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Association between Sarcopenia, Oxidative Stress and Inflammatory Biomarkers in the Elderly Diabetic Populations

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ABSTRACT

Background: Diabetes mellitus and other chronic medical conditions are associated with ageing. Sarcopenia is also affected elderly populations. The role of inflammation and oxidative stress in both conditions is poorly investigated.

The aim of the work: The current work was designed to examine the possible association of oxidative stress and inflammation in sarcopenia with diabetes in elderly subjects.

Patients and Methods: Eighty patients older than 65 years of age with diabetes were included in the current work. They were categorized into two equal groups; the first for sarcopenia with diabetes and the second for diabetics without sarcopenia. All were clinically evaluated, in addition to laboratory workup to check diabetes and oxidant-antioxidant system besides some of the inflammatory markers.

Results: No significant differences were recognized regarding patient demographics, associated comorbid conditions or duration of diabetes. There was significant reduction of BMI, hip circumference, skeletal muscle mass and gait speed in the sarcopenic than the non-sarcopenic group [25.51 ± 0.67, 98.15 ± 3.97, 7.07 ± 0.83 and 0.68 ± 0.11 vs. 27.07 ± 1.31, 105.53 ± 4.59, 9.44 ± 1.01 and 0.98 ± 0.12, successively]. There was significant increase of CRP, xanthine oxidase, in the sarcopenic than non-sarcopenic groups [5.15 ± 0.72, 0.532 ± 0.109 vs. 3.03 ± 0.78, 0.344 ± 0.063, respectively]. However, plasma glutathione was significantly reduced in sarcopenic than non-sarcopenic groups [0.190±0.057 vs. 0.233±0.047, respectively]. Finally, plasma xanthine oxidase, glutathione, CRP, BMI and absolute skeletal muscle mass are significantly associated with the development of sarcopenia.

Conclusion: Oxidative stress and disturbance of oxidant-antioxidant systems seems to play a crucial role in sarcopenia associated with diabetes mellitus in elderly subjects.

Keywords: Elderly; Oxidative stress; Oxygen Radicals; Diabetes Mellitus; Sarcopenia.

INTRODUCTION

There is a growing of aging populations [older than 65 years of age] all over the world due to increased life expectancy with advancement of health care. This increase in aging populations is associated with a gradual increase of old age-related disease [e.g., neurodegenerative, cardiovascular, metabolic, osteoporosis and sarcopenia]. This adds burden on the healthcare system, economy and had social deleterious effects. It is crucial to understand the pathophysiology of aging process and its related chronic disease to develop effective and economic therapies [1-4].

Sarcopenia is best described as a disease of ageing or as a geriatric syndrome. It is characterized by a progressive, age-related loss of muscle mass and its strength. This associated with an increased risk of physical disability, falls, loss of independence and poor quality of life [5-7].

The pathophysiology of sarcopenia is poorly understood. However, several mechanisms are suggested to be included in the development of the condition. These include reduced regeneration of muscle cells, increased apoptosis, alterations in mitochondrial function, reduced anabolic hormones, metabolic disturbances [e.g., of lipids and proteins], disturbed Redox equilibrium and increased production of myokines [8-10].

Oxidative stress seems to play a significant role in the pathogenesis of sarcopenia due to its effects on mitochondria with induced apoptosis in myofibrils [11-13].

Type 2 diabetes mellitus [T2DM] is a major health issue of the ageing populations. It is associated with muscular changes [e.g., reduced strength and poor muscle quality]. It may contribute to aging process acceleration and shares in the development of age-related sarcopenia. Oxidative stress seems to play a significant role in pathogenesis of diabetes mellitus as well as in sarcopenia [14].

The risk of diabetes in sarcopenia is high. However, mechanism and effects of such association is poorly understood. In addition, factors associated with sarcopenia in diabetic patients are not well-studied. Hence, the current work was designed to examine the possible association of oxidative stress and inflammation in sarcopenia with diabetes.

PATIENTS AND METHODS

This was a cross sectional comparative study. Patients were selected from Geriatric Medicine, Rheumatology and Internal Medicine Departments [Al-Azhar University Hospitals]. This was completed from January 2021 to January 2024. A final sample of 80 elderly subjects with diabetes associated with sarcopenia or not were included. They were subdivided into two groups, the first included 40 sarcopenic patients and the other 40 non-sarcopenic patients.

To be included in the study, patient must be older than 65 years of age, with a confirmed diagnosis of diabetes mellitus, type 2 and his/her body mass index [BMI] lower than 30 kg/m^2 [i.e., non-obese]. On the extreme side, the exclusion criteria were the presence of acute disease, advance liver or renal failure, active cancers or cachexia, using pacemakers, had dementia, bed-ridden and those who use anti-oxidant supplementations.

Ethical considerations: The study protocol was approved by the local research and ethics committee, Damietta Faculty of Medicine, Al-Azhar University. In addition the study was performed in accordance with Helsinki codes of research conduct and reporting. Each patient signed a written informed consent and his/her rights were guaranteed. Collected data was used only to express results of the research.

Methods

First of all, a comprehensive clinical assessment was performed. This included history taking and physical examination. The demographic data were collected and documented. In addition, the duration of diabetes was inquired and associated co-morbid chronic disease conditions were recognized and documented. The total number of drugs [for diabetes and for any other condition] was recognized, especially of the last year before inclusion in the study.

For each patient, anthropometric measurements were documented. It included the height, weight and body mass index [BMI] was calculated from the equation [BMI= weight [kg] divided by squared height [m]. in addition, waist and hip circumferences were measured. The waist circumference was measured at the midpoint between iliac bone and the lower rip, while hip circumference was measured at the widest point on the side of the hip [15].

Diagnosis of Sarcopenia: Sarcopenia was assessed according to the European Working Group on Sarcopenia in Older People [EWGSOP]

criteria. The presence of both low muscle mass and low muscle function [strength or performance] was used to diagnose sarcopenia [16]. The gait speed was determined by the four meter gait speed test, while the participant walked at his/him usual speed. The 4 meters were marked on the floor, and the time was measured by a digital stopwatch. Values ≤ 0.8 m/s denoting the reduced gait speed. In addition, the hand grip strength < 30 kg in men and < 20 kg for women was set as the lower hand grip strength. It was measured by a handheld digital dynamometer [TKKI 5101, Tekei, Japan]. Two measurements for the dominant hand were recorded. The highest value was used in statistical analysis. A bioelectrical impedance analysis used to assess the skeletal muscle mass by Quadscan 4000 body composition analyzer. It was calculated from the following equation: "Skeletal muscle mass [kg]= [height^2 [cm] / BIA resistance [X0.401] + [gender X 0.825] + [age [years] X – 0.071] + 5.102 [for gender, female = 0, male = 1]". Then the following equation was used to calculate absolute skeletal muscle mass. "Absolute muscle mass = skeletal muscle mass [kg] / height^2 [m^2]". Values < 8.87 and 6.42 kg/m^2 for males and females, respectively, was used to define low skeletal muscle mass [16].

Laboratory workup included the following: hemoglobin concentration, urea and creatinine, serum uric acid, glycated hemoglobin and IL-6, IL-8, tumor necrosis factor-alpha and C-reactive protein [CRP] levels. In addition, the oxidative stress markers in the serum were calculated. It included Malondialdehyde [MDA] level and Xanthine oxidase [XO] enzyme as oxidant parameters, while glutathione [GSH] was anti-oxidant indicator.

For oxidative and antioxidant indicators, 10 ml of venous blood were drawn from antecubital vein, 5 on heparin tubes [for oxidant-antioxidant indicators] and 5 ml on non-heparinized tubes [for inflammatory markers]. Then, the sample was centrifuged to separate plasma [from heparin tubes] or serum from dry tubes. Collected serum and plasma were kept in – 80 °C till the time of analysis. MDA was measured spectorophotometrically at absorbance band of 532 nm for the pink complex of MDA and thiobarbituric acid, as described elsewhere. In addition, the GSH activity was measured by spectrophotometric way, as glutathione with hydrogen peroxide prevent conversion of NADPH to oxidized glutathione based on the concentration of oxidized glutathione formed [15].

CRP levels were measured by an immune-nephelometric method using available kits [Behring N Latex C-Reactive Protein Mono-Analyzer; Behring Diagnostic, Marburg, Germany] in the clinical pathology department. "Briefly, polystyrene particles coated with monoclonal antibodies specific to human CRP are aggregated when mixed with samples containing CRP". A beam of light passed in the sample was scattered by aggregates. The scattered light intensity is proportional to the concentration of CRP in the sample, and concentrations were determined by comparison with a standard of a known concentration [17].

Inflammation biomarkers [TNF-α, IL-6 and IL-8] have been measured by a sandwich ELISA, according to the manufacturer guidelines [Thermo Fisher Scientific / Invitrogen [Carlsbad, CA, USA] specific for human cytokines].

Statistical analysis

The collected data were coded and entered to personal computer on an excel sheet. Then, transferred to the statistical analysis of social sciences [SPSS], version 22 [IBM Inc., Armonk, USA] running on the widows-based personal computer. The normally distributed continuous variables were presented by their mean and standard deviation [SD], while median and interquartile range were used to express non-normally distributed data. Qualitative data were summarized by their relative frequency and percentages. Groups were compared by suitable tests. For example, independent samples "t" test for comparison between two means, while Chi square test was used to examine the association between two qualitative variables. Multiple regression analysis was used to test predictors for development of sarcopenia. All significant variables in single regression were fed for the multiple regression analysis. P value < 0.05 was considered significant.

RESULTS

In the current work, 80 patients older than 65 years of age with diabetes were included. They were of two groups, 40 had sarcopenia and the other 40 are non-sarcopenic. The majority of subjects were females with no significant difference between sarcopenic and non-sarcopenic groups regarding age or gender. In addition, both groups were comparable [there was no significant differences] regarding associated comorbid conditions. The diabetes duration ranged between 4 to 22 years, with no significant differences. Finally, no significant differences were found regarding number of drugs [Table 1].

In the current work, the non-sarcopenic group, BMI ranged between 23.53 to 29.37 kg/m^2, while hip circumference ranged between 91 and 120 cm.

The absolute muscle mass ranged between 5.8 to 11.80 kg/m^2 and finally gait speed ranged between 0.50 to 1.30 m/s. There was significant decrease of BMI, hip circumference, skeletal muscle mass and gait speed in the sarcopenic than the non-sarcopenic group. However, the hand grip strength did no differ significantly between groups [Table 2].

Data of laboratory workup reveled that, there was significant increase of CRP in the sarcopenic than non-sarcopenic groups [5.15±0.72 vs 3.03 ± 0.78 mg/dl, respectively]. In addition, there was significant increase of xanthine oxidase [XO] in the sarcopenic than non-sarcopenic group [0.532 ± 0.109 vs. 0.344 ± 0.063]. However, plasma GSH-P was significantly reduced in sarcopenic than non-sarcopenic groups [0.190 ± 0.057 vs. 0.233 ± 0.047, respectively] [Table 3].

Running multiple linear regression analysis to determine factors associated with development of sarcopenia in the elderly diabetic populations showed that, plasma xanthine oxidase, glutathione, CRP, BMI and absolute skeletal muscle mass are significantly associated with the development of sarcopenia [Table 4].

Table [1]: Comparison between sarcopenic and non-sarcopenic groups regarding patient demographics, associated comorbid conditions and number of drugs

Variable	Measures	Sarcopenic [n=40]	Non-sarcopenic [n=40]	Test	P
Age [years]	Mean±SD	74.33±5.55	72.70±3.55	1.56	0.123
	Min.- Max.	66-85	67- 79		
Gender [n, %]	Male	13 [32.5%]	14 [35.0%]	0.07	0.81
	Female	27 [67.5%]	26 [65.0%]		
Hypertension	[n,%]	24 [60.0%]	28 [70.0%]	0.879	0.35
Cardiovascular disease	[n,%]	12 [30.0%]	10 [25.0%]	0.25	0.61
Cerebrovascular disease	[n,%]	6 [15.0%]	4 [10.0%]	0.45	0.50
Dyslipidemia	[n,%]	12 [30.0%]	14 [35.0%]	0.23	0.63
Psychiatric disorder	[n,%]	16 [40.0%]	12 [30.0%]	0.879	0.348
Diabetes duration [years]	Median [IQR]	9 [7]	9 [4]	1.03	0.305
	Min. – Max.	4- 20	4- 22		
Number of antidiabetic drugs	Mean±SD	2.45±0.50	2.50±0.51	0.44	0.66
	Min. – Max.	2-3	2 -3		
Number of other drugs	Mean±SD	3.32±1.56	3.53±1.28	0.63	0.53
	Min. – Max.	0-6	1- 6		
Number of all drugs	Mean±SD	5.78±1.67	6.03±1.51	0.70	0.48
	Min. – Max.	3-9	3-9		

Table [2]: Comparison between sarcopenic and non-sarcopenic groups regarding components of sarcopenia

Variable	Measures	Sarcopenic [n=40]	Non-sarcopenic [n=40]	Test	P
BMI [kg/m^2]	Mean±SD	25.51±0.67	27.07±1.31	**6.71**	**<0.001***
	Min.- Max.	23.53- 26.95	24.86-29.37		
Hip circumference [cm]	Mean±SD	98.15±3.97	105.53±4.59	**7.68**	**<0.001***
	Min.- Max.	91- 107	99- 120		
Absolute Skeletal muscle mass [kg/m^2]	Mean±SD	7.07±0.83	9.44±1.01	**11.54**	**<0.001***
	Min.- Max.	5.8-9.20	7.40-11.80		
Hand grip strength [kg]	Mean±SD	18.43±1.85	19.25±2.75	1.57	0.120
	Min.- Max.	15-22	15-29		
Gait speed [m/s]	Mean±SD	0.68±0.11	0.98±0.12	**11.34**	**<0.001***
	Min.- Max.	0.50- 0.8	0.90 - 1.30		

Table [3]: Laboratory workup in the sarcopenic and non-sarcopenic groups

Variable	Sarcopenic [n=40]	Non-sarcopenic [n=40]	Test	P
Hemoglobin [g/dl]	11.03±0.51	11.18±0.49	1.32	0.19
HbA1c	6.14±0.27	6.08±0.28	1.01	0.31
Fasting blood sugar	123.65±3.05	122.60±2.00	1.82	0.07
Serum uric acid	4.82±0.56	4.99±0.67	1.21	0.23
CRP [mg/dl]	5.15±0.72	3.03±0.78	**12.62**	**<0.001***
TNF-α [pg/ml]	26.93±2.22	26.68±2.13	0.513	0.605
IL-6 [pg/ml]	21.65±2.24	20.13±5.57	1.61	0.11
IL-8 [pg/ml]	12.88±1.79	13.23±2.34	0.75	0.45
Plasma MDA [nmol/g protein]	9.23±0.66	9.44±0.59	1.48	0.14
Plasma GSH [nmol/g protein]	0.190±0.057	0.233±0.047	**3.72**	**<0.001***
Plasma XO [nmol/g protein]	0.532±0.109	0.344±0.063	**9.39**	**<0.001***

Table [4]: Linear regression analysis to determine predictors of sarcopenia

Model	Unstandardized Coefficients		Standardized Coefficients	Sig.
	B	Std. Error	Beta	
Plasma XO	-0.836	0.223	-0.215	<0.001*
GS	0.836	0.420	0.094	0.050*
CRP	-0.160	0.022	-0.415	<0.001*
BMI	0.092	0.023	0.238	<0.001*
Hip circumference	-0.003	0.006	-0.028	0.678
Absolute skeletal muscle mass	0.090	0.022	0.271	<0.001*

DISCUSSION

In the view point of the clinical practice, the early recognition of sarcopenia and associated risk factors and biological indicators is essential for the early treatment intervention to minimize the impact of the disease and improve quality of life in elderly [3]. The current work was designed to examine the association between oxidative stress and inflammatory biomarkers in diabetic patients with sarcopenia. The results of the current study, showed that, sarcopenia was associated with lower BMI, hip circumference, absolute skeletal muscle mass, and slow gait speed. In addition, sarcopenia was linked to lower concentrations of serum uric acid, higher CRP, higher xanthine oxidase and lower plasma glutathione. However, plasma MDA did not differ significantly between groups. With multiple regression, plasma xanthine oxidase, glutathione, body mass index and absolute skeletal muscle mass remains significant.

In sarcopenia, oxidative stress seems to share in its pathophysiology by increased oxidation of proteins and cholesterols with formation of oxysterols and reactive oxygen species [oxygen radicals] which play a central role in the process of aging and age-related chronic diseases [e.g., neurodegenerative, cardiovascular and musculo-skeletal conditions] [18-20]. Oxidative stress by itself increased with aging and is an inflammatory inducer. In addition, ageing predisposes the skeletal muscle to the effects of oxidative stress. Thus, it may contribute to the development of sarcopenia [21, 22].

Coming to the presence of diabetes with sarcopenia, previous studies showed bidirectional relationship [23, 24]. Factors lead to increased sarcopenia in diabetes include impaired synthesis of proteins, insulin resistance and oxidative stress [25, 26]. On the other side, sarcopenia may contribute to the T2D development and progression by changing of glucose disposal. It is attributed to the loss of muscle mass, increased inflammation and oxidative stress, and muscular adipose tissue accumulation [27]. However, previous studies evaluating the association of oxidative stress with sarcopenia as a complication of diabetes showed inconsistent results [26, 28].

The current work is consistent with **Baharirad *et al.*** [29] who reported significant differences between sarcopenic and non-sarcopenic patients regarding body mass index, and hip circumference. However, they included younger patients than the current one. In addition, the same authors reported significantly reduced muscle mass in sarcopenia with diabetes than non-sarcopenic diabetic subjects.

Sugimoto *et al.* [26] reported that, among patients with T2D and sarcopenia, the poor glycemic control was associated with low skeletal mass index. This could not be detected in the current work, where there were no significant differences between both

groups regarding glycated hemoglobin A1c. This may be due to strict control of diabetes among our patients as noted from the number of anti-diabetic drugs, patients stick to in the last year before the study. In addition, different inclusion criteria may play a role.

Our results are supported by **Perry *et al.*** [30] who reported that T2DM is associated with mild form of muscle atrophy in adults of middle age. This intensified in old age leading to reduction in skeletal muscle mass and muscular dysfunction [weakness] with development of sarcopenia. This reflected in the current work by the reduction of absolute skeletal muscle mass in sarcopenic diabetic patients than those who had diabetes without sarcopenia.

In addition, the current work is consistent with previous studies showed that aging is associated with reduction of the antioxidant capacity. Diabetes at the same time increased the production of reactive oxygen species by different mechanisms [e.g., changes in lipid metabolism, increased production of glycation end products, insulin resistance, inflammatory changes and mitochondrial dysfunction] [31, 32]. This reflected in the current work by significant differences between groups regarding GSH, XO and CRP. These factors remain significant in development of sarcopenia in addition, to body mass index and absolute skeletal muscle mass.

The current study had some limitations: the first is the small number of patients. In addition, the cross-sectional design just explores the association, but the causal relationship could not be estimated. However, it is one of the few studies dealing with the oxidative stress in patients who had sarcopenia with diabetes.

Conclusion: Diabetes mellitus seems to have bidirectional relationship with sarcopenia. Both conditions aggravate each other and this seems to be due to oxidative stress which was associated with both conditions. However, future large-scale studies are recommended. In addition, the role of antioxidant substances must be investigated in the future studies.

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