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Role of oxidative stress and severity of diabetic retinopathy in type 2 diabetes

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***Abstract*---**The study included 60 diabetic patients (30 patients with type 2 diabetes mellitus complicated with diabetic retinopathy (DR) and 30 patients with T2DM not complicated with DR). The study also included 30 healthy control individuals defended as subjects who apparently haven't any chronic diseases. Fundus examination was carried out by an expert ophthalmologist. The study showed that the highest mean of serum MDA was recorded (P<0.05) in DR patients (55.96 ng/ml) and DM patients (37.86 ng/ml), the lowest (P<0.05) was in the control group gave an MDA (16.94 ng/ml). also demonstrated that there was the lowest mean of serum SOD was recorded (P<0.05) in DR patients (10.056 IU/ml) and the highest was (P<0.05) in the control group gave a SOD (42.865 IU/ml) While it also recorded a significant decrease (P<0.05) for DM patients (12.64 IU/ml). Additionally, the level of serum GSH was reduced significantly (P<0.05) in DR patients (1.100 ug/mL) as compared with the control group (14.745 ug/mL), which also showed that serum GSH was reduced significantly(P<0.05) in DM patients (2.766 ug/mL). Furthermore, the level of serum zinc was reduced significantly (P<0.05) in DR patients (33.6 ug/dL) as compared with the control group (98.5 ug/dL), Moreover showed that serum zinc was reduced significantly (P<0.05) in DM patients (44.05 ug/dL). Lower serum Zn, SOD, and GSH levels, as well as elevated MDA levels, are associated with DR severity in T2DM patients.

***Keywords*---** xidative stress, antioxidant, type 2 diabetes mellitus, diabetic retinopathy.

Introduction

Diabetes mellitus is a chronic illness characterized by an increase in blood sugar levels caused by insufficient insulin production, either absolute or relative(Scanlon et al., 2017). In terms of public health, this is a major concern. Diabetes mellitus is becoming more common, and by 2025, the number of people with the disease will have doubled. It is estimated that it affects around 170 million people worldwide. It is sometimes referred to as the "silent disease," because it causes no symptoms until it has progressed to the point of causing serious organ damage(Haneen et al., 2021). Diabetic retinopathy is the leading cause of lengthy visual loss in those over the age of 20. Retinopathy is a vasculopathy caused by the breakdown of the blood-retinal barrier and the closure of retinal capillaries. Recent research suggests that DR begins as a neuro-retinopathy, with vascular changes occurring early in the illness(Stewart, 2017). Nonetheless, Diabetic retinopathy continues to be a major cause of acquired vision loss in working-age adults around the world.

Oxidative damage is a crucial element in the development of DR. Reactive oxygen species (ROS) formed as a result of hyperglycemia through various processes have a tendency to destroy important biomolecules such as DNA, proteins, and lipid membranes, hence impairing the normal physiology of the cells (Oguntibeju, 2019). Especially susceptible to oxidative stress damage is the retina. In people with DR, the development of proliferative DR (PDR) and/or diabetic macular edema may result in visual impairment. Consequently, retinal blood vessel disruption is regarded as a crucial factor in the etiology of DR (Bokhary et al., 2021). The increased production of reactive oxygen species (ROS) in conjunction with low antioxidant status (enzymes) leads to increased cellular oxidation. Moreover, the cells are prone to oxidative damage owing to inadequate control by antioxidant enzymes, and this may be the cause of DM development and related problems. The two most important antioxidant enzymes are superoxide dismutase (SOD) and catalase (CAT). SOD catalyzes the disproportionation of the superoxide radical into molecular oxygen (O2) and hydrogen peroxide (H2O2) (Bokhary et al., 2021).

Materials and Methods

Study design

This case-control (comparative) study was conducted in Ramadi General Hospital from November 1, 2021 to February 28, 2022.

Study protocol and laboratory analysis

The study comprised 60 diabetic patients (30 with T2DM complicated by DR and 30 without T2DM complicated by DR), aged 50 to 70, who attended Al Nahrain Clinics. An expert ophthalmologist performed a fundus examination on all participants to determine whether they had diabetic retinopathy. The study also included 30 healthy control volunteers who did not appear to have any chronic conditions. Clinical data and anthropometric parameters were collected after obtaining informed written consent from each study patients. About 5 ml of

venous blood was drawn from all patients. The sample was centrifuged at 4000 rpm for 5 mintues and serum was separated. Serum levels of MDA (SunLong Biotech Co.,LTD, China) SOD (SunLong Biotech Co.,LTD, China) and GSH (SunLong Biotech Co.,LTD, China) estimated using commercially available ELISA kits and readings taken using Biotech ELISA reader. Addaitionally Serum levels of zinc (ZINCO LTA, Italia) measured using the enzymo-calorimetric technique.

Statistical analysis

A statistical analysis of data was carried out using SPSS version 22. The statistical importance level was set as P value less than 0.05. Descriptive statistics consist of mean, standard deviation (SD), and standard error (SE) was calculated for each parameter. The comparisons among cases and controls were computed by Independent-Samples T-Test.The Correlations between the diffrente of parameters were studied via Pearson's correlation (r=−1 to 1).

Results

The study showed that the highest mean of serum MDA was recorded (P<0.05) in DR patients (55.96 ng/ml) and DM patients (37.86 ng/ml), the lowest (P<0.05) was in the control group gave an MDA (16.94 ng/ml) as shown in figure 1. also demonstrated that there was the lowest mean of serum SOD was recorded (P<0.05) in DR patients (10.056 IU/ml) and the highest was (P<0.05) in the control group gave a SOD (42.865 IU/ml) While it also recorded a significant decrease (P<0.05) for DM patients (12.64 IU/ml) as shown in figure 2. Additionally, the level of serum GSH was reduced significantly (P<0.05) in DR patients (1.100 ug/mL) as compared with the control group (14.745 ug/mL), which also showed that serum GSH was reduced significantly(P<0.05) in DM patients (2.766 ug/mL) as shown in figure 3. Furthermore, the level of serum zinc was reduced significantly (P<0.05) in DR patients (33.6 ug/dL) as compared with the control group (98.5 ug/dL), Moreover showed that serum zinc was reduced significantly (P<0.05) in DM patients (44.05 ug/dL) as shown in figure 3. The study showed a negative correlation (P<0.05) in DR patients between serum GSH (r: -.982**), SOD (r: -.975**), and Zinc (r: -.924**) concentrations with MDA in DR patients. which is mean that serum MDA is decreased when antioxidants is raised and vice versa.

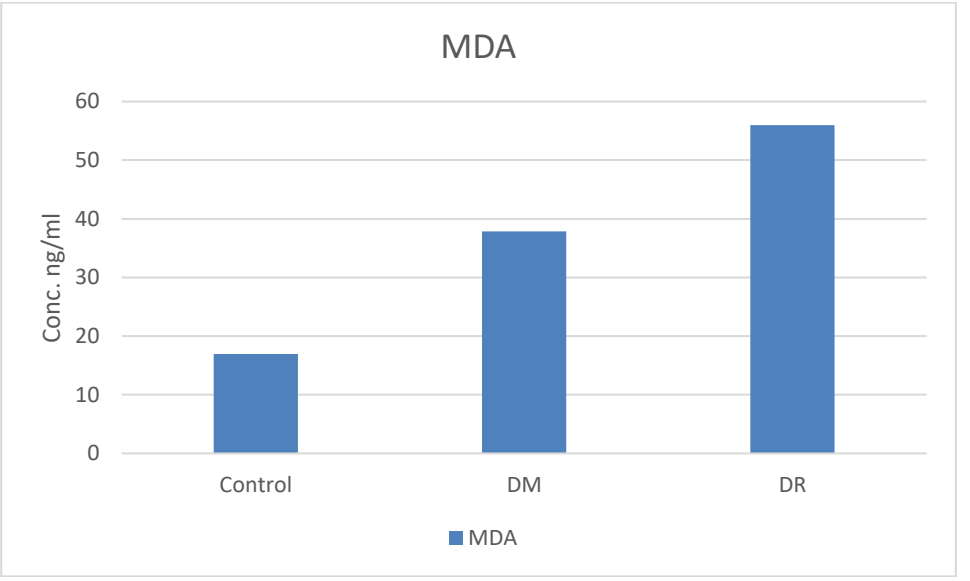

Figure 1. shows the significant effect of diabetes mellitus type 2 and diabetic retinopathy on the level of MDA in the serum

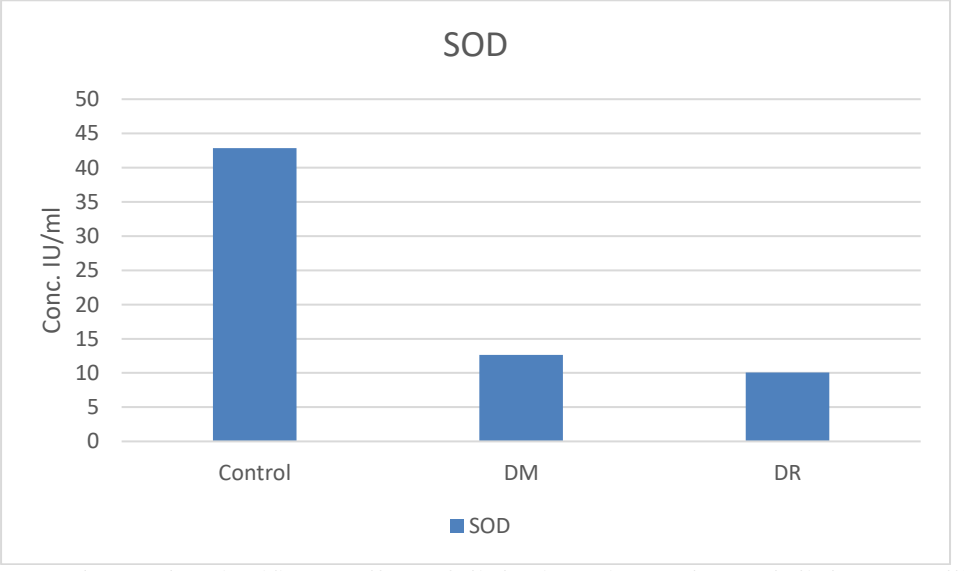

Figure 2. shows the significant effect of diabetic retinopathy and diabetes mellitus type 2 on the level of SOD in the serum

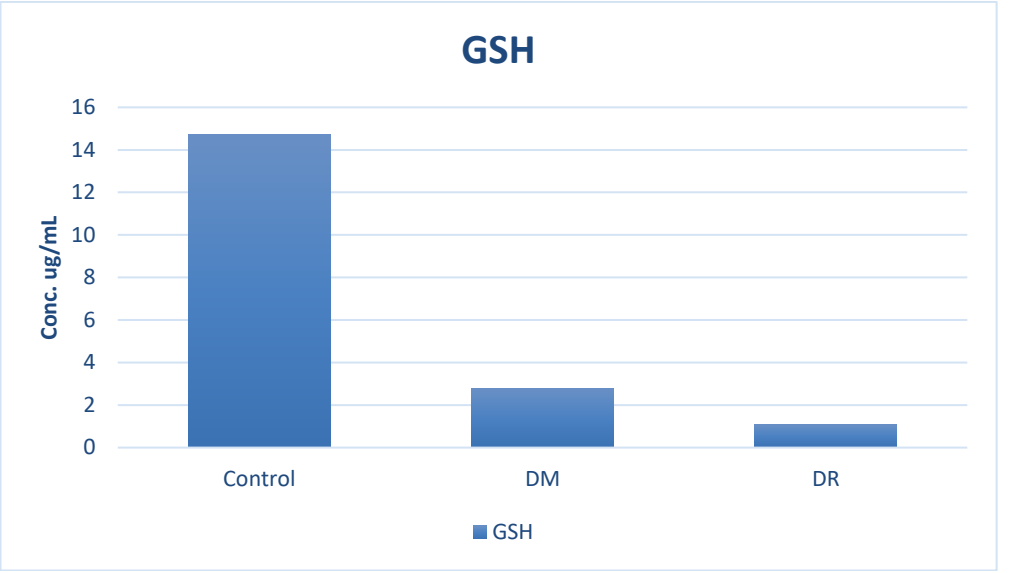

Figure 3. shows the significant effect of diabetic retinopathy and diabetes mellitus type 2 on the level of GSH in the serum

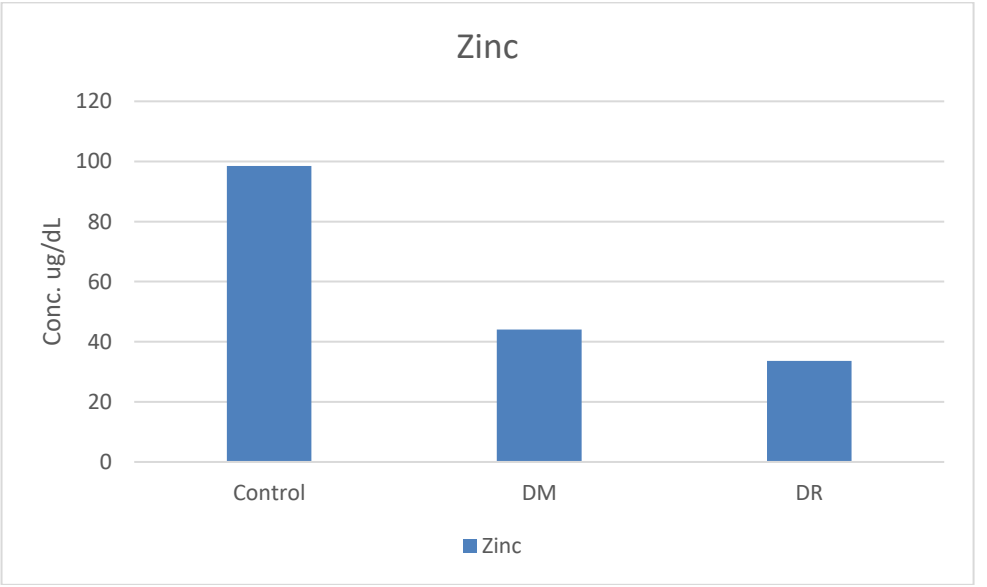

Figure 4. shows the significant effect of diabetic retinopathy and diabetes mellitus type 2 on the level of zinc in the serum

Discussion

Relation of serum MDA with diabetic retinopathy

In vivo, free radicals are produced as a byproduct of regular metabolism, the body produces free radicals such as superoxide, nitric oxide, and hydroxyl radicals, as well as other reactive species such as hydrogen peroxide, peroxynitrite, and

hypochlorous acid, mostly as a byproduct of aerobic metabolism, Chemically, free radicals are generally reactive, with some (e.g. HO•) being particularly reactive, These reactive radicals and oxidants may cause damage to cells and tissue both directly and indirectly via the oxidative destruction of critical biological components (Chatterjee & Chakraborti, 2020). findings were in agreement with the study done by (Chatterjee & Chakraborti, 2020) who showed increased MDA levels in cases compared to controls suggest a role for free radicals in the pathogenesis of diabetes complications such as retinopathy. also revealed higher level of MDA were observed in patients with retinopathy compared with controls (Khalili et al., 2022).

Relation of serum SOD with diabetic retinopathy

Aerobic organisms have integrated antioxidant systems that comprise enzymatic and non-enzymatic antioxidants that are often efficient in preventing the deleterious effects of reactive oxygen species (ROS). SODs are metal-containing enzymes that catalyze the dismutation of superoxide radicals to oxygen and hydrogen peroxide. They are present in all aerobic organisms studied and play a critical role in the defense against harmful reduced oxygen species (Chatterjee & Chakraborti, 2020). In agreement with this finding (Chatterjee & Chakraborti, 2020) which was found to be decreased in cases significantly with respect to controls. Our results were agreed with the findings reported by (Bokhary et al., 2021) SOD levels were found to be significantly lower in diabetic participants than in nondiabetic controls. Additionally,(Hou et al., 2021) demonstrated that SOD activity was shown to be lowest in diabetic patients with complications; this automatically increased the amount of lipid peroxides (malondialdehyde), as compared to individuals who were not diagnosed with MVC complications or those in the control group.

Relation of serum GSH with diabetic retinopathy

In agreement with this finding (Khalili et al., 2022) demonstrated that a GSH levels were considerably decreased in individuals with diabetic retinopathy compared to T2DM patients without complications and controls. GSH is the most abundant antioxidant in cells, and it is critical for antioxidant defense by controlling the redox state and neutralizing free radicals. Indirectly, hyperglycemia depletes GSH through the polyol pathway, which utilizes NADPH to regenerate GSH via glutathione reductase-catalyzed reactions (Khalili et al., 2022). Our results were agreed with the findings reported by (Bokhary et al., 2021) Diabetes increased the MDA level in the retina while lowering the SOD and GSH levels

Correlation MDA with SOD, GSH and Zinc in diabetic patients with and without DR

The study showed a negative correlation ($P<0.05$) in DR patients between serum GSH (r: -.982**), SOD (r: -.975**), and Zinc (r: -.924**) concentrations with MDA in DR patients. (Kumari et al., 2014) was MDA and Zn exhibited a high inverse correlation ($r = -0.82$). Also our findings were in agreement with the study done by (Tabatabaei-Malazy et al., 2019) shown that a significant correlation between

MDA and zinc. Another research demonstrated that Compared to controls, superoxide dismutase levels were drastically reduced in cases, although malondialdehyde levels were dramatically elevated (Chatterjee & Chakraborti, 2020) . Additionally,(Hou et al., 2021) demonstrated that SOD activity was shown to be lowest in diabetic patients with complications; this automatically increased the amount of lipid peroxides (malondialdehyde), as compared to individuals who were not diagnosed with MVC complications or those in the control group.

Ethical Clearance

All experimental protocols were approved under the Anbar Health Directorate and all experiments were carried out in accordance with approved guidelines

Conclusion

In conclusion, Antioxidants may influence the development of DR by targeting several stages of oxidative stress and mitochondrial dysfunction. A notable Serum levels of SOD, MDA, GSH, and Zinc may serve as an early indication or marker of diabetic retinopathy.

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