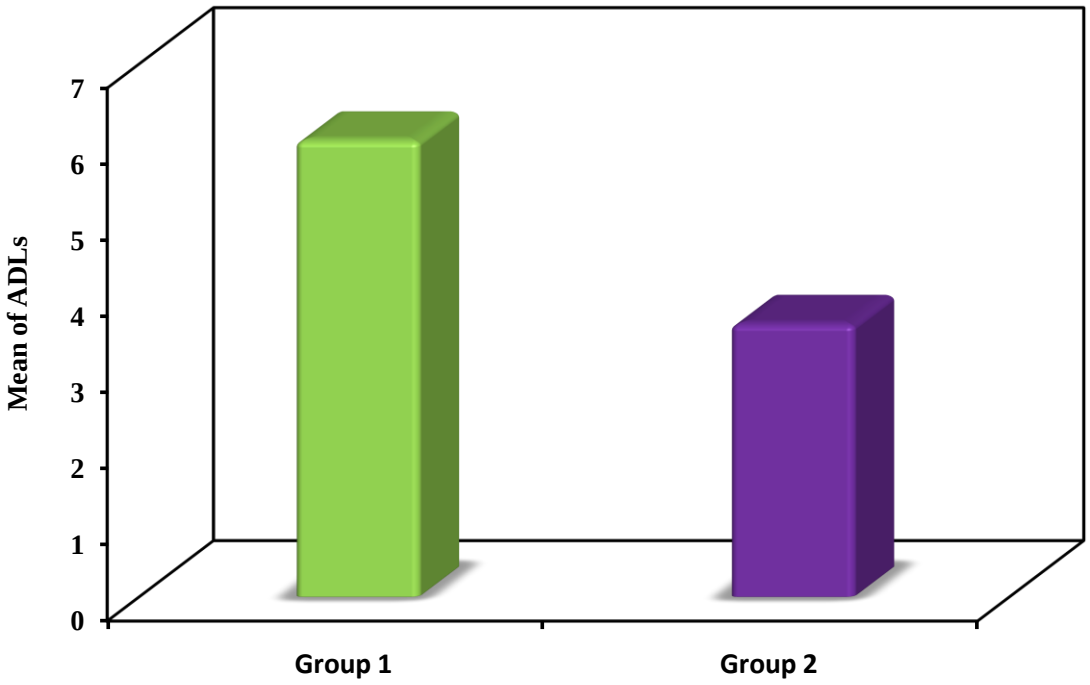

Figure (3): Comparison between the two studied groups according to ADLs

Table (3): Comparison between the two studied groups according to MMSE

MMSE (points)	Group 1 Control (n=20)	Group 2 Cases (n=30)	p
Min. – Max.	27.0 – 30.0	21.0 – 30.0	
Mean ± SD.	29.47 ± 1.07	26.19 ± 2.13	<0.001*

t: Student t-test
p: p-value for comparing **the two studied groups**
*: Statistically significant at $p \leq 0.05$

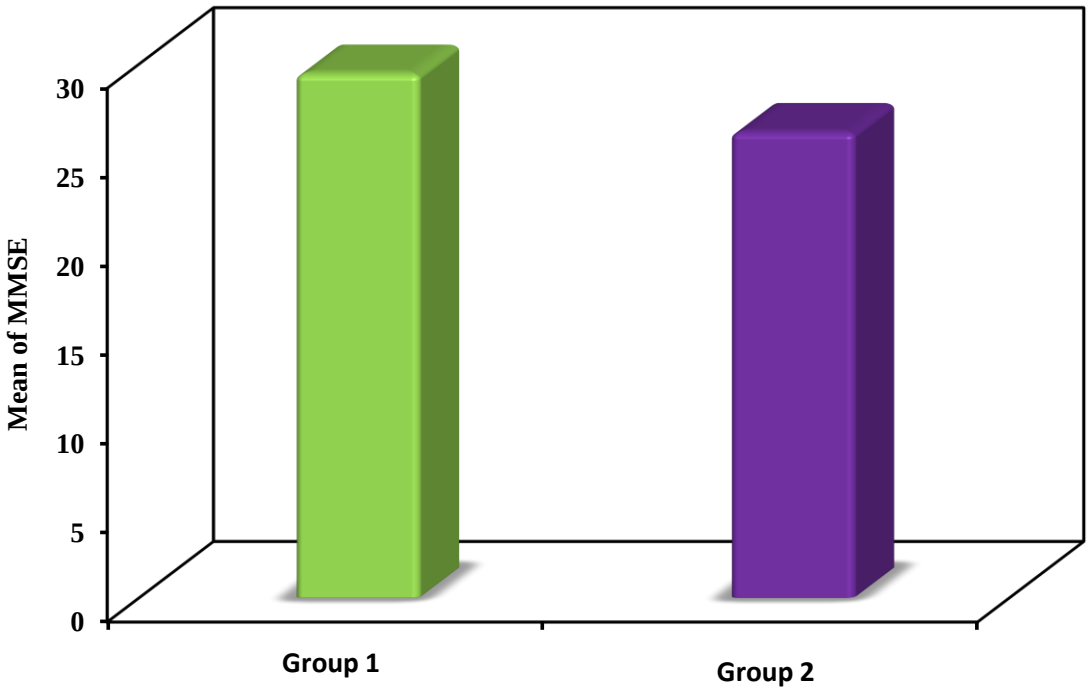

Figure (4): Comparison between the two studied groups according to MMSE

Table (4): Comparison between the two studied groups according to nutritional assessment (MNA)

MNA (points)	Group 1 Control (n=20)	Group 2 Cases (n=30)	p
Min. – Max.	11.0 – 14.0	9.0 – 14.0	
Mean ± SD.	12.05 ± 1.47	10.40 ± 1.38	<0.001*

t: Student t-test
p: p-value for comparing the two studied groups
*: Statistically significant at $p \leq 0.05$

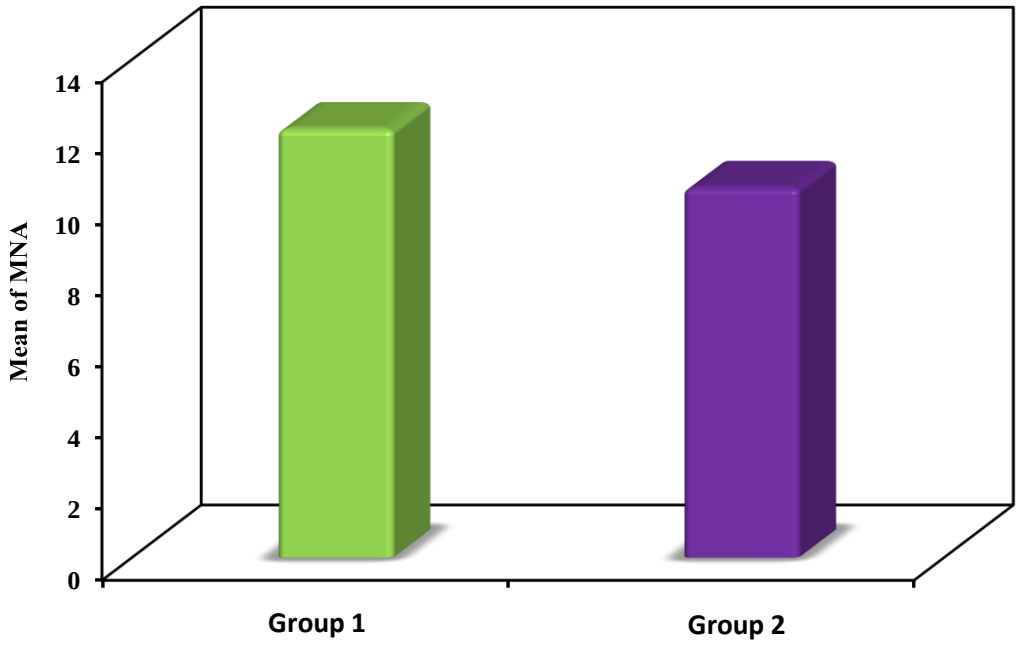

Figure (5): Comparison between the two studied groups according to mini nutritional assessment (MNA)

Table (5): Comparison between the two studied groups according to CML

CML (pg\ml)	Group 1 Control (n=20)	Group 2 Cases (n=30)	p
Min. – Max.	49.35 – 85.50	45.79 – 101.22	
Mean ± SD.	62.33 ± 7.92	62.72 ± 12.89	0.390

U: Mann-Whitney test
p: p-value for comparing **the two studied groups**

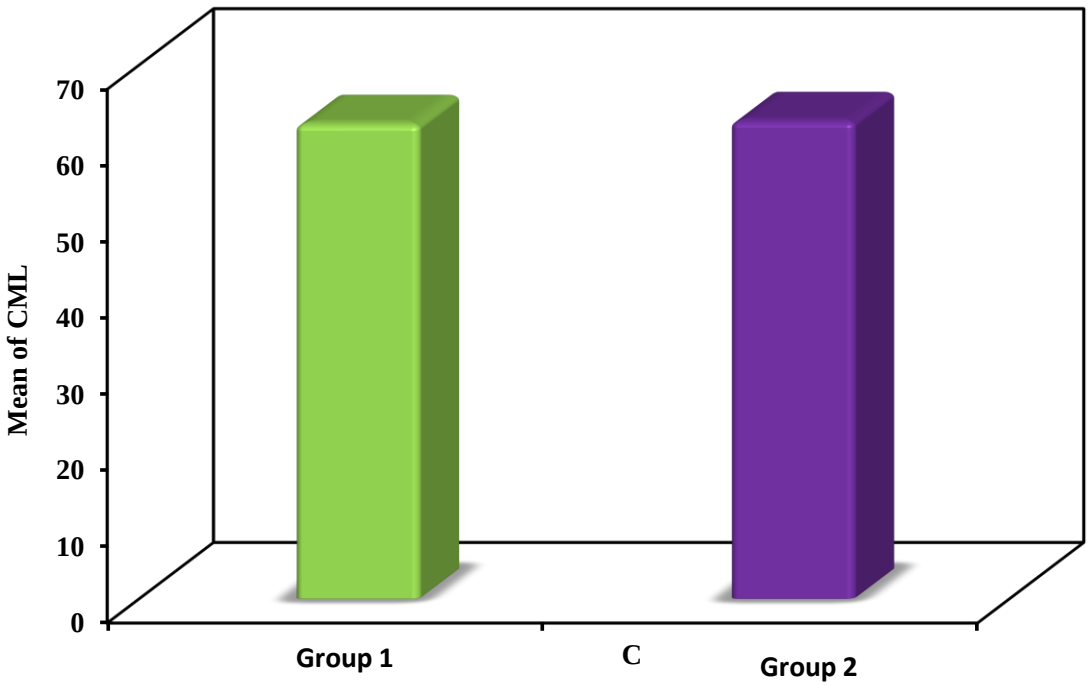

Figure (6): Comparison between the two studied groups according to CML

Table (6): Comparison between the two studied groups according to estimated GFR (eGFR)

eGFR (ml\min\1.73m^2)	Group 1 Control (n=20)	Group 2 Cases (n=30)	p
Min. – Max.	61.86 – 108.0	63.50 – 118.80	
Mean ± SD.	83.44 ± 16.40	87.17 ± 13.99	0.412

t: Student t-test
p: p-value for comparing **the two studied groups**

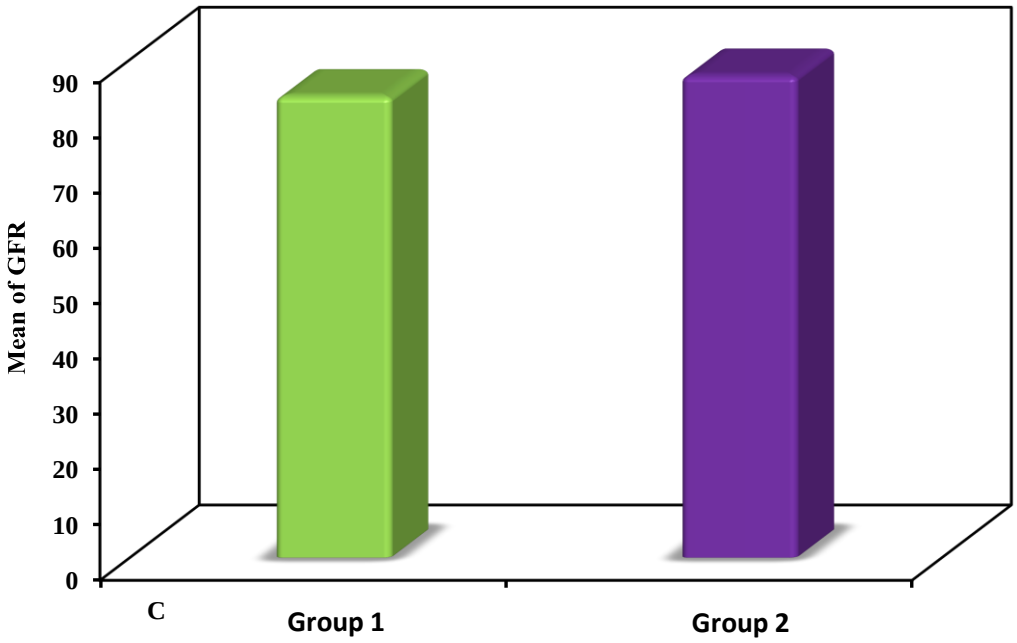

Figure (7): Comparison between the two studied groups according to eGFR

Table (7): Correlation between CML and different parameters

	CML (pg\ml)			
	Group 1 Control (n=20)		Group 2 Cases (n=30)	
	r_s	p	r_s	p
Age (years)	0.966	<0.001*	0.855	<0.001*
TUG test (seconds)	0.670	0.002*	0.553	0.003*
Hand Grip Strength (kg)	-0.838	<0.001*	-0.730	<0.001*
MMSE (points)	-0.150	0.539	-0.017	0.934
ADLs (points)	–	–	0.093	0.643
MNA (points)	-0.413	0.079	0.411	0.033*
eGFR (ml\min\1.73m^2)	-0.132	0.591	0.032	0.873

r_s: Spearman coefficient *: Statistically significant at $p \leq 0.05$
#: No correlation due to constant value (6)

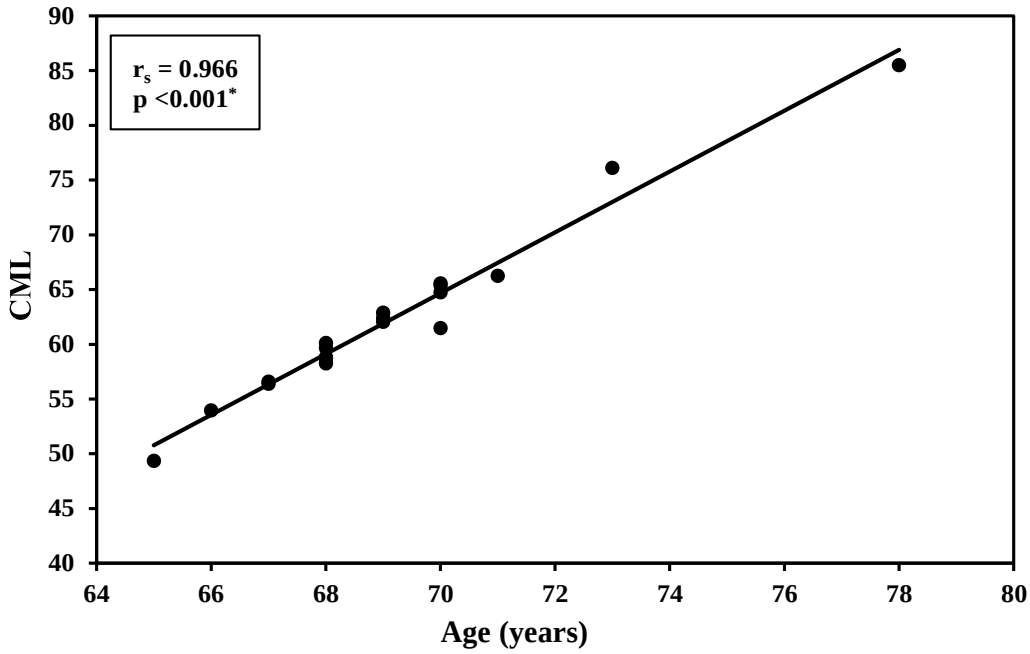

Figure (8): Correlation between CML and age (years) in group 1.

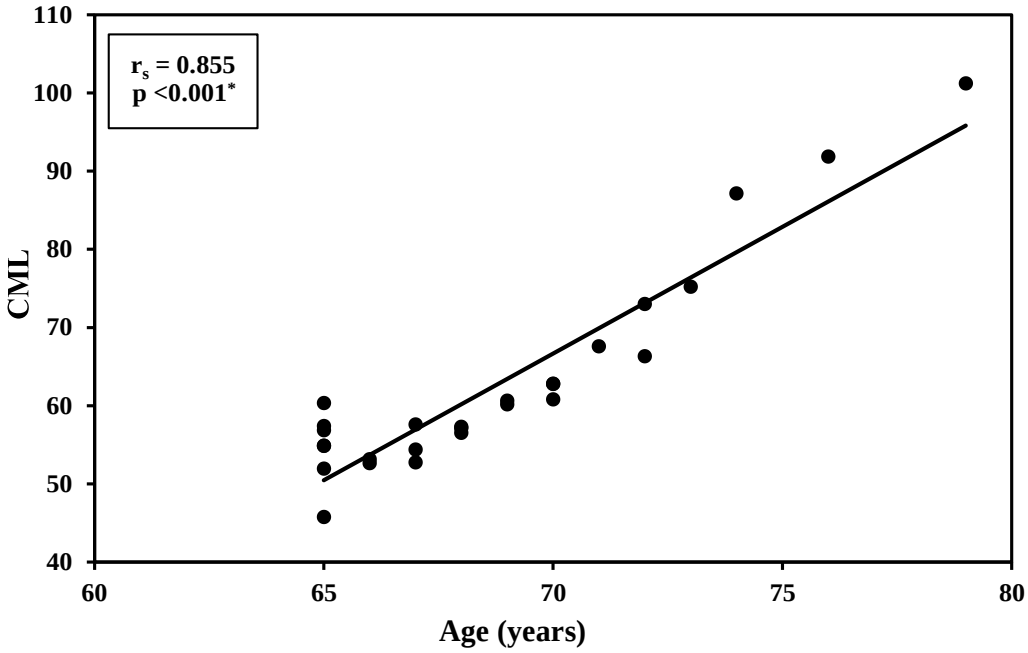

Figure (9): Correlation between CML and age (years) in group 2

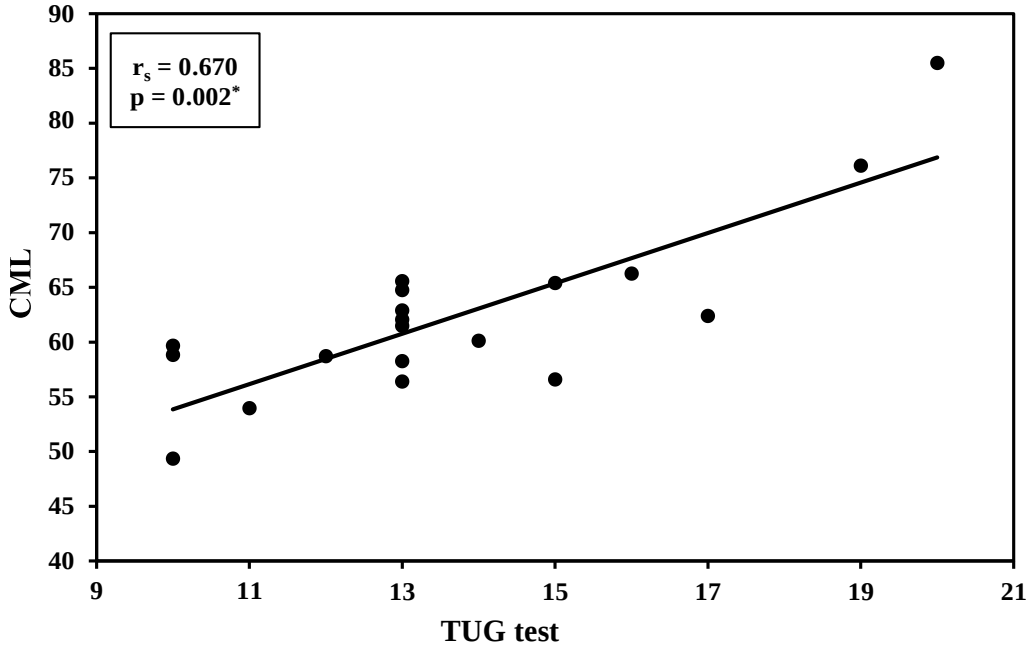

Figure (10): Correlation between CML and TUG test in group 1

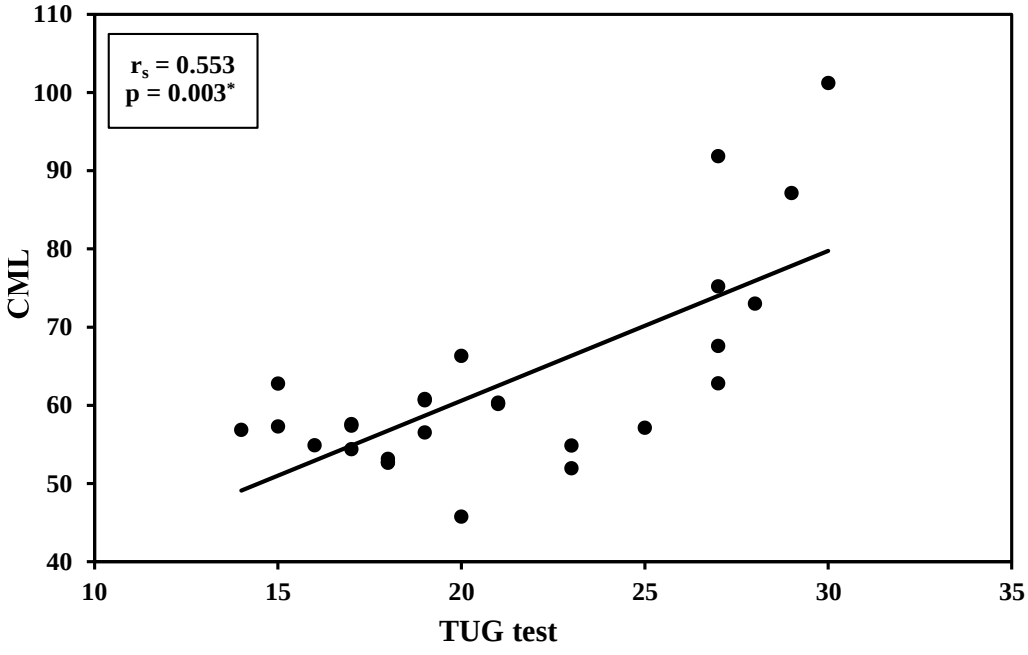

Figure (11): Correlation between CML and TUG test in group 2

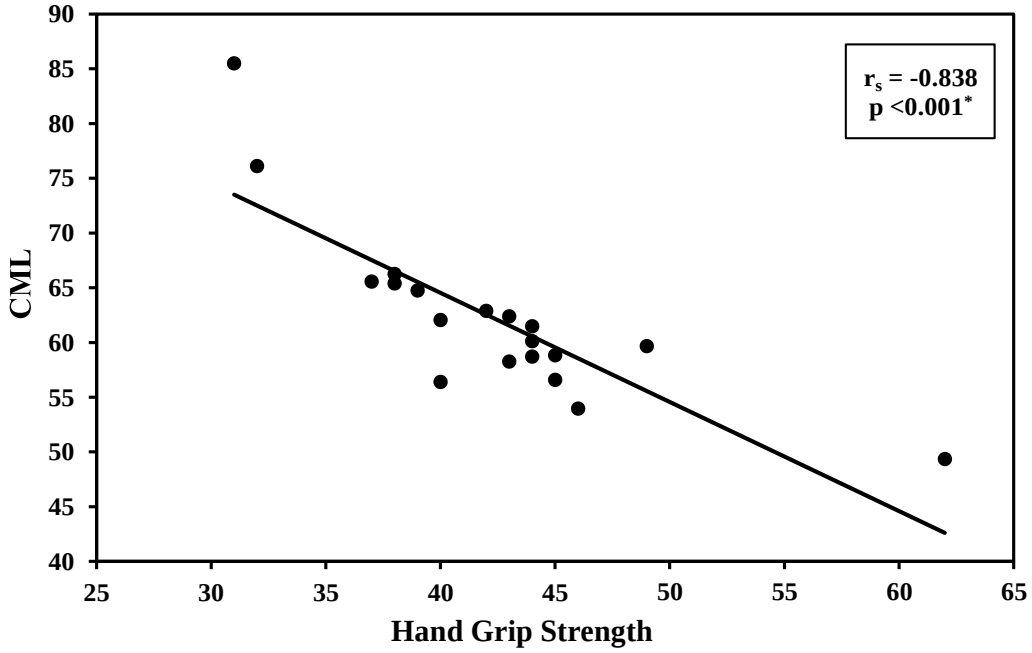

Figure (12): Correlation between CML and handgrip strength in group 1

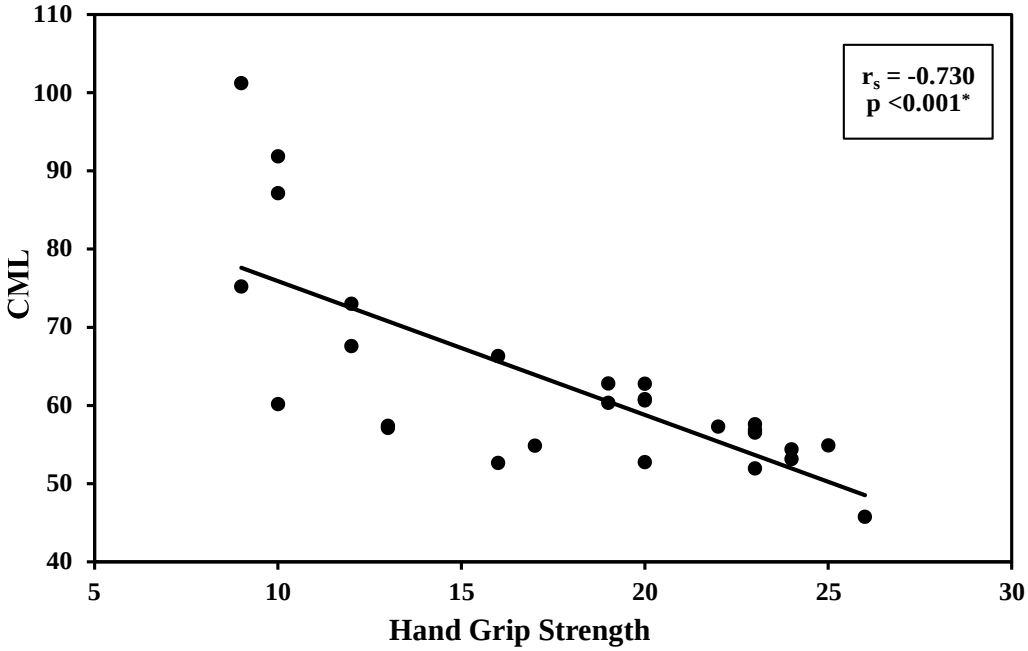

Figure (13): Correlation between CML and handgrip strength in group 2

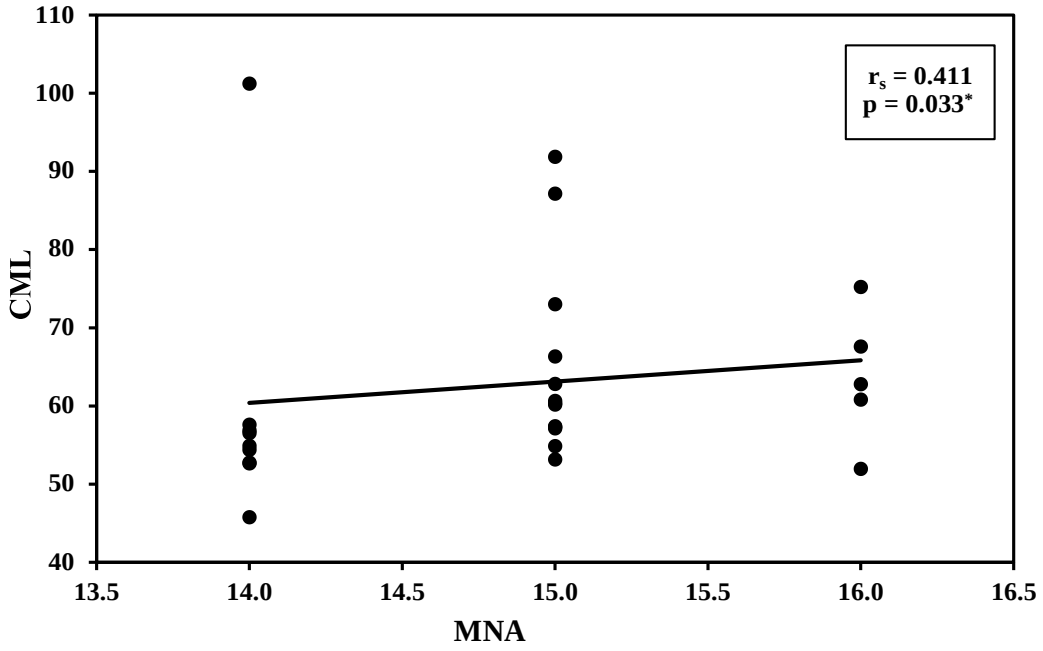

Figure (14): Correlation between CML and MNA in group 2

Table (8): Univariate and multivariate linear regression analysis for the parameters affecting CML in group 1; control (n=20)

	Univariate		#Multivariate	
	p	**B (95%C. I)**	**p**	**B (95%C. I)**
Age (years)	**<0.001***	2.777(2.541 – 3.013)	**<0.001***	2.384(1.978 – 2.789)
TUG test (seconds)	**<0.001***	2.302(1.468 – 3.135)	0.384	0.154(-0.212 – 0.521)
Hand Grip Strength (kg)	**<0.001***	-0.997(-1.334–-0.659)	0.065	-0.145(-0.300– 0.010)
MMSE (points)	**0.398**	-1.517(-5.213– 2.178)	–	–
ADLs (points)	**–**	–	–	–
MNA (points)	**0.059**	-4.433(-9.055–0.189)	–	–
eGFR (ml\min\1.73m²)	**0.263**	-0.131(-0.369– 0.107)	–	–

B: Unstandardized Coefficients
C.I: Confidence interval LL: Lower limit UL: Upper Limit
#: All variables with p<0.05 was included in the multivariate
*: Statistically significant at $p \leq 0.05$

Table (9): Univariate and multivariate linear regression analysis for the parameters affecting CML in group 2; cases (n=30)

	Univariate		#Multivariate	
	p	**B (95%C. I)**	**p**	**B (95%C. I)**
Age (years)	**<0.001***	3.237(2.722 – 3.752)	**<0.001***	2.761(1.992 – 3.530)
TUG test (seconds)	**<0.001***	1.916(1.138 – 2.694)	0.555	0.178(-0.438 – 0.795)
Hand Grip Strength (kg)	**<0.001***	-1.711(-2.357 –1.065)	0.259	-0.301(0.840 – 0.238)
MMSE (points)	**0.797**	-0.314(-2.802– 2.174)	–	–
ADLs (points)	**0.786**	0.796(-5.172 – 6.763)	–	–
MNA (points)	**0.450**	2.724(-4.584– 10.031)	–	–
eGFR (Ml\min\1.73m²)	**0.973**	-0.006(-0.386 – 0.373)	–	–

B: Unstandardized Coefficients
C.I: Confidence interval LL: Lower limit UL: Upper Limit
#: All variables with p<0.05 was included in the multivariate
*: Statistically significant at $p \leq 0.05$

Discussion

Muscular aging is multifactorial, involving extrinsic and intrinsic mechanisms that attack both the cellular components and extracellular matrix (ECM). Advanced glycation end-products (AGEs) accumulate in musculoskeletal tissues in old age and are thought to play a role in the development of motor dysfunction. (26)

Our study found a significant discrepancy between the two studied groups concerning MMSE (p<0.001). MMSE was statistically lower in cases than in control. The mean for cases was 26.19 ± 2.13 and for the control was 29.47 ± 1.07.
In line with our findings, Liu Y et al. study found that the highest strength of handgrip was associated with better cognition and slower rates of decline. (27) Another study by Auyeung TW showed that physical frailty and weaker handgrip strength both in men and women were associated with cognitive decline over 4 years. (28)

Although a connection between physical functioning and cognitive abilities has been suggested, the etiology of that relationship has yet to be fully explained. Three main possibilities have been proposed. Physical functioning drives age-related changes in cognition; cognition drives age-related changes in physical functioning, or a third factor affects both. (29)

Our study found a significant discrepancy between the two studied groups regarding MNA ($p<0.001$) as MNA was lower in the cases group than in the control group. These results supported the previous study of Guo et al. in which handgrip strength correlated with nutritional status, which was assessed by arm circumference and creatinine index. [30]

Flood et al. studied patients at several hospitals in Australia and found that handgrip strength correlated with nutritional status, which was measured using a Patient-Generated Subjective Global Assessment (PG-SGA) questionnaire, and these factors can be used as nutritional status predictors and nutritional status changes. Most subjects were observed prospectively for 3 weeks. Changes in handgrip strength correlated with nutritional status changes. [31]

Our study found no significant discrepancy between the two studied groups regarding CML ($p=0.390$). the mean of CML for the cases group was 62.72 ± 12.89 and for the control group was 62.33 ± 7.92.

In contradiction to our finding Ren et al found that serum AGE levels were significantly increased according to the frailty status and inversely associated with physical performance and physical activity. [32]

Also, Semba et al found that high levels of AGE were significantly associated with slowness and weight loss. These findings were consistent with Whitson et al. findings.

Whitson et al found a significant cross-sectional association between CML and physical activity, exhaustion, and muscle strength as components of physical frailty among men. [33,34]

A cohort study of 559 elderly women (≥ 65 years old) in the United States has found an inverse relationship between blood CML level and grip strength. [35] Furthermore, the Nagahama Cohort Study in Japan, which enrolled 9203 middle-aged people (average age 57.8 years), has shown that the more advanced the accumulation of skin AGEs the lower the muscle mass and grip strength. [36]

Conclusion

CML showed no significant correlation with MMSE, ADLs, and eGFR. As regarded univariate and multivariant linear regression analysis for the parameters affecting CML, age is the most significant independent variable of CML in both studied groups. TUG test and handgrip strength are cofounders their scores changed according to CML but had no significant effect on linear regression. CML showed a positive correlation with age and TUG test in both groups and with MNA in group II. CML also showed a negative correlation with handgrip strength. From the last two correlations, we concluded that decreasing levels of AGEs will improve both TUG and handgrip strength and improve motor dysfunction in the elderly.

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