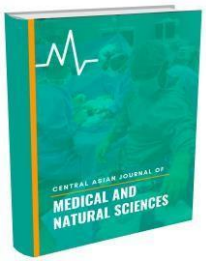

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Article

The Role of Biochemical Markers of Oxidative Damage in The Progression of Coronary Heart Disease Among Residents of Kirkuk City

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Abstract: Coronary heart disease (CHD) still accounted for a large proportion of all-cause mortality, oxidative stress has been proven to play an important role in the pathogenesis of CHD besides the traditional lipid abnormality. Objective: This work was oriented to the study of oxidative stress biomarkers in CHD patients versus healthy subjects and to investigate the association between these parameters with demographic and clinical variables in Kirkuk City residents in the north of Iraq. A case-control study was conducted on 60 CHD patients (30 males, 30 females; age ranged 40–69 years) and 30 apparently healthy controls (15 males, 15 females; age ranged 40–67 years); all were non-smokers, non-alcoholics, and without hypertension or diabetes. Venous blood samples were taken to estimate malondialdehyde (MDA), glutathione peroxidase (GPx) activity and levels of vitamin C and ceruloplasmin. The independent t test and two-way ANOVA were involved in the statistical analysis. Results: In CHD patients, all OS markers were significantly raised compared with controls, and in patients MDA was significantly higher (4.87 ± 1.23 nmol/mL) than in controls (2.15 ± 0.67 nmol/mL)). Antioxidant defenses were equally severely impaired: GPx activity was decreased (28.64 ± 6.71 U/L vs.58 ± 8.45 U/L), as well as vitamin C levels (0.58 ± 0.21 mg/dl vs. 1.26 ± 0.34 mg/dl) and ceruloplasmin concentrations (28. 93 ± 5.67 mg/dl vs. 41.75 ± 7.82 mg/dl). Gendered analysis showed male patients had greater oxidative imbalance than females. Age stratification showed progressive increase of MDA and decrease of antioxidants with age. Body mass index (BMI) correlated significantly positively with MDA and negatively with antioxidant parameters. Our results indicate an extreme disruption of the oxidant-antioxidant equilibrium in CHD patients with increased lipid peroxidation and impaired antioxidant defense, which indicates that these biomarkers may be of value as additional tools in the risk stratification and follow-up of the disease.

Keywords: Coronary Heart Disease, Oxidative Stress, Malondialdehyde, Glutathione Peroxidase, Antioxidants

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1. Introduction

Coronary heart disease (CHD) remains a burden of morbidity and mortality globally, with around 9 million deaths annually, and even with advances in diagnostics and pharmacological treatment and revascularization methods, it still represents a significant challenge to public health [1]. Established risk factors such as hyperlipidemia, hypertension, diabetes mellitus and smoking have been identified through robust epidemiological data, however they do not account for all cases of CHD, as a significant number of individuals affected by the disease do not possess any of these traditional risk

factors, indicating that other pathophysiological processes must play an important role in the development and progression of [2]. An imbalance in the formation of reactive oxygen species (ROS) and the stratification of antioxidant defense system to counteract these reactive species or the repair of the molecular damages caused by them known as oxidative stress, has now become a pivotal event in the development and evolution of atherosclerosis [3]. The oxidative modification hypothesis of atherosclerosis was initially suggested by Steinberg and colleagues and states that oxidation of low-density lipoprotein (LDL) is a key early event during atherogenesis in which, oxidized LDL binds to scavenger receptors on macrophages that mediates its extensive unregulated uptake and, unlike native LDL, oxidized LDL uptake is not subjected to feedback inhibition and leads to [4]. Elevated ROS in CHD induce endothelial dysfunction by diminishing nitric oxide bioavailability, mediate vascular inflammation by inducing redox-sensitive transcription factors such as nuclear factor kappa B (NF-κB), enhance vascular smooth muscle cell proliferation and migration, which contributes to intimal thickening, and promote plaque instability by activating matrix metalloproteinases, which are all essential for atherogenesis and its complications [5]. Malondialdehyde (MDA), a dialdehyde, is formed as a result of the peroxidation of polyunsaturated fatty acids in cell membranes and lipoproteins and is considered as an appropriate marker of lipid peroxidation which binds covalently to protein and DNA; indicating oxidative damage and also in LDL modification [6]. The antioxidant system of defense also consists of enzymes, including glutathione peroxidase (GPx), which is a selenoprotein that reduces hydrogen peroxide and organic hydroperoxides at the expense of glutathione as a reducing submit and protects cells from oxidative stress and influences the delicate balance between required and too much ROS [7]. Ascorbic acid (vitamin C), a powerful water-soluble antioxidant has in vivo free radical scavenger activity and directly reacts with superoxide, hydroxyl radicals and singlet oxygen in the aqueous phase; is a co-factor for the recycling of the oxidized form of the lipophilic antioxidant vitamin E to its active form [8]. Ceruloplasmin, which has ferroxidase activity, is a copper containing α2-glycoprotein that catalyzes the oxidation of ferrous iron to ferric iron, allowing iron binding to transferrin and inhibiting iron-catalyzed free radical formation through the Fenton reaction, although its association with cardiovascular disease is not straightforward because it is a positive acute-phase reactant and may be subject to oxidative modification converting it from a protective agent to a pro-oxidant species in [constrained] [oxidative] stress [9]. Although the link between oxidative stress and CHD is now established across the world, the specific biomarkers of oxidative stress vary greatly depending on geographical and ethnic factors as a consequence of environmental exposure, food consumption, genetic polymorphisms and local allergens [10]. Introduction Kirkuk City in the north of Iraq is a special region distinguished by its environment, diet, and people, but little is known about oxidative stress in CHD patients from this region. Therefore, the present study was designed to evaluate the oxidative stress and antioxidant defiance of CHD patients in Kirkuk City via measuring serum MDA as marker of lipid peroxidation, GPx activity as marker of enzymatic antioxidant defense, vitamin C as a non enzymatic antioxidant, and ceruloplasmin Cp a protein with diverse redox functions, and to investigate the correlation of these biomarkers with some demographic parameters such as gender, age, and body mass index (BMI) after disposing subjects with major confounders including smoking, drinking, hypertension, and diabetes to isolate the oxidative stress aspect in CHD pathogenesis from these well established risk factors [11].

2. Materials and Methods

2.1. Study Design and Participants

This a case-control study that was carried out in the Kirkuk City, Iraq between October 2024 and May 2025. A total of 90 subjects were recruited, 60 patients with CHD (30 male, 30 female; aged 40–69 years) from coronary care units (CCU's) and cardiology

outpatient clinics in Kirkuk General Hospital and Azadi Teaching Hospital and 30 healthy controls (15 male, 15 female; aged 40–67 years) from the community. Consultant cardiologists were confirmed the diagnosis of CHD on the basis of clinical manifestation, changes in ECG, and echocardiography.

2.2. Inclusion and exclusion criteria

All were non-smoker and non-alcoholics, with no history of hypertension, diabetes mellitus, chronic inflammatory diseases, renal or hepatic diseases, and malignancy. None of them has been using antioxidant supplements or anti-lipid drugs for a period of at least three months before the study.

2.3. Sample Collection and Biochemical Analysis

Fasting blood from a vein (10 mL) was drawn, centrifuged, and the serum stored at -80°C until analysis. MDA was determined by the thiobarbituric acid reactive substances (TBARS) assay [12]. GPx activity was measured by the Ransel RS-505 kit (Randox Laboratories, UK) [13]. Vitamin C was determined by the 2,4-dinitrophenylhydrazine colorimetric method [14]. Ceruloplasmin was quantified by immunoturbidimetric method (BioSystems, Spain) [15]. BMI was computed as weight (kg)/height^2(m^2).

2.4. Statistical Analysis

Data were analyzed with SPSS (version 26). Values are reported as mean ± SD. The independent t-test was used to compare the CHD and the control groups. We used two-way ANOVA to analyze the effects of gender and age. Pearson's correlation was used to investigate associations with BMI. $P \leq 0.05$ was deemed significant.

3. Results

3.1. Demographic characteristics

The demographic variables of the participants of this study including age, gender, body mass index, fasting glucose and total cholesterol levels are presented in Table 1.

Table 1. Demographic characteristics of study participants

Parameter	CHD Group (n=60)	Control Group (n=30)	P-value
Age (years)	54.6 ± 8.3	53.1 ± 7.9	0.412
Age range (years)	40-69	40-67	—
Gender (M/F)	30/30	15/15	1.000
BMI (kg/m^2)	27.8 ± 2.5	26.1 ± 2.1	0.052
Fasting glucose (mg/dL)	96.4 ± 8.7	91.2 ± 7.5	0.058
Total cholesterol (mg/dL)	198.6 ± 24.3	189.7 ± 21.8	0.102

The CHD and control groups were similar in age and proportion of male and female subjects. The CHD group had a marginally higher BMI, trend toward/significance ($p = 0.06$).

3.2. Comparison of oxidative stress biomarkers between CHD patients and controls

Table 2 shows the oxidative stress and antioxidants parameters in CHD patients and control subjects.

Table 2. Comparison of Biomarkers Between CHD Patients and Controls

Parameter	CHD Group (n=60)	Control Group (n=30)	Mean Difference (95% CI)	Percent Change	P-value
MDA (nmol/mL)	4.87 ± 1.23	2.15 ± 0.67	2.72 (2.31-3.13)	+126.5%	<0.001
GPx (U/L)	28.64 ± 6.71	52.38 ± 8.45	-23.74 (-26.98 to -20.50)	-45.3%	<0.001
Vitamin C (mg/dL)	0.58 ± 0.21	1.26 ± 0.34	-0.68 (-0.80 to -0.56)	-54.0%	<0.001
Ceruloplasmin (mg/dL)	28.93 ± 5.67	41.75 ± 7.82	-12.82 (-15.80 to -9.84)	-30.7%	<0.001

Patients with CHD had significantly higher MDA levels (more than double) and lower antioxidant defense than controls. The extent of these changes was quite large, show a 126.5% increase in MDA level, and a decrease of 45.3%, 54.0%, and 30.7% in GPx, vitamin C and ceruloplasmin, respectively. These results are in line with recent meta-analyses which demonstrated that markers of oxidative stress, mainly MDA, are significantly higher in patients with CVD than in healthy individuals [16].

3.3. Gender-based analysis

The distribution of oxidative stress biomarkers among male and female CHD patients is illustrated in Table 3.

Table 3. Biomarkers in CHD Patients Stratified by Gender

Parameter	Male CHD (n=30)	Female CHD (n=30)	Mean Difference (95% CI)	Percent Difference	P-value
MDA (nmol/mL)	5.34 ± 1.10	4.40 ± 1.15	0.94 (0.36-1.52)	+21.4%	0.002
GPx (U/L)	25.91 ± 5.80	31.37 ± 6.52	-5.46 (-8.67 to -2.25)	-17.4%	0.001
Vitamin C (mg/dL)	0.49 ± 0.18	0.67 ± 0.20	-0.18 (-0.28 to -0.08)	-26.9%	<0.001
Ceruloplasmin (mg/dL)	27.82 ± 5.11	30.04 ± 6.02	-2.22 (-5.14 to 0.70)	-7.4%	0.134

Male CHD patients exhibited a more pronounced oxidative status than females, with MDA being 21.4% higher and GPx and vitamin C 17.4% and 26.9% lower, respectively. Ceruloplasmin was tending to be lower in males but not significantly. These sex differences are consistent with the view of estrogen as an antioxidant and an upregulator of antioxidant enzyme expression [17].

3.4. Age-related changes

The comparison of oxidative stress biomarkers between different age groups of CHD patients is summarized in Table 4.

Table 4. Biomarkers in CHD patients stratified by age

Parameter	40-54 years (n=28)	55-69 years (n=32)	Mean Difference (95% CI)	Percent Difference	P-value
MDA (nmol/mL)	4.21 ± 1.05	5.45 ± 1.18	-1.24 (-1.83 to -0.65)	+29.5%	<0.001
GPx (U/L)	32.15 ± 6.44	25.57 ± 5.89	6.58 (3.39-9.77)	-20.5%	<0.001
Vitamin C (mg/dL)	0.67 ± 0.19	0.50 ± 0.17	0.17 (0.08-0.26)	-25.4%	<0.001
Ceruloplasmin (mg/dL)	30.12 ± 5.98	27.89 ± 5.32	2.23 (-0.75 to 5.21)	-7.4%	0.140

Notably, the older CHD subjects (55-69 years) exhibited a more severe oxidative status impairment compared to the younger CHD subjects (40-54 years), with 29.5% increase in MDA, 20.5% decrease in GPx, and 25.4% decrease in vitamin C levels, indicating a progressive oxidative stress-related deterioration with age.The reduction in antioxidant capacity with age in this study supports the cumulative oxidative damage theory of aging [18].

3.5. Correlation with body mass index

The correlations between BMI and the measured oxidative stress biomarkers in CHD patients are presented in Table 5.

Table 5. Pearson's correlation between BMI and biomarkers in CHD patients

Biomarker	Correlation Coefficient (r)	95% CI	P-value	Strength
MDA	0.42	0.19 to 0.61	0.001	Moderate positive
GPx	-0.38	-0.58 to -0.14	0.003	Moderate negative
Vitamin C	-0.35	-0.56 to -0.10	0.008	Moderate negative

Ceruloplasmin	-0.18	-0.42 to 0.08	0.174	Weak negative

BMI was significantly correlatedere: positiviteitMDA and negatively with GBx, vitamin C with overweight, suggesting that adiposity was relatedenranOxratiersopidation and decreased antioxidant line defenses. These resultssignify were also the obviously associated with the fact that the adipose tissue can induce oxidative stress due to pro-inflammatory cytokine production and mitochondrial impairment [19].

3.6. Inter-correlations between biomarkers

The relationships between the studied biomarkers are summarized in the correlation matrix shown in Table 6.

Table 6. Pearson's correlation matrix between biomarkers in CHD patients

Biomarker Pair	Correlation Coefficient (r)	P-value	Interpretation
MDA vs. GPx	-0.44	<0.001	Moderate negative
MDA vs. Vitamin C	-0.39	0.002	Moderate negative
GPx vs. Vitamin C	0.41	0.001	Moderate positive

Correlations among biomarkers are meaningful, indicating that oxidative stress and antioxidant defenses are integrated systems and that lipid peroxidation is increasing as antioxidant defences decrease.

4. Discussion

4.1. Overview and comparison with recent studies

Results from this study indicate a significant impairment of oxidant and antioxidant status in both lipid peroxidation and antioxidant capacity in CHD patient living in Kirkuk City. These data corroborate an accumulating body of evidence pointing to a role for oxidative stress in the pathogenesis of CHD in different [16].The markedly increased MDA levels in CHD patients as compared to the controls (4.87 ± 1.23 versus 2.15 ± 0.67 nmol/mL) represent a percent increase of 126.5%, which indicates increased lipid peroxidation. This result is in accordance with the recent study of Karakayali et al. (2025) showing that serum MDA level on admission can be used as predictor of in-hospital mortality in patients with acute coronary syndrome, with the best cut off value of >33.1 nmol/mL predicting mortality with a sensitivity of 85% and a specificity of 88% [20].Their prospective study of 556 ACS patients demonstrated that MDA was an independent predictor of mortality in conjunction with age, creatinine and NT-proBNP, thereby providing a powerful clinical application of this biomarker. In a similar vein, Milani et al also report that a meta-analysis of studies measuring OxS biomarkers in HF (number of studies=4; number of participants=582) showed a significantly higher MDA level (ROM = 1.87, 95% CI: 1.49–2. 36) compared with controls, reflecting the stability of this relation with past studies linking CVDs [16].

4.2. Glutathione peroxidase depletion and therapeutic implications

Decreased GPx activities (45.3% decrease) demonstrated in the present study confirmed in CHD patients that supports diminished enzymatic antioxidant defense. GPx is essential for detoxifying hydrogen peroxide and lipid peroxides and its depletion can be attributed to overutilization in chronic oxidative stress situation, limited enzyme production by the means of selenium deficiency, or downregulation of expression [7]. Whole-blood Se concentrations increased significantly (+17.4%, p<0.001) in the Se supplemented group, while there was a decrease (−3.1%, p=0.27) in the placebo group, while GPx activity was also significantly raised (+51.9%, p<0.001) after Se supplementation, as reported by Zhang et al. (2025) who recently observed a reduction in major adverse cardiovascular events (9.1% vs. 21.8%, p = 0.042) in acute coronary syndrome patients [21].

In their Mendelian randomization analysis no statistically strong causal association between genetically predicted GPx activity and the risk of cardiovascular was detected, and the weighted median approach indicated a borderline protective trend (OR: 0.958, 95% CI: 0.918–1.000, p = 0.048), which highlights the importance of GPx in the reactive oxygen species modulation. In a thorough review Forman and Zhang (2021) highlighted that intervention on oxidative stress through antioxidant enzymes might be more promising than on direct antioxidant supplement [22]. These data underline the promise of Se supplementation in the context of adjunctive therapy in high-risk cardiovascular patients and are consistent with our finding in CHD patients with diminished GPx activity.

4.3. Vitamin C depletion and dietary considerations

The significant decrease (by 54.0%) in vitamin C among CHD patients is alarming, since vitamin C is the major water-soluble antioxidant. The finding that 80% of the CHD patients had vitamin C levels < 0.75 mg/dL points to a borderline deficiency, which might be a result of enhanced oxidative consumption or deficient dietary intake or both. "Vitamin C in Patients with type 2 diabetes" Toffalini et al. Vitamin C deficiency was identified in 12.2% of subjects, and lower vitamin C concentrations were independently related to cardiovascular disease after adjusting for multiple variables ($p < 0.05$) [23]. They also importantly demonstrated that vitamin C was strongly linked with fresh fruit and vegetable consumption (28.7 ± 14.8 μmol/L, <1 serving/day, 45.4 ± 17.9 μmol/L, 1-2 servings/day and 49.8 ± 19.2 μmol/L, >2 servings/day), indicating that the dietary source of vitamin C were more important than supplement. In a systematic review by Morelli et al. (2020) on vitamin C and prevention of cardiovascular disease, it was concluded that observational studies have consistently observed inverse relationships, but randomized trials have been disappointing, potentially because of suboptimal dose or duration, or because benefit may be confined to those with deficiency [24]. This is in keeping with our findings, and supports that dietary advice should be a focus in CHD care.

4.4. Ceruloplasmin: Reconciling lower levels with current evidence

The surprising result of decreased ceruloplasmin (CP) in CHD patients (a 30.7% decrease) should be interpreted with caution in the context of recent findings. A systematic review by Arenas de Larriva et al. (2020) of 18 included studies found that the majority report a positive association between high ceruloplasmin levels and risk of coronary heart disease, suggesting that ceruloplasmin may serve as an acute-phase reactant in inflammatory diseases [25]. However, the authors mentioned that it is not yet known whether ceruloplasmin is a passive biomarker or causative factor in inflammation, and they emphasized that more clinical trials to assess its functions are warranted. In a recent study, Wazir et al. (2025) studied serum ceruloplasmin as a risk predictor in cardiovascular disease and concluded that elevation of levels was associated with increased risk in certain populations, but that the association was influenced by inflammatory status, as well as copper levels [26]. The decreased values we detected may reflect consumption under conditions of chronic oxidative stress, or they may be attributable to the strict exclusion criteria (hypertension, diabetes, smoking) applied in this study that favored patients without systemic inflammation, which would explain the lack of an acute-phase reaction. This observation emphasizes the double-faced character of CP and the role of clinical considerations in the assessments of its levels.

4.5. Gender differences and mechanistic insights

The observation of male CHD patients having a more pronounced oxidative imbalance than their female counterparts indicated by 21.4% higher MDA, 17.4%lower GPx, and 26.9% lower vitamin C fits well into the current knowledge of sex-specific features of oxidative stress. A. review by Iboleon-Jimenez et al. (2025) in on mitochondria, sex and the heart indicates female cardiac mitochondria may have a higher antioxidant potential and generate less reactive oxygen species (ROS) when compared to male mitochondria leading to greater cardioprotection [17]. Estrogen has been demonstrated to increase expression of antioxidant enzymes through estrogen response elements and

through activation of MAPK/ERK signaling pathway and to inhibit NADPH oxidase, a key producer of vascular ROS. A study by Maleki et al. on sex differences in oxidative stress markers in patients with metabolic syndrome reported similar results with males suffering from increased oxidative damage and reduced antioxidant capacity [27]. These effects mediated by estrogen may well have a role in the relative protection females have against oxidative insults and provide a potential explanation for the sex differences in our findings.

4.6. Age-related oxidative damage

The progressive worsening of oxidative status with advancing age, with older patients showing 29.5% higher MDA, 20.5% lower GPx, and 25.4% lower vitamin C compared to younger patients, is consistent with the free radical theory of aging. The meta-analysis by Milani et al. also examined telomere length as a marker of cellular aging and found significantly shorter telomeres in cardiovascular patients (ROM = 0.66, 95% CI: 0.53–0.81), indicating accelerated cellular aging [16]. With advancing age, mitochondrial function declines due to accumulation of mutations in mitochondrial DNA, impaired electron transport chain efficiency, and reduced activity of antioxidant enzymes, leading to increased ROS production [18]. A comprehensive review by Liguori et al. (2018) detailed the mechanisms linking aging to increased oxidative stress, including mitochondrial dysfunction, impaired antioxidant enzyme expression, and reduced efficiency of repair mechanisms [28]. These age-related changes may explain, in part, the exponential increase in cardiovascular disease incidence with advancing age.

4.5. BMI and oxidative stress: clinical implications

The significant positive correlations of BMI with MDA and the negative associations of BMI with GPx and vitamin C highlight the importance of body fat in inducing oxidative stress. 3. Adipose tissue, especially visceral adipose tissue, releases pro-inflammatory cytokines such as tumor necrosis factor (TNF)-alpha and interleukin (Il)-6 that promote ROS generation via stimulation of NADPH oxidases [19]. Sixty-one point seven percent of patients with CHD were overweight or obese, a finding that reinforces the need for weight control for reduction of cardiovascular risk. A recent study by Son et al. indicated that total antioxidant status was significantly increased while oxidative stress index was decreased and nitric oxide was elevated after circuit training in obese men, which implies that lifestyle modifications with weight reduction may enhance oxidative status [29]. Moreover, a systematic review conducted by Pinho et al. on the effects of diet and physical exercise on oxidative stress and inflammatory markers in cardiovascular disease found that the synergistic effect of interventions yields the best outcomes in enhancing oxidative status [30].

4.6. Clinical implications and future directions

This study has potential applicability to clinical practice. Firstly, the striking differences in oxidative stress biomarkers indicate that these markers may be useful adjuncts in risk stratification. Karakayali et. found that ranging of MDA in admission could predict ACS patients at the highest risk of in hospital mortality with a high accuracy (AUC:0.905) [20]. Secondly, the pronounced vitamin C depletion suggests that nutritional support with increased intake of fresh fruits and vegetables could be considered, especially since there is a strong dose response relationship between dietary intake and vitamin C status as shown by Toffalini et al. [23]. Thirdly, the correlations between BMI and oxidative stress biomarkers further highlight the pivotal role of body weight management via lifestyle modifications [29]. Fourth, the pronounced GPx depletion raises the possibility that selenium supplementation could be of benefit in selected patients though the evidence from Mendelian randomization argues for caution in interpreting causality [21]. In their review of 2020, Fiorino et al. analyzed the complex interplay between oxidative stress, inflammation, and atherosclerosis, and concluded that novel multi-targeted strategies, aimed at combating both oxidative damage and inflammation could be more effective than monotherapies [31-35]. Continued research should

concentrate on prospective investigations to establish causal associations and on randomized controlled trials to assess the advantages of targeted antioxidant enhancement via dietary modification and lifestyle change.

5. Conclusion

This study demonstrates that CHD patients in Kirkuk City exhibit profound oxidative stress characterized by significantly elevated MDA levels (126.5% increase) and compromised antioxidant defenses including reduced GPx activity (45.3% decrease), vitamin C depletion (54.0% reduction), and lower ceruloplasmin levels (30.7% reduction). Male patients show more severe oxidative imbalance than females, with significantly higher MDA and lower GPx and vitamin C levels. Oxidative stress worsens with advancing age, with older patients showing 29.5% higher MDA, 20.5% lower GPx, and 25.4% lower vitamin C compared to younger patients. BMI correlates positively with lipid peroxidation and negatively with antioxidant markers. These findings highlight the importance of oxidative stress in CHD pathogenesis and suggest that assessment of these biomarkers may aid in risk stratification and monitoring of disease progression. Further research is needed to establish causal relationships and evaluate the benefits of targeted antioxidant optimization through dietary modification and lifestyle interventions in this population.

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