IJMA

International Journal of Medical Arts

2/2022 (volume 4, Issue 2)

http://ijma.journals.ekb.eg/

Print ISSN: 2636-4174

Online ISSN: 2682-3780

Available online at Journal Website
https://ijma.journals.ekb.eg/
Main Subject [Internal Medicine]

Original Article

Markers of Oxidative Stress in Metabolic Syndrome and Antioxidants as an Add-on Therapy in the Reversal of Changes

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Article information

Received: 25-11-2021

Accepted: 18-02-2022

DOI: 10.21608/ijma.2022.106339.1398

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Citation: Soundharapandiyan S, Rajaram G, Tiruvalavan SR. Markers of Oxidative Stress in Metabolic Syndrome and Antioxidants as an Add-on Therapy in the Reversal of Changes. IJMA 2022 Feb; 4 [2]: 2182-2187. doi: 10.21608/ijma.2022.106339.1398

ABSTRACT

Background: Metabolic syndrome is a collection of dyslipidemia, central obesity, hypertension, and diabetes. Pathogenesis is influenced by psychological and oxidative stress. RBCs can also be damaged by oxidative stress. [Crenated cells with Heinz bodies].

The Aim of The Work: To analyze the red blood cell morphological changes as oxidative stress markers and to investigate the efficacy of vitamins C and E as supplements to standard metabolic syndrome treatment.

Patients and Methods: For eight weeks, 60 patients with diabetes, hypertension, and dyslipidemia who had been on medication for 1-2 years were randomly assigned to one of two groups: standard treatment alone or vitamin C capsule 500mg once daily [OD] and vitamin E 400 mg OD in addition to standard treatment. Standard treatment includes Enalapril 5 mg twice daily [BD] and/or tablet Amlodipine 5 mg OD, Metformin 500 mg BD, and Atorvastatin 10 mg at bedtime [HS]. Both groups were monitored for four weeks after treatment. At 0, 4, and 8 weeks, parameters such as red blood cell [RBC] morphological changes, fasting blood sugar, blood pressure, and lipid profile were examined.

Results: Both groups had similar baseline characteristics. When compared to the control group, the study group had a significant reduction in fasting blood sugar [$p = 0.023$], an increase in high density lipoprotein [HDL] [$p = 0.03$], low density lipoprotein [LDL] [$p = 0.001$], systolic blood pressure [$p = 0.024$], diastolic blood pressure [$p = 0.005$], percentage of crenated RBCs with Heinz bodies [$p<0.001$], and total cholesterol [$p<0.001$].

Conclusion: Vitamin C and E as add-on therapy to the standard treatment is effective in reducing insulin resistance, blood pressure, and improving the lipid profile.

Keywords: Oxidative Stress; Red Blood Cell; Metabolic Syndrome; Antioxidants.

INTRODUCTION

The metabolic syndrome is marked by the presence of various risk factors for cardiovascular disease, including dyslipidemia, hypertension, insulin resistance, and obesity [1]. Patients with metabolic syndrome have a two-fold higher chance of having cardiovascular disease when compared to normal people in the next five to ten years, and the risk is undoubtedly higher across their lifetime [2]. The metabolic syndrome increases oxidative stress, which leads to chronic inflammation. [3] In metabolic syndrome, oxidative stress is elevated [4, 5], and erythrocytes play a major role in scavenging free radicals [6], and the systemic chronic inflammation that results in the pathogenesis of atherosclerosis and insulin resistance [7].

In the past few years, metabolic syndrome has become one of the most serious public health issues. Its prevalence has been growing worldwide because of unhealthy lifestyles, reduced physical activity, and obesity. The International Diabetic Federation has estimated that the prevalence of metabolic syndrome worldwide is about 20–25% among the adult population [8].

Oxidative stress plays a key factor in the progression of insulin resistance and micro and macrovascular complications of diabetes and also causes an imbalance between the parasympathetic and sympathetic systems, contributing to hypertension [9].

In oxidative stress, the red blood cells [RBCs] as oxygen carriers are exposed to reactive oxygen stress. When they are continuously exposed, it damages the RBC cell membrane, which eventually impairs oxygen delivery and induces red cell aging, leading to hemolysis. Normally, RBCs contain intracellular antioxidants like Glutathione [GSH], which protect them from hemolysis induced by oxidative stress. The intracellular pool of reduced glutathione is maintained by Nicotinamide adenine dinucleotide phosphate [NADPH]. NADPH production in RBCs is entirely dependent on the enzyme called glucose-6-phosphate dehydrogenase. In metabolic syndrome, there will be insulin resistance, which leads to reduced expression of the G6PD enzyme and the following inhibition of the pentose phosphate pathway. As a result of the reduced expression of the G6PD enzyme, the production of NADPH will decrease. Reduced glutathione concentrations will be lower in cells with decreased NADPH levels. Glutathione [GSH] is oxidised to glutathione disulfide [GSSG] under extreme oxidative stress, which leaks through the damaged red cell membrane. Due to the lack of a nucleus and mitochondria, RBCs are unable to generate GSH and enzymes, making them more susceptible to free radicals. ROS [reactive oxygen species] can cause structural damage to cells, such as crenated edges in cell membranes and Heinz bodies owing to hemoglobin destruction [10].

Free radicals due to oxidative stress produce an increase in eicosanoid isomers [8isoPGF2α] via non-enzymatic oxidation of arachidonic acid, which activates prostanoid receptors and leads to inflammation. [10].

It is also a potent mediator of oxidative stress that damages the RBC, thereby producing an irregularly contracted, crenated RBC. The decreased deformability of RBC contributes to the removal of RBC from the circulation, which leads to hemolytic anemia. As a result, RBC morphology can be employed as an oxidative stress marker [11].

Antioxidants are known as free radical scavengers. Many antioxidants are present in ascorbic acid [Vitamin C], the strongest radical scavenger. It reacts with free radicals and converts itself into a non-reactive intermediate by undergoing single-electron oxidation. It also regenerates the tocopherol [metabolically active reduced form of vitamin E], therefore producing a synergistic effect when combined with vitamin E [12].

Type 2 diabetes mellitus is the leading metabolic disorder that accounts for the most mortality and morbidity, which is mostly associated with metabolic syndrome. Cardiovascular complications are common in the same group, posing a significant burden [13].

The coexistence of the same factors proves the common etiopathogenesis. Oxidative stress is also a common co-factor that has a promising role in recent health care. Oxidative stress leads to various cell damage in our body, of which RBC damage alters the morphology of RBCs is one of the most common. In this study, we used RBC morphology as a tool [biomarker] for oxidative stress. In order to prove that free radical injury is responsible for insulin resistance, raised blood pressure, and dyslipidemia, we supplement antioxidants like α-tocopherol and Ascorbic acid in patients with metabolic syndrome.

THE AIM OF THE WORK

Our study aimed to determine the marker of oxidative stress in metabolic syndrome and the efficacy of adjuvant add-on antioxidant therapy such as vitamin C and vitamin E in metabolic syndrome and to analyze the change in blood sugar levels, hypertension, and lipid profile levels.

PATIENTS AND METHODS

Study type: A randomized, open-label, comparative pilot study.

Study period: The study was conducted from September 2015 to April 2016.

Study Location: Institute of Internal Medicine, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai, Tamilnadu, India.

Inclusion criteria: Patients aged between 40-70 years of both genders diagnosed with metabolic syndrome were included in the study.

Exclusion criteria: Patients aged less than 40 years and more than 70 years, smokers, alcoholics and those

who were not willing to participate in the study were excluded from the study. Patients having conditions like hypothyroidism, connective tissue disorders, pregnancy, hematological disorder, renal failure, secondary hypertension and subjects on steroid therapy were also excluded from the study.

After randomization of 121 subjects, 60 patients were shortlisted as fitting our inclusion and exclusion criteria. Out of 60, after careful assessment, 61 were rejected from the study. Each of the 60 subjects was divided into 30 test and control groups. All subjects included in the study were assessed using standard case performa including demographic details, history, clinical examination findings with vitals, and lab investigations.

Thirty subjects in the control group [n = 30] were only given the standard protocol drugs for dyslipidemia, hypertension, and diabetes [tablet Metformin, tablet Atorvastatin, Enalapril, and/or tablet Amlodipine] for 8 weeks. The study [test] group was given standard treatment plus vitamin C capsules of 500mg and vitamin E capsules of 400mg once daily as an adjuvant [n = 30]. Drugs were issued for 4 weeks, and subjects were reviewed after 4 weeks for compliance and extended to the next 4 weeks.

Assessment of oxidative stress was assessed by the percentage of crenated RBCs with Heinz bodies. Clinical examination of systolic and diastolic blood pressure, fasting and postprandial blood sugar levels, lipid profile, hemoglobin, and RBC were also assessed in our study to prove the benefits in each group at the beginning of the study and post 8 weeks of treatment.

Our study was approved by the Institutional Ethics Committee at Madras Medical College, Chennai, on September 8, 2015. As per protocol, written informed consent was obtained from all the patients included in the study in their own language after explaining the study design clearly. The collected data was statistically analyzed.

Statistical Analysis

The obtained data were statistically analyzed using SPSS vs. 21 [IBM, Chicago, USA], with a P-value of 0.05 considered statistically significant. Pearson's Chi square was used to investigate the association between groups and categorical variables. Student's Paired samples "t" test used to investigate differences within the same group before and after treatment. Finally, independent samples "t" test used to compare between two groups regarding parametric variables.

RESULTS

In our study, no significant difference was reported between study and control groups regarding patient age or gender. The mean age was 50.73 and 51.13 years in study and control groups, respectively [Table 1].

Total cholesterol levels in the study group were 243.20 mg/dl at the start, but dropped to 191.93 mg/dl [p<0.001] after 8 weeks, with a significant p-value [p0.001]. There was a substantial reduction [p<0.001] when both groups were compared. At week 0, the LDL cholesterol levels in the control and study groups were 163.01 mg/dl and 159.98 mg/dl, respectively. In the control and study groups, it was lowered to 152.68 mg/dl, p = 0.030, and 126.51 mg/dl, p = 0.001, respectively, with a significant p-value [Table 2].

The control group's mean fasting blood glucose was 148.37 mg/dl at week 0, while the study group's was 154.47 mg/dl. The control group's mean fasting blood glucose level was 132.30mg/dl [p = 0.024], while the study group's mean fasting blood glucose level was 112.93mg/dl [p = 0.001].

In our study, as per our protocol, mean systolic blood pressure at 0 and 8 weeks was recorded. In the test group, we observed 141.53 mmHg at week 0 and 133.13 mmHg at 8 weeks, which was also statistically significant [p-0.024]. In the control group, we observed 139.27 mmHg at week 0 and 137.73 mmHg at 8 weeks. In our study, as per our protocol, mean diastolic blood pressure at 0 and 8 weeks was recorded. In the test group, we observed 82.13 mmHg at week 0 and 76.93 mmHg at 8 weeks, which was also statistically significant [p-0.005]. In the control group, we observed 84.13 mmHg at week 0 and 82.60 mmHg at 8 weeks [Table 3].

Liver and kidney function showed non significant differences between study and control groups before and at the end of the study. In addition, in each group, values did not differ significantly at the end of the study compared to corresponding values before the study [table 4].

In the study group, 63.3 percent and in the control group 56.7 percent had normal BMI. The control group had 36.7 percent of overweight patients while the study group had 33.3 percent of overweight patients [25–29.9 kg/m^2]. Obesity [measured in kilograms per square meter] was found in only 6.6 percent of those in the control group and 3.3 percent of those in the experimental group [Table 5].

Figure [1], a and b depict red blood cell morphology in the patient 1 before and after the end of the study. This followed by graphical representation of blood pressure [figures 2 and 3], mean percentage of crenated RBCs with Heinz bodies [figure 4], Mean fasting glucose [figure 5] and adverse events [figure 6].

Table [1]: Baseline characteristics of study population

Parameters		Control group [n=30]	Study group [n=30]	p value
Age in years	Mean [SD]	51.13[3.46]	50.73[3.60]	**>0.05**
Gender [n,%]	Male	18 [60%]	20[66.7%]	**0.67**
	Female	12[40%]	10 [33.3%]	

Table [2]: Lipid profile in both control and study group

Parameters		0 week Mean [SD]	8 weeks Mean [SD]	p value
Total Cholesterol [mg/dl]	Control group	240.20[41.90]	228.80[32.62]	0.017
	Study group	243.20[36.25]	191.93[27.42]	<0.001
LDL Cholesterol [mg/dl]	Control group	163.01[44.09]	152.68[32.36]	0.030
	Study group	159.98[33.82]	126.51[27.45]	<0.001
Triglycerides [mg/dl]	Control group	172.80[24.32]	161.93[15.75]	0.011
	Study group	174.03[23.01]	157.67[12.59]	0.002
vLDL Cholesterol [mg/dl]	Control group	34.56[4.86]	32.38[3.15]	0.011
	Study group	34.29[4.48]	31.63[2.55]	0.008
HDL Cholesterol[mg/dl]	Control group	39.00[1.53]	39.97[2.29]	0.053
	Study group	39.26[2.25]	41.23[2.12]	0.001

LDL: Low density lipoprotein; vLDL: Very low-density lipoprotein; HDL: High density lipoprotein

Table [3]: Various parameters studied in both control and study group

Parameters		week 0 Mean [SD]	8 weeks Mean [SD]	p value
Fasting blood sugar [mg/dl]	Control group	148.37 [45.15]	132.30[36.07]	0.024
	Study group	154.47[40.01]	112.93[26.92]	<0.001
Systolic blood pressure[mmHg]	Control group	139.27[8.92]	137.73[8.25]	0.023
	Study group	141.53[8.87]	133.13[7.02]	<0.001
Diastolic blood pressure[mmHg]	Control group	84.13[8.95]	82.60[8.38]	0.005
	Study group	82.13[8.62]	76.93[6.55]	<0.001
Crenated RBCs with Heinz bodies	Control group	84.03[10.63]	81.83[9.76]	0.072
	Study group	87.73[7.86]	5.90[1.97]	<0.001
Haemoglobin gm%	Control group	10.46[1.37]	10.42[1.34]	0.42
	Study group	10.23[1.56]	11.49[1.49]	<0.001
Red blood cell [millions/µL]	Control group	3.59[0.53]	3.55[0.48]	0.19
	Study group	3.53[0.60]	3.95[0.60]	<0.001

Table [4]: Liver function in both control and study group

Parameter	Control Group			Study Group		
	0 week	At the end of 8 weeks	p	0 week	At the end of 8 weeks	p
SGOT	30	29.93	0.90	30.50	30.30	0.71
SGPT	31.73	31.67	0.78	31.90	31.77	0.71
Bilirubin	0.83	0.85	0.56	0.83	0.81	0.53
Urea	25.70	25.07	0.45	26.87	25.90	0.18
Creatinine	0.77	0.72	0.70	0.72	0.67	0.17

Table [5]: Body mass index in both control and study group

BODY MASS INDEX	GROUPS			
	CONTROL		STUDY	
	n	%	n	%
<18.5 kg/m²	0	0%	0	0%
18.5 – 24.9 kg/m²	17	56.7%	19	63.3%
25– 29.9 kg/m²	11	36.7%	10	33.3%
≥30 kg/m²	2	6.6%	1	3.3%

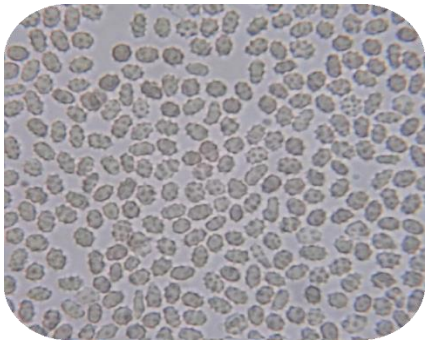

Figure [1a]: Morphology of RBCs in patient 1 before treatment

Figure [1b]: Morphology of RBCs in patient 1 after treatment

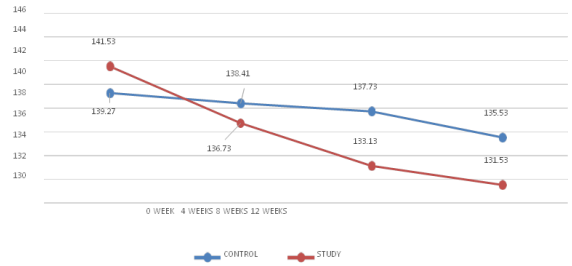

Figure [2]: Mean systolic blood pressure during study and follow up period

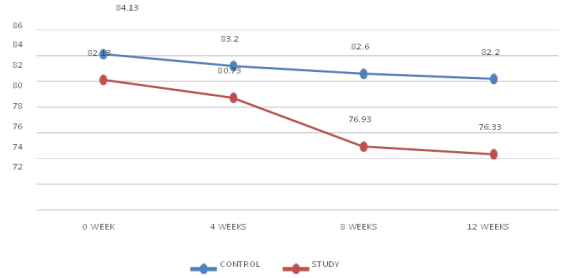

Figure [3]: Mean diastolic blood pressure during study and follow up period during study and follow up period

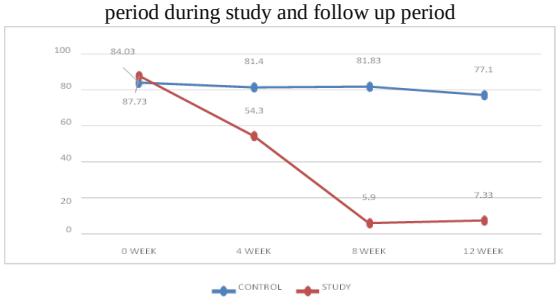

Figure [4]: Mean percentage of crenated RBCs with Heinz bodies during study and follow up period

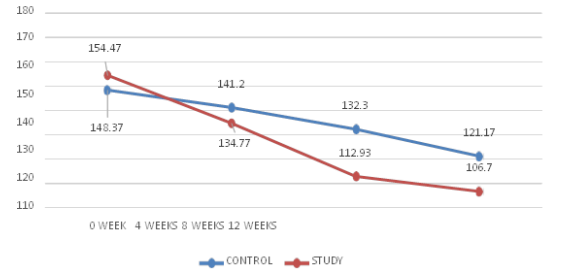

Figure [5]: Mean fasting glucose during study and follow up period

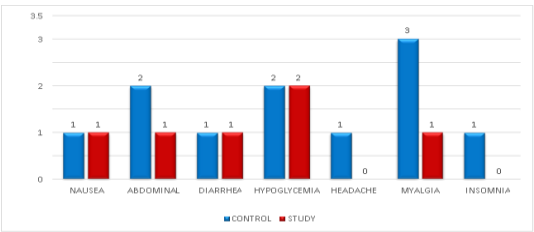

Figure [6]: Adverse event profile

DISCUSSION

Our study observes prevalence of metabolic syndrome in the middle age group. As expected, males dominated both the groups, and the mean age was also similar in both the groups. Kwon HS *et al*. investigated the prevalence of the metabolic syndrome and reported that 20.8% of the total study population were between 40 and 49 years old, 26.4% were between 50 and 59 years old, 30.8% were between 60 and 69 years old, and 29.7% were over 70 years old, indicating that the prevalence of the metabolic syndrome increases with age. The same study found that in men, the prevalence was highest in their 40s and then declined as they aged [40-49 years; 18.8%, 50-59 years; 17.4%, 60-69 years; 18.3%, over 70 years; 14.5%] [14].

The BMI of the majority of patients in both groups in our study was within normal ranges [18.5–24.9 kg/m^2]. According to Mata A *et al*., the prevalence of metabolic syndrome varied by BMI category, 29.6% had normal BMI, 38.9% overweight, 56.9% percent pre-obesity, and 62.4% were obese. Obesity is less prevalent among the people we studied. Mata A *et al*. observed significant prevalence of metabolic syndrome in people with normal BMI; therefore, screening and diagnosis should not be limited to those with a higher BMI [15].

At the end of the 8 weeks, the study group had a statistically significant decrease in mean fasting blood glucose. However, a meta-analysis by Balbi *et al*, showed no substantial differences in subgroup analyses comparing vitamins C or D with placebo were detected in the glycemic control parameters investigated in 17 trials. However, the benefits of vitamin E were considerably superior to the control for both outcomes of mean change in blood glucose [mg/dL] and reduction in HbA1c [16]. Insulin resistance occurs when inflammatory mediators such as isoprostanes [PGF2] attach to the insulin receptor, preventing insulin from binding to its receptor and resulting in hyperinsulinemia [17, 18]. There was a significant drop in blood glucose levels in the study group after receiving antioxidant treatment [vitamin E and C]. This supports the theory that free radical induced isoprostanes induce insulin resistance in type 2 diabetes.

At the start of the trial, both the control and experimental groups had 84.03% and 87.73% of crenated RBCs with Heinz bodies at the start of the trial, respectively. This shows that RBCs in people with metabolic syndrome have been damaged by free radicals. The study group demonstrated a statistically significant reduction in the percentage of crenated RBCs with Heinz bodies to 5.90% [p<0.001] at the end of 8 weeks of antioxidant therapy. But there was no significant difference in the control group [81.83 percent, p = 0.072]. This explains why antioxidant treatment improves the integrity of the RBC membrane, resulting in less fragility and hemolysis [11].

The control group's mean hemoglobin was 10.46 gm/dl at week 0, whereas in the study group it was 10.23 gm/dl. After 8 weeks of antioxidant treatment, the study group's hemoglobin [11.49 gm/dl] increased statistically significantly [p<0.001] as compared to the control group's hemoglobin [10.42 gm/dl]. Arabi *et al*. conducted a systematic review and meta-analysis on the overall impact of vitamin D on hemoglobin; ten clinical trials [n = 1385] reported overall hemoglobin levels. The pooled analysis showed that vitamin D supplementation had no effect on hemoglobin levels [19]. Furthermore, the mean total RBC count in the experimental group increased significantly [p<0.001] from 3.53 million/L at week 0 to 3.95 million/L at the end of 8 weeks. However, there was no significant

difference in the control group [week 0–3.59 million/L and 8 weeks–3.55 million/L, p = 0.19]. At 8 weeks, the inter-group difference was statistically significant [p = 0.006]. This proves that the anemia generated by free radicals in metabolic syndrome is hemolytic anemia [11].

Lipid profile showed non significant changes from the start to the end of the experiment in the control group. however, significant differences were observed in the study group. These results shows that vitamin C and vitamin E inhibited free radical-mediated oxidation of LDL, enhanced LDL binding to its receptor, cellular absorption, and degradation of LDL, increased bile acid synthesis, and decreased total cholesterol and LDL levels in the blood. The level of cholesterol in peripheral cells is refilled, and HDL picks it up and transports it to the liver. As there is no degradation of HDL, we saw an increase in HDL levels in our research [12]. Our study found evidence of a reduction in systolic and diastolic blood pressure in the test group. Similarly, one research found that taking 500 mg of vitamin C every day for 30 days reduced blood pressure levels. However, a review and a randomised controlled trials showed that there was no significant evidence for an impact of antioxidant vitamin intake in preventing or treating high blood pressure [20-22].

Conclusion: Hereby, we conclude that treatment with antioxidants like vitamin C and vitamin E can have a disease-modifying effect on metabolic syndrome. Also, the study of RBC morphological changes is a cost-effective biomarker for diagnosing oxidative stress.

Conflict of interest: None

Financial disclosure: None

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2/2022

International Journal of Medical Arts

https://ijma.journals.ekb.eg/
Print ISSN: 2636-4174
Online ISSN: 2682-3780