Relationship of SOD-1 Activity in Metabolic Syndrome and/or Frailty Elderly Individuals

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Posted Date: 6 August 2024

doi: 10.20944/preprints202408.0380.v1

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Article

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Abstract: Introduction: Although aging is a natural phenomenon, in recent years it has accelerated. One key factor implicated in the aging process is oxidative stress. Oxidative stress play also role in frailty (frail) and metabolic syndrome (MetS). Methods: 66 elderly persons (65 years old and older) with no acute or severe chronic disorders were assessed: waist circumference (WC), arterial blood pressure, glycemia, glycated hemoglobin (HbA1c), plasma lipids and activity of erythrocyte superoxide dismutase (SOD-1). Patients were classified as NonMetS-Nonfrail (n=19), NonMetS-frail (n=20), MetS-Nonfrail (n=17), and MetS-frail (n=10). Results: There were no significant differences in superoxide dismutase activity among investigated elderly groups. However, the data suggests that MetS individuals, both frail and nonfrail, have higher risk factors for cardiovascular disease compared to NonMetS individuals. The correlations analyses of SOD-1 and other metabolic indices suggest that SOD-1 levels may be influenced by age, total cholesterol, HDL cholesterol, and fasting glucose levels in certain groups of seniors. Conclusions: Aging is associated with decreased antioxidant enzyme SOD-1 activity with glucose alteration in frailty syndrome as well as with lipids disturbances in metabolic syndrome.

Keywords: aging; metabolic syndrome; frailty syndrome; SOD-1

1. Introduction

Due to increasing human lifespan, advancements in civilization, and improvements in the quality of life worldwide, the percentage of people in the post-productive age group is steadily rising [1]. Although aging is a natural phenomenon, in recent years it has accelerated significantly compared to the birth rate and the number of people in the working age group [2]. The percentage of elderly individuals globally is projected to double by 2050, with developed countries like Japan and EU showing high numbers [3–5]. In Poland, the proportion of working age group is projected to decrease by 2050, with implications on healthcare services [6].

The aging process of the body contributes to an increase in health issues, chronic diseases, and disabilities. Studies on the health status of individuals aged 60 and above reveal that 50% of them suffer from three or more metabolic disorders and chronic diseases, forming a unique health profile for each patient [7–10]. Common disorders include hyperglycemia, dyslipidemia and hypertension which characterize metabolic syndrome [11]. However, disease symptoms in old age often present atypically and nonspecifically, making early detection and treatment challenging [12]. Age-related health problems, alongside a decline in bodily reserves, can lead to multiple organ dysfunctions. These dysfunctions result in functional changes that reduce the operational capacities of all organs and systems, giving rise to geriatric syndromes such as frailty syndrome, heightened fall risks, increased mortality rates, nutrition disorders, cognitive impairments, and depression [13–15].

The frailty syndrome is a clinical description of multisystem changes related to the aging process and is often mistakenly equated with multimorbidity or disability, which may only be an underlying cause. The syndrome is described as a complex, multidimensional state marked by a reduced

 doi:10.20944/preprints202408.0380.v1

physiological reserve and decreased resilience to stressors due to diminished organ and system functioning [16,17].

Despite aging is a natural process characterized by a gradual decline in physiological functions the process increases susceptibility to diseases. One key factor implicated in the aging process is oxidative stress, resulting from an imbalance between reactive oxygen species (ROS) production and the body's detoxification ability [18,19].

Reactive oxygen species (ROS) and free radicals are important components of cellular metabolism, playing roles in both normal physiological functions and the pathogenesis of various diseases. The following are the primary sources of ROS and free radicals:

- Mitochondrial Electron Transport Chain: Within mitochondria, the oxidative phosphorylation involves electron transfer that can produce ROS such as superoxide anion ($O2^{\bullet-}$) and hydrogen peroxide (H_2O_2). Imperfections in the electron transport system may increase ROS production.
- Reactions Catalyzed by Oxidoreductases: Oxidoreductase enzymes participate in redox reactions during metabolic processes, which can inadvertently produce ROS as metabolic byproducts, playing a role in regular cellular metabolism.
- Oxidation of Low-Molecular-Weight Compounds (RH2): Various compounds such as amino acids, thiols, and reducing sugars can undergo oxidation, leading to the production of ROS, including superoxide anions and free radicals derived from oxidized compounds (•RH).
- Peroxisomes: are organelles that contain enzymes, such as xanthine oxidase, responsible for purine metabolism and the oxidation of fatty acids, which also generates ROS.
- Phagocyte Activation: Neutrophils and other phagocytic cells produce ROS, such as superoxide anion and hydrogen peroxide, in response to infections via NADPH oxidase. This process is crucial for their bactericidal activity, and the Fenton reaction (production of hydroxyl radical in the presence of Fe2+ ions) can further increase the amount of ROS [20,21].

All these sources generate ROS that are crucial for various biological processes, but their excess can lead to oxidative stress and cellular damage. Therefore regulation of reactive oxygen species levels is crucial for maintaining balance in the organism. What is more reports have supported the role of oxidative stress in the development of aging processes in human organism [22].

The first line of protection features enzymatic antioxidants that transform already existing ROS into less harmful entities, along with proteins that restrict the availability of transition metal ions for Fenton reactions, thereby preventing the generation of additional ROS. Studies have revealed interesting links between antioxidant enzymatic defense capacity and aging, showing a decrease in the crucial activity of antioxidative enzymes with age [23]. The enzyme, such as superoxide dismutase 1 (SOD-1), is fundamental component of the intracellular defense system. Superoxide dismutase 1 (SOD-1) plays a crucial role in protecting cells from oxidative stress by converting superoxide radicals into oxygen and hydrogen peroxide. Several studies have suggested that the decrease in SOD-1 activity may contribute to the aging process by increasing the accumulation of ROS and causing oxidative damage to cells and tissues [24].

The imbalance between pro-oxidative processes and the capabilities of antioxidant defense plays also a significant role in conditions such as diabetes, cardiovascular diseases, cancer, and inflammation. Studies conducted on patients like metabolic syndrome or ischemic heart disease — allow us to consider oxidative stress as a connecting element linking various directions of metabolic disturbances in the aforementioned lifestyle diseases [25]. Additionally, researches has shown that SOD-1 activity is reduced in frail individuals, which may contribute to the aging process and the development of age-related diseases [26,27]. This can lead to the development of age-related diseases such as neurodegenerative disorders, cancers and cardiovascular diseases. Furthermore, changes in the SOD-1 activity have been linked to metabolic syndrome – the metabolic disorders characterized

 doi:10.20944/preprints202408.0380.v1

by the obesity, hypertension, hyperglycemia and dyslipidemia [28]. This suggests that impaired SOD-1 function may also play a role in the pathogenesis of age-related diseases.

Thus, we have studied an activity of superoxide dismutase-1 with regard to metabolic syndrome and/or frailty syndrome diagnosis in elderly population.

2. Materials and Methods

The study was performed in accordance with the Declaration of Helsinki of 1975 for Human Research revised in 2013. The Bioethics Committee of Medical University of Silesia in Katowice (statement number: PCN/0022/KB1/75/I/20/21) approved the study protocol; All participants signed consent, after they had been informed.

Inclusion criteria

541 elderly Caucasian individuals aged ≥ 65 years old who did not have any diagnosed acute and/or chronic disorders, were not taking medication, were not on any special diets or supplements were invited to the study.

Exclusion criteria

Individuals with a history of certain medical conditions such as cardiovascular diseases, diabetes, cancers, inflammatory disorders, liver failure and impaired kidney function (eGFR lower than 60 mL/min/1.73m2) were not part of the study. Additionally, participants who were smokers and alcohol drinkers (former or current) were also excluded from the study. Furtermore those elderly who were taking any medications such as for elevated blood pressure, hypertriglicerydemia, low HDL-cholesterol, antihyperglycemic or antioxidants (including OTC vitamins and supplements were excluded.

Clinical examination

Following a medical history, physical examination was done, which included measuring waist circumference (WC) at the smallest girth around the navel using a non-elastic tape (recorded to the nearest 0.1 cm) and blood pressure (BP). The systolic (SBP) and diastolic (DBP) blood pressure were measured as per the guidelines of the European Society of Hypertension [29]. The average of blood pressure readings was calculated and utilized in all the analyses.

Frailty diagnosis

Clinical Frailty Scale (CFS) was used to determine if elderly patients were or not frail [30] The components of this syndrome: unintentional weight loss, strength reduction, slowness (walking speed reduction), low physical activity and fatigue were of authors interests. The patients were considered frail older people who scored for three or more components and non frail those who score two or less of the components described.

Blood sampling and biochemical analysis

The test samples, serum and heparin plasma, were obtained from patients following current guidelines for patient preparation and sample collection. Finally 66 individuals were investigated fasting blood samples. The samples were collected into vacutainer tubes, in the morning after at least 12 h of fasting.

Glucose and lipids measurements.

The concentrations of glucose, total cholesterol (T-C), HDL cholesterol (HDL-C), LDL cholesterol (LDL-C), and triglycerides (TG) were measured in fresh blood samples on the automatic biochemistry analyzer Dimension EXL (Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA) with enzymatic methods. Low density lipoproteins (LDL) was calculated using Friedewald formula.

The activity of Red Blood Cell Cu-, Zn-Superoxide Dismutase (SOD-1).

The method uses xanthine and xanthine oxidase to produce superoxide radicals, which then interact with 2-(4-iodophenyl)-3-(4-nitrophenol)-5-phenyltetrazolium chloride (INT) to create a red formazan dye. The activity of SOD-1 is determined by measuring the extent of inhibition in this reaction, with kinetics measured at 505 nm. The intra-assay and inter-assay coefficients of variation for SOD-1 were 2.0% and 3.9%, respectively.

Metabolic Syndrome

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The metabolic syndrome was identified as recommended by the NCEP ATPIII [31], which considers the combination of at least three components: abdominal obesity (measured by waist circumference, >102cm for men and >88cm for women); blood pressure ≥130mmHg (systolic) or ≥85mmHg (diastolic); triglycerides ≥150mg/dl, HDL cholesterol <40mg/dl for men and <50mg/dl for women, fasting glucose ≥100mg/dl. The presence of three out of five abnormal findings constituted a diagnosis of the MetS and allowed to divide groups into: MetS and NonMetS.

Group analysed in the study.

Based on metabolic syndrome diagnosis and frailty scale finally four gropus were considered: NonMetS-Nonfrail (n=19), NonMetS-frail (n=20), MetS-Nonfrail (n=17), and MetS-frail (n=10)

Statistical analysis

Statistical analysis was calculated by Statistica (version 13.3) for Windows. The Shapiro-Wilk test was used to check the normality of distributions of variables in the 66 elderly individuals (all elderly) and metabolic syndrome and frailty syndrome elderly groups. Because most of the data had a non-normal distribution, data was shown as medians, lower, and upper quartiles and a nonparametric Kruskal-Wallis test with post hoc analysis of multiple comparisons were done. Correlations between the studied variables were assessed using Spearman's R coefficient. P value less than 0.05 was consideredas significant.

3. Results

The data provided in table 1 is a comparison of various clinical and biochemical parameters among different elderly groups of individuals categorized as NonMetS- Nonfrail (0), NonMetS-frail (1), MetS-Nonfrail (2), and MetS-frail (3). There were no significant differences in diastolic blood pressure, mean glucose concentration, glycated hemoglobin levels, and superoxide dismutase activity among investigated groups. Overall, the data suggests that MetS individuals, both frail and nonfrail, have higher risk factors for cardiovascular disease compared to NonMetS individuals.

MetS-Nonfrail elderly individuals had significantly higher waist circumference, systolic blood pressure, fasting glucose concentration and significantly worst lipid profile compared to the other groups. However, post-hoc analyses showed only significant results in MetS-Nonfrail gropu for waist circumference (MetS-Nonfrail vs NonMetS-Nonfrail p=0.04 and MetS-Nonfrail vs. NonMetS-frail p=0.00003), systolic blood pressure (MetS-Nonfrail vs NonMetS-Nonfrail p=0.002), fasting glucose concentration (MetS-Nonfrail vs NonMetS-Nonfrail p=0.02 and MetS-Nonfrail vs. NonMetS-frail p=0.001), total cholesterol (MetS-Nonfrail vs MetS-frail p=0.03), HDL-cholesterol (MetS-Nonfrail vs MetS-frail p=0.02). The diferencess may be due to definition of the metabolic syndrome.

NonMetS-Nonfrail individuals had the best HDL cholesterol level compared to the other groups and post hoc analysis showed the highest difference with NonMetS-frail group (p=0.002) and MetS-frail elderly patients (p=0.0001).

Table 1. Characteristics of the studied groups.

	NonMetS-Nonfrail n=19	NonMetS-frail n=20	MetS-Nonfrail n=17	MetS-frail n=10	p
Age [years]	70.0 (66.0–75.0)	81.0 (73.0-88.5)	71.0 (68.0-74.0)	71.5 (68.0-78.0)	0.004
Waist [cm]	83.0 (78.0-92.0)	80.0 (71.0–86.5)	95.0 (92.0-102.0)	80.0 (74.0-98.0)	0.0001
SBP [mmHg]	130.0 (125.0–140.0)	122.5 (107.5 -140.0)	140.0 (135.0-150.0)	142.5 (140.0-145.0)	0.001
DBP [mmHg]	80.0	77.5	85.0	77.5	>0.05

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	(70.0–90.0)	(67.5–80.0)	(80.0-85.0)	(70.0-90.0)	
G 0′ [mg/dl]	93.0 (90.4–97.5)	89.1 (86.0–101.0)	111.0 (103.2-115.2)	125.2 (114.8-149.0)	0.0000
MeanG [mg/dl]	117.0 (111.0-123.0)	117.0 (108.0-131.0)	123.0 (114.0-131.0)	126.0 (108.0-126.0)	>0.05
HbA_{1c} [%]	5.7 (5.5–5.9)	5.7 (5.4–6.2)	5.9 (5.6-6.2)	6.0 (5.4-6.0)	>0.05
TC [mg/dl]	200.0 (185.0-222.0)	164.5 (125.5-184.0)	186.0 (160.0-201.0)	133.5 (116.0-151.0)	0.0000
TG [mg/dl]	82.0 (70.0-120.0)	95.0 (70.0-133.0)	92.0 (70.0-182.0)	148.5 (116.0-188.0)	>0.05
HDL-C [mg/dl]	66.7 (59.2-71.4)	45.5 (39.0-50.8)	54.0 (45.0-65.8)	27.0 (24.1-37.0)	0.0000
LDL-C [mg/dl]	116.0 (99.6-134.8)	78.0 (62.6-113.2)	107.6 (90.0-118.7)	74.4 (70.0-88.0)	0.003
SOD-1 [U/gHGB]	1202.8 (1002.6-1622.7)	1067.2 (759.1-1496.5)	919.8 (809.7-1166.6)	1270.3 (1121.0-1407.4)	>0.05

SBP – systolic blood pressure, DBP – diastolic blood pressure, G0′ – fasting glucose, Mean G – mean glucose concentration, HbA_{1c} – glycated haemoglobin, T-C – total cholesterol, TG - triacylglycerols, HDL-C - high density lipoproteins cholesterol, LDL-C - low density lipoproteins cholesterol, SOD-1 – superoxide dismutase

A study examining the correlations between SOD-1 activity and various factors in the entire group of seniors, no statistically significant correlation was found for SOD-1. In group NonMetS-Nonfrail SOD-1 was negatively correlated with age, meaning the older the age, the lower the SOD-1 ($r=-0.6293$; $p<0.05$). In group NonMetS-frail SOD-1 was negatively correlated with TC ($r=-0.4527$, $p<0.05$) and HDL-C ($r=-0.4586$; $p<0.05$). In group MetS-Nonfrail, no significant correlations were found for SOD-1. In group MetS-frail SOD-1 was strongly negatively correlated with fasting glucose ($r=-0.8426$, $p<0.05$). The findings suggest that SOD-1 levels may be influenced by age, total cholesterol, HDL cholesterol, and fasting glucose levels in certain groups of seniors.

4. Discussion

The SOD-1 is a crucial antioxidant enzyme in humans, that regulates the amount of superoxide anion in the cytosol — essential for normal cellular metabolism (regulating signaling pathways, combating pathogens) — but it also arises under the influence of pathological processes and external factors, limiting the potential formation of hydroxyl radicals from $\bullet O2^-$ [32]. With SOD-1 cells transform superoxide anion radicals into oxygen and hydrogen peroxide.

Decreased activity of the enzyme could lead to the build-up of hydrogen peroxide, potentially contributing to cellular aging [33]. Excess O_2^- production is seen in individuals who use to use etanol and/or smoke. However, research examining the activity of SOD in erythrocytes has produced varying outcomes: some studies found increased activity in individuals consuming alcohol/smoke, while others reported reduced levels in alcoholics, and a few observed no significant differences at all [34–36]. Thus to avoid interpretation problems with the results of SOD-1 activity, in our study, we only examined individuals who did not consume neither alcohol, nor smoke.

 doi:10.20944/preprints202408.0380.v1

The result of enzyme activity are not solely determined by the gene structure related to the quantity of the protein and its enzymatic role. Recently, we've have gained insight into epigenetic regulation, which encompasses changes in gene expression that do not involve DNA sequence. Epigenetics explains for the phenotypic variations that occur due to varying levels of gene expression in genetically identical cells [37,38].

To maintain the enzyme's full activity, Zn^{2+} ions are required and stabilize SOD-1, whereas Cu^{2+} ions are crucial for its catalytic (red-ox) activity [39] It was observed there was reduced SOD-1 activity and zinc concentration in obese men compared to a group of healthy, normal BMI persons [40]. There is evidence to suggest that SOD-1 activity may be affected by metabolic syndrome in elderly individuals [28]. Metabolic syndrome is a cluster of conditions that includes excess body fat around the waist, high blood pressure, elevated blood sugar and abnormal cholesterol levels. It is associated with chronic low-grade inflammation and oxidative stress, which can impact the activity of antioxidant enzymes such as SOD-1. In our elderly patients we did not found significant differences of SOD-1 among elderly metabolic and non metabolic syndrome populations. However, in those with metabolic syndrome who also were frail the SOD-1 activity was adversely corespond with fasting glucose sugseting the role of declining antioxidant capacity in the multiple syndroms. Furthermore, researchers found that patients with diabetes exhibited greater superoxide dismutase activity in erythrocytes compared to individuals without diabetes (including those with normal and abnormal fasting glucose levels) [41]. Jet, it was also found, in non-alcoholic fatty liver disease (NAFLD) with and without diabetes mellitus , SOD-1 activity was decreased [42].

Additionally, maintaining optimal activity of SOD-1 by staying active, adopting nutritous diet and incorporqting other healthy habits may lower the chance to develop metabolic syndrome and slow down the frailty [43]. Grygiel et al discovered a link between between high HDL-C levels and increased SOD-1 activity among postmenopausal obese women [44]. In our investigated NonMetS-Nonfrail elderly patients there were only age and SOD-1 association, while in those with metabolic syndrome and/or frailty, SOD-1 related to metabolic parameters. Furthermore in those with frailty syndrome SOD-1 was inversly related to HDL-cholesterol.

Dyslipidemia was found to play a role in the generation of oxidative stress in senior individuals, leading to reduced levels of HDL cholesterol [45]. The HDL particles has beneficial effect against atherosclerosis as well as with their capacity to induce insulin secretion [46]. There are inverse relationships between SOD activity and various cardiovascular markers such as pressure wave velocity, augmentation index, arterial stiffness index, pulse pressure, and HDL-cholesterol levels [47]. Our elderly frail and metabolic syndrome patients had dramatically low HDL-cholesterol level. Additionally, the correlation between fasting glucose and SOD-1 was highly negative indicating metabolic factors are related with antioxidants reduction. Yet, there has been little research on the relationship between SOD-1 and metabolic indices as HDL-cholesterol and glycemia, especially regarding metabolic and frailty syndromes in elderly poluupation, further investigation is needed to better understand the associations between these biomarker groups.

Strengths and limitations of the study: With a growing elderly population globally, it is increasingly important to address health concerns related to aging, particularly the connections between antioxidant defense, metabolic syndrome and frailty in older adults. However, the limited number of individuals in this study with both metabolic syndrome and frailty may reduce the statistical power of the findings and hinder the ability to generalize the results to the wider elderly population. Longitudinal studies may be necessary to determine whether changes in SOD-1 activity and metabolic factors truly affect one another over time.

5. Conclusions

The results of this study highlight the intricate relationship between superoxide dismutase 1, metabolic syndrome and/or frailty syndrome in the elderly population. Specifically, our results demonstrate that aging is accompanied by a significant decrease in the activity of the antioxidant enzyme superoxide dismutase-1 (SOD-1), with variations observed depending on the presence of metabolic syndrome and/or frailty syndrome. In particular, the correlation between SOD-1 activity

and fasting glucose levels in frail individuals highlights how metabolic dysregulation may exacerbate oxidative stress, potentially accelerating the aging process and contributing to the development of chronic conditions. What is more, the inverse relationship between SOD-1 activity and critical metabolic parameters such as total cholesterol and HDL-C raises important questions about the efficacy of existing therapeutic strategies to manage these conditions in the elderly.

Understanding the underlying mechanisms that lead to decreased SOD-1 activity and how these might be influenced by lifestyle factors (such as diet and physical activity) could open new avenues for preventive health strategies aimed at maintaining antioxidant defenses in older adults. Further research should focus on exploring the therapeutic potential of enhancing SOD-1 activity in this vulnerable population. By tackling both metabolic and oxidative stress challenges, we may promote healthier aging, enhance the quality of life for older adults, and ultimately reduce healthcare costs.

Author Contributions: Conceptualization, SDG; methodology, SDG and EW; software, SDG and MMW; validation, EW and MMW; formal analysis, SDG and EW; investigation, SDG, EW and EF; resources, SDG; data curation, SDG, EW, EF and MMW; writing—original draft preparation, SDG and EF; writing—review and editing, EW and MMW; visualization, SDG; supervision, MMW; project administration, SDG; funding acquisition, SDG. All authors have read and agreed to the published version of the manuscript.

Funding: The APC was funded by Medical University of Silesia, grant no.: PCN-1-210/N/2/0.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Conflicts of Interest: The authors declare no conflicts of interest.

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