Assessing the Intervention Factors of Oxidative Stress Among Elderly with Metabolic Syndrome: A Systematic Review and Meta-Analysis

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Abstract

Oxidative stress is a known pathogenesis in the development of chronic diseases including metabolic syndrome (MetS). Hence, interventions should be taken to prevent or treat MetS. A systematic review and meta-analysis were performed to estimate the interventions of oxidative stress in MetS among elderly. Hindawi, Google Scholar, PubMed and Science Direct were the databases used for this systematic review and meta-analysis. Furthermore, heterogeneity was observed using the I-squared (I²) statistic to determine the source of heterogeneity if the I²-value was >40%. After all the screening processes, 20 studies met the eligibility criteria and were analysed. Meta-analysis found that physical activity on MetS shows reduction in malondialdehyde (MDA) level (MD = -0.24, 95% CI (-0.43, -0.04), P = 0.02) and increased glutathione peroxidase (GPx) level (MD = 22.92, 95% CI (10.77, 35.08), P<0.001). On the other hand, supplement intervention on MetS increased the GPx level (MD = 805.51, 95% CI (123.23, 1487.80), P = 0.02). Dietary changes on MetS may decrease the MDA level (MD = -0.78, 95% CI (-1.02, -0.54), P<0.001) however, it also increases the total antioxidant capacity (TAC) level (MD = 0.16, 95% CI (0.88 to 0.24), P<0.001). Thus, this meta-analysis showed a positive effect of physical activity, supplementation and dietary intervention as a tool to decrease oxidative stress level in elderly with MetS.

Keywords: Oxidative stress, Metabolic syndrome, Elderly

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Introduction

Metabolic syndrome (MetS), which is known as syndrome X, is a constellation of metabolic abnormalities such as hypertension, dyslipidemia, obesity and insulin resistance \cite{1}. MetS is also known as a pathological condition that can increase an individual’s risk of developing chronic diseases such as type 2 diabetes mellitus, cardiovascular diseases and non-alcoholic fatty liver disease \cite{2}. The more metabolic abnormalities an individual possesses, the higher the risk of that individual to develop chronic disease. Globally, MetS was estimated to be around 20-25% among adults \cite{3}. In Malaysia, MetS affects approximately 25-40% of adults, with its risks being preeminent with advancing age \cite{4}. The risks of MetS upsurges as the age increases \cite{5}. Previous finding has stated that prevalence of MetS in Malaysia does not exceed 25% for population under the age of 40 years old while the prevalence rises up to 40% for population above the age of 40 years old \cite{6}. MetS occurs largely in the elderly as these individuals may face physiological changes such as decrease in muscle mass that can lead to decrease peripheral uptake and increasing intra-abdominal fats \cite{7}.

The generation of reactive oxygen species (ROS) is due to the excess of free fatty acids build up in adipocytes \cite{8}. Presence of high glucose or lipid concentration in the body can induce excessive production of energy substrates for metabolic pathways \cite{9}. For instance, when glucose or lipid level is high, mitochondria respond to this environment by increasing its biological activity and synthesis of its natural by-product known as the ROS \cite{10}. Oxidative damages is also one of the main pathogenesis associated with the development of metabolic syndrome. Hence, this study is conducted to focus on interventions that are taken to reduce the oxidative stress in order to decrease the risk of developing MetS and cognitive impairment. These findings are summarised to provide an up to-date systematic review and meta-analysis of possible intervention among the elderly individual.

Methodology

Search procedures

We searched Hindawi, Google Scholar, PubMed and Science Direct from 2000 to April 2021 using the following key words: (metabolic syndrome OR MetS) AND (elderly OR older adults), (intervention AND (metabolic syndrome OR MetS), (oxidative stress) AND (metabolic syndrome OR MetS) and (causes of oxidative stress). We reviewed the titles and abstract to select potential papers. Then, we manually searched the references and relevant articles for inclusion.

Inclusion criteria

Studies were included in our analysis if they met the following criteria: 1) studies showing intervention on elderly individuals aged 50 years old and above, meeting criteria of metabolic syndrome or with any individual components of metabolic syndrome such as insulin resistance, hypertension, obesity and dyslipidemia; 2) any types of interventions including physical activity, dietary intervention or supplementation; and 3) any analysis including retrospective experimental, cross-sectional and cohort studies that indicated the factors associated with oxidative stress in metabolic syndrome and elderly.

Exclusion criteria

Studies were excluded from our analysis if they met the following criteria: studies that were written other than English language and articles without English translation; 2) studies that were only present in form of abstract and without full texts; 3) studies that are literature reviews, qualitative studies, or protocols; 4) studies with publication dates before the year 2000; and 5) studies that reports different outcome measures that is not associated with oxidative stress.

Statistical Analysis

Assessment of risk of bias were conducted through Cochrane ‘Risk of bias’ assessment with the aid of Cochrane Review Manager 5 software \cite{11}. Meta-analysis was conducted using the Review Manager 5 software to examine the changes in biomarkers of oxidative stress among intervention and control group among elderly individuals with metabolic syndrome. Pooled results were calculated as mean differences (MD) in biomarkers level between control group and intervention group with 95% confidence intervals (95% CI) for continuous variables. The meta-analysis was performed using forest plots whereas the significance of the results was represented from 5% level of significance. The I² statistic was used to quantify the statistical heterogeneity. Cochrane guidance was used to interpret the I² statistic in which values below 39% resembles non crucial heterogeneity. This meta-analysis is only appropriate and accepts results that supports I² values below 39% whereas values of 40% and above are considered inappropriate for meta-analysis \cite{11}.

Results

The review processes

The process for selecting the relevant studies is summarised in Figure 1. In total, 110133 records were identified via database searches. After removing all duplicates, we scanned the titles and abstract of 1635 articles and further reviewed via full text. Out of these articles, only 42 articles met the inclusion criteria and were selected for this review.
A total of twelve studies were included in this meta-analysis. Three studies resembled physical activity intervention, three studies resembled dietary intervention and six studies showed supplementation as intervention.

a) Physical Intervention

The three studies measured oxidative stress biomarkers such as malondialdehyde (MDA), and antioxidant biomarkers such as total antioxidant capacity (TAC), superoxide dismutase (SOD), and glutathione peroxidase (GPx). As shown in Figure 2, evidence from forest plot of mean difference for MDA level between groups who received exercise intervention and control in post-intervention period suggested that there is no crucial heterogeneity among the studies (P = 0.39, I^2 = 0%). Hence, the meta-analysis is appropriate, and results can be taken into consideration. The results showed a significant difference between both groups whereby the results favor the intervention (MD = -0.24, 95% CI (-0.43, -0.04), P = 0.02).

Figure 2. Forest plot of mean difference of MDA level between intervention and control group during intervention period (Physical activity intervention).

Figure 3 shows the forest plot of mean difference for overall concentration of antioxidant biomarkers such as SOD and GPx between intervention and control group of all studies. Meta-analysis of subgroup SOD showed no significant difference between both groups (MD = 37.17, 95% CI (-45.76, 120.09), P = 0.38) while presenting no crucial heterogeneity (P = 0.26, I^2 = 25%). Meanwhile, meta-analysis of subgroup GPx showed significant differences between both groups of two studies (MD= 22.92, 95% CI (10.77, 35.08), P<0.001) whereby this result supported the intervention group. Evidence also suggested that there is no crucial heterogeneity presented in subgroup GPx forest plot (P = 0.27, I^2 = 18%). Based on the pooled result of all antioxidant biomarkers, significant difference of antioxidant biomarker levels was presented between intervention and control group (MD = 22.13, 95% CI (11.57, 32.68), P<0.001) while the result showed an increase in antioxidant biomarkers as seen in the intervention group. Moreover, no heterogeneity is presented in the pooled result of antioxidant biomarkers (P = 0.40, I^2 = 0%), hence, meta-analysis is presentable.
b) Dietary intervention

The three studies reported oxidative stress biomarkers such as MDA, and antioxidative biomarker such as TAC. Based on Figure 4, significant mean differences of MDA level were observed between both groups after the intervention period (MD = -0.78, 95% CI (-1.02, -0.54), P<0.001). The forest plot proved that intervention group was favoured as these groups had decreased MDA levels as compared to control group. Evidence of no crucial heterogeneity was also presented (P = 0.78, I² = 0%), thus, the result is presentable.

Figure 4. Forest plot of mean differences in MDA level between intervention and control group during intervention period. (Dietary changes intervention).

c) Supplement intervention

The six studies reported oxidative stress biomarkers such as MDA, and antioxidant biomarkers such as TAC, SOD, GPx and glutathione (GSH). Forest plot of mean differences for MDA level between both groups in and after intervention period was excluded for the result section due to high heterogeneity, hence the result is not presentable. Figure 6 shows the forest plot of pooled mean difference for the antioxidant biomarkers such as TAC, SOD and GPx level which was between intervention and control groups. The subgroup analysis of TAC and SOD level showed no significant mean differences between both groups (MD TAC = -0.03, 95% CI (-0.10, 0.05), P = 0.48; MD SOD= 0.05, 95% CI (-0.32, 0.42), P = 0.79) thus, the evidence suggested no crucial heterogeneity for both parameters. The subgroup analysis of GPx level suggested that there is significant difference between intervention and control group (MD = 805.51, 95% CI (123.23, 1487.80), P = 0.02) whereas the analysis supports that intervention group exhibits higher GPx concentration than control. Furthermore, there is no heterogeneity presented in this subgroup analysis (P = 0.67, I² = 0%). In general, the pooled mean differences were not significant between intervention and control group (MD = 0.16, 95% CI (0.08, 0.24), P < 0.001) whereby the result suggested that increased TAC level is favourable in intervention group. Moreover, no crucial heterogeneity is presented (P = 0.88, I² = 0%), thus, meta-analysis is appropriate.

Figure 6. Forest plot of mean difference of overall antioxidant biomarkers level between intervention and control groups during post-intervention period. (Supplement intervention)
## Table 1 Characteristics of included studies for intervention to reduce oxidative stress associated with MetS and its components in older adults.

<table>
<thead>
<tr>
<th>Study design</th>
<th>Number of participants involved (Age)</th>
<th>Method</th>
<th>Parameters of oxidative stress</th>
<th>Outcomes</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical activity</td>
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<tr>
<td>Quasi experimental study</td>
<td>150 MetS individuals (60-74 years old)</td>
<td>Tai Chi exercise training program (50 minutes/session) and (5 days/week) 6 months program 2 groups: control group and intervention group Fasting blood sample taken for measurement Measurement of oxidative stress: lipoperoxide using thiobarbituric acid reactive substance (TBARS) assay and TAS using 2,2'-azino-bis (3-ethylbenzthiazoline-6-sulfonic acid) (ABTS)</td>
<td>Total plasma antioxidant status (TAS), glutathione peroxidase (GPx), lipoperoxide, superoxide dismutase (SOD) and oxidative stress score</td>
<td>Intervention group: ↑ TAS and ↓ oxidative stress score compared to control group.</td>
<td>[12]</td>
</tr>
<tr>
<td>Interventional study</td>
<td>49 obese subjects (60-72 years)</td>
<td>Resistance exercise training 24 weeks study duration Involving normal weight and overweight subjects 2 groups: non-exercise control group and exercise group Measurement: exercise-induced lipid hydroperoxides (PEROXs) and TBARS using colorimetric technique</td>
<td>PEROXs and TBARS</td>
<td>PEROXs and TBARS are lowered in intervention participants by 23% and 70% respectively</td>
<td>[13]</td>
</tr>
<tr>
<td>Randomized controlled trial</td>
<td>25 hypertensive women (60 – 75 years)</td>
<td>Strength training 10 weeks study duration 2 groups: control and trained group Measurement of oxidative stress: MDA using thiobarbituric acid reaction</td>
<td>MDA and TAC</td>
<td>The strength training group increased the TAC and reduced the MDA concentration compared to control group.</td>
<td>[14]</td>
</tr>
<tr>
<td>Randomized controlled trial</td>
<td>45 type 2 diabetic patients (50 – 70 years)</td>
<td>Aerobic training 12 weeks study duration 3 groups: interval aerobic training (INT), continuous aerobic training (CON) and sedentary control Measurement of oxidative stress: MDA using TBARS, SOD and GPx using erythrocyte assay kit</td>
<td>SOD, GPx and MDA</td>
<td>Significant decrease in MDA concentration and increase in plasma GPx concentration in INT group and control group post intervention.</td>
<td>[15]</td>
</tr>
</tbody>
</table>
### Dietary intervention

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Number of MetS individuals</th>
<th>Age Range</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized controlled trial</td>
<td>75</td>
<td>(60 - 70 years)</td>
<td>Soybean intake in diet (35 grams/day) 12 weeks study</td>
<td>MDA, and TAC</td>
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<td>3 groups: soy nut group, textured soy protein (TSP) group and control group</td>
<td>Soybean is a low glycemic food that has antioxidant properties. Group that consumes soybean exhibits significant decrease of MDA and increase of TAC compared to the control group.</td>
</tr>
<tr>
<td></td>
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<td>Blood sample taken for measurement</td>
<td>Measurement: MDA evaluated by TBARS method, and TAC evaluated by FRAP</td>
</tr>
<tr>
<td>Randomized cross-over trial</td>
<td>42</td>
<td>(51-60 years)</td>
<td>Dietary soy intake 3 groups: control with DASH diet, intervention group with DASH and soy nuts diet, and intervention group with DASH and soy protein. All women start with usual diet for 3 weeks and follows intervention diet for 8 weeks Each woman receives all three diets Two wash out periods (each wash out period duration for 4 weeks) Measurements: plasma TAC using ferric reducing ability of plasma method, and MDA using HPLC</td>
<td>TAC and MDA</td>
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<td></td>
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<td>Both soy nuts and soy proteins reduce MDA significantly compared to control diet. There is no difference in MDA level among diet with soy nuts and diet with soy protein. Both soy nuts and soy protein increase TAC compared to control diet. Diet with soy nut shows higher TAC compared to diet with soy protein</td>
</tr>
<tr>
<td>Randomized controlled trial</td>
<td>75</td>
<td>(55-80 years)</td>
<td>Mediterranean diet supplemented with virgin olive oil and nuts Three groups: mediterranean diet with olive oil group, mediterranean diet with nuts group and control group with low fat diet. 5 years program Measurements using plasma: SOD, catalase by spectrophotometric method, and protein carbonyl by immunological method using detection kit</td>
<td>SOD, CAT and protein carbonyl</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td>SOD and catalase are increased in both intervention groups No difference is seen in values of protein carbonyl among groups.</td>
</tr>
<tr>
<td>Randomized, controlled, parallel clinical trials</td>
<td>110</td>
<td>(55-80 years)</td>
<td>Mediterranean diet supplemented with virgin olive oil and nuts Three groups: mediterranean diet with olive oil group, mediterranean diet with nuts group and control group with low fat diet. 1 year intervention period Measurements using urine: F₂-isoprostanes (F₂-IP) by commercial enzyme immunoassay kit, and 8-oxo-dG using HPLC</td>
<td>F₂-isoprostanes (F₂-IP) and 8-oxo-dG</td>
</tr>
<tr>
<td></td>
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<td>Urine concentration of F₂-IP is lower in mediterranean diet with virgin olive oil group compared to another group. Urinary level of 8-oxo-dG is lowered in both intervention group compared to control group.</td>
</tr>
<tr>
<td>Study Type</td>
<td>Participants</td>
<td>Intervention/Method</td>
<td>Biomarkers Assessed</td>
<td>Results</td>
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<tr>
<td>Randomized controlled trial</td>
<td>138 MetS individuals (≥50 years)</td>
<td>Oral advanced glycation end products (AGE) restriction 1 year intervention program 2 groups: low-AGE diet and high-AGE diet Measurement: plasma 8-isoprostanes using enzyme-linked immunosorbent assay (ELISA) kit</td>
<td>MDA, ox-LDL, TAC and CAT</td>
<td>Levels of 8-isoprostanes were decreased after consumption of low-AGE diet while increased after consumption of high-AGE diet. There is significant difference in level of 8-isoprostanes between low-AGE diet group and high-AGE diet group.</td>
</tr>
<tr>
<td>Randomized crossover clinical trial</td>
<td>40 overweight diabetic subjects</td>
<td>Legume based diet and legume free diet. Each diet for a period of 8 weeks with 4 weeks of washout period. 3 diet groups: legume-based diet and legume free diet. Measurement of oxidative stress: MDA using TBARS assay kit, ox-LDL using ELISA kit, TAC using antioxidant assay kit, and catalase (CAT) activity using commercial kits.</td>
<td>MDA, ox-LDL, TAC and CAT</td>
<td>Legume based diet showed significant decrease in MDA, ox-LDL and increase in CAT compared to legume free diet.</td>
</tr>
</tbody>
</table>

**Supplementations**

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Participants</th>
<th>Intervention/Method</th>
<th>Biomarkers Assessed</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double blind quasi experimental study</td>
<td>100 MetS individuals (67±6 years)</td>
<td>Supplementation of <em>Sechium edule</em> var. <em>nigrum spinosum</em> known as Chayote (500mg three times per day) 4 months intervention program 2 groups: placebo group and intervention group Blood samples taken for measurement</td>
<td>Total plasma antioxidant status, SOD, GPx, lipoperoxides, protein carbonyl, catalase (CAT)</td>
<td>Consumption of <em>Sechium edule var. nigrum spinosum</em> acts as an antioxidant that significantly increases SOD level. Consumption of this capsule also showed decreased lipoperoxides and POC.</td>
</tr>
<tr>
<td>Study Type</td>
<td>Number</td>
<td>Age Range</td>
<td>Intervention</td>
<td>Measurements</td>
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<td>--------------------------------</td>
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<td>-------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Randomized controlled trial</td>
<td>53</td>
<td>50 - 65 years</td>
<td>Consumption of citrus-based juice with 5% of Aronia melanocarpa extract.</td>
<td>15-F2t-isoprostane, ox-LDL, 8-hydroxydeoxyguanosine (8-OHdG), protein carbonyls and ratio of reduced glutathione to oxidised glutathione (GSH/GSSH) using colourimetric determination.</td>
</tr>
<tr>
<td>Randomized clinical trial</td>
<td>110</td>
<td>≥ 60 years</td>
<td>Quercetin supplementation.</td>
<td>Catalase (CAT), SOD, GSH and advanced glycation end products (AGEs)</td>
</tr>
<tr>
<td>Quasi-experimental study</td>
<td>135</td>
<td>60 – 74 years</td>
<td>Alpha-lipoic acid supplementation.</td>
<td>8-Isoprostane, TAC, GPx and SOD</td>
</tr>
<tr>
<td>Randomized clinical trial</td>
<td>60</td>
<td>50 – 85 years</td>
<td>Melatonin supplementation.</td>
<td>GSH, TAC, plasma protein carbonyl and MDA</td>
</tr>
</tbody>
</table>
The result in this systematic review provides proof that all types of physical activities such as Tai Chi, aerobic exercise training, strength training, resistance training and interval aerobic training contributed to decreased oxidative stress level. Moreover, the meta-analysis of this study supported those physical activities intervention shows reduction in MDA level and increased in overall antioxidants especially GPx activity. Physical exercises are shown as a potential intervention that shows drastic effects on weight loss, decreasing cholesterol and triglyceride level, improving glucose uptake by cells, as well as reducing inflammation and oxidative stress in MetS patients [27]. Tai-chi is one of the moderate exercises that had proven to lessen the oxidative stress level. Additionally, the Tai Chi exercise also decreased the inflammatory products such as interleukin 8. A previous study suggested that Tai Chi exercise may reduce lipoperoxide level and increases SOD level [28]. In addition, reduction of MDA level is mainly due to the reduction of adipose tissue, that does not contribute to the excess production of endothelial ROS and deteriorate of antioxidant system. Hence, chronic exposure towards aerobic exercise gives a rise to a balanced relationship between oxidant and antioxidant system by upregulating the antioxidant system.

Systematic review in this study also provides proof that supplementation such as chayote, nano-curcumin, citrus-based juice with 5% of Aronia melanocarpa extract, melatonin, alpha-lipoic acid and herbal medicine composed of ginkgo leaf tablet and Liuwei Dihuang pills contributed to decreased oxidative stress in elderly with MetS. This meta-analysis also suggested that supplementation did not increase antioxidant biomarkers, but it may only increase the GPx level. Based on meta-analysis, although the overall antioxidant biomarkers show no changes after the intervention, GPx value was increased in the supplemented group. Hence, the supplementation also increases the GPx antioxidant enzyme. This review supported that antioxidant supplementations are recommended to subjects with metabolic disorders in order to improve their nutritional status and immune system. A previous study also supported that the intake of antioxidant supplementation can improve MetS [29].

Furthermore, all dietary changes such as dietary soy intake, Mediterranean diet with virgin olive oil, Mediterranean diet with nuts, combination of soy diet and DASH diet, low AGEs diet and legume-based diet also contributed to decreased oxidative stress level in MetS. The meta-analysis supported that dietary intervention can decrease the oxidative stress by decreasing the MDA levels and increasing TAC level. Excessive intake of food with high AGEs is correlated to insulin resistance, causing inflammation and oxidative stress. Hence, consumption of low AGEs might minimize the risk of developing insulin resistance and metabolic abnormalities. In our meta-analysis, the MDA level before the intervention is decreased in the intervention group even though individual studies supported that there is no difference between control and intervention group before the intervention. This possible result may be due to differences in methodology, sample sizes or subjects that were involved in the study. After dietary intervention, a significant decrease in MDA level was shown. Dietary changes show significant increase in TAC level. Combination of soy and DASH diet and Mediterranean diet may bring potential choices to reduce oxidative stress in elderly with MetS. This healthy diet pattern is known to benefit the elderly by decreasing the prevalence of chronic diseases, MetS and all of the MetS components [30].

Conclusion

In conclusion, we should cautiously interpret these results because the limitations of minor studies, public bias and between-study heterogeneity in our study. The results of our meta-analysis revealed that physical activity, supplementation and healthy diet may reduce the oxidative stress level in elderly with MetS. Therefore, further investigation needs to explore the oxidative stress biomarkers in the pathophysiology of MetS.

Conflict of interest

No conflict of interest.

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References


