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RESEARCH PAPER

Evaluation of Advanced Glycation End Products, Oxidative Stress and Antioxidants and their Relationship in Diabetic patients

Zahraa Saad Tahseen[1], Kamaran Abdoulrahman[2]

1 Department of Chemistry, Faculty of Science and Health, Koya University, Koya KOY45, Kurdistan Region - F.R. Iraq
2Department of Chemistry, College of Science, Salahaddin University-Erbil, Kurdistan Region, Iraq.

A B S T R A C T:

Objective: Diabetes Mellitus (DM) is a major public health problem in developed countries; which also plays a vital role in providing information about advanced glycation end products (AGEs) and these induce oxidative stress (OS). The aim of this study is to evaluate the AGEs, OS, antioxidant, and lipid profile parameters in sera of DM patients.

Methods: The current study includes 82 subjects (50 patients with type II DM and 32 healthy subjects, men and women). Demographic factors and medication intake of every subject were obtained. The advanced glycation end products (AGEs), oxidative stress (OS), antioxidant, and lipid profile parameters were measured using a spectrometric method and ELISA test.

Results: The present study elucidated that the serum levels of CML, CEL, Pyralline, 8-OHdG, and MDA were significantly increased in diabetic patients compared with the healthy group. The serum levels of GSH, NO, and GSH-Px were significantly decreased in patients with DM rather than in the healthy group. While the serum levels of CAT and SOD were non-significantly decreased in patients with DM.

Conclusion: Meanwhile, the elevation of AGEs and OS are associated with DM patients. NO and CML could be potential biomarkers for DM.

KEY WORDS: Advanced Glycation End products (AGEs), Oxidative Stress (OS), Antioxidants, lipid profile, Diabetes Mellitus (DM)
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1. INTRODUCTION :

Diabetes mellitus (DM) is one of the major threats to human health and is the most significant health system challenge in the twenty-first century (Iacobini et al., 2021). Based on the International Diabetic Federation's 2019 report, 351.7 million individuals in the age range 20 to 65 have been diagnosed or suspected of having diabetes in 2019 (Byrne et al., 2021). The global prevalence of diabetes mellitus is predicted to rise from 415 million to 440 million cases in 2030 and 645 million in 2040 (Darenskaya et al., 2021). Approximately 90% suffer from type II DM while only 5–10% have type I DM (Jud and Sourij, 2019).

Diabetic nephropathy, neuropathy, and retinopathy are known as microvascular complications and diabetic nephropathy nowadays is the major source of end-stage renal disease and diabetic retinopathy represents the main cause of blindness (Ahuja et al., 2022). Furthermore, diabetics are more likely to develop angiopathies such as coronary heart disease, lower extremity arterial disease, and cerebrovascular disease (Wang et al., 2022). The risk for cardiovascular death is approximately twice as high as compared to non-diabetic counterparts (Pickering et al., 2018). Additionally, people with diabetes are more likely to develop cataracts, erectile dysfunction, or cognitive impairment, such as Alzheimer's disease (Luc et al., 2019, Poretsky, 2010, Agushaka and Ezugwu, 2020).

Diabetes mellitus is characterized by chronic hyperglycemia, which results in the generation of detrimental products known as AGEs (Korac et

* **Corresponding Author:**
Zahraa Saad Tahseen
E-mail: zahra.00697467@gmail.com
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al., 2021, Yuan et al., 2019, Ito et al., 2019). AGEs are a heterogeneous class that generates either endogenously or exogenously derived glycated proteins and lipoproteins (Shen et al., 2020). These compounds are formed by non-enzymatic glycation of lipid and protein molecules when they come into contact with sugars, both exogenously from the diet during high-temperature food preparations and endogenously in the body during hyperglycemia (Shi et al., 2021, Corica et al., 2021, Serveaux-Dancer et al., 2019). Metabolism of glucose during glycolysis leads to the formation of methylglyoxal, a carbonyl intermediate in the synthesis of certain AGEs (Plemmenos and Piperi, 2022, Sellegounder et al., 2021, Pinto et al., 2022). Under conditions of oxidative stress, amino acids, reducing sugars, and lipids undergo autoxidation to generate additional reactive carbonyl compounds and increase the production of AGEs leading to tissue accumulation (Abdoulrahman, 2016, Abdoulrahman, 2017). Modifications in the tertiary structure of proteins by AGEs lead to physiological disturbances, thereby causing multiple organ damages in diabetes (Fishman et al., 2018, Dobi et al., 2021, Rungratanawanich et al., 2021). As a result, in the last decade inhibiting AGE formation, antagonizing RAGE, or suppressing RAGE expression have all become viable therapeutic targets for this condition (Kamil Kadhim Lawi et al., 2021). Increasing evidence supports the role of the AGE/RAGE axis in the development and progression of diabetic patients (Cao et al., 2021, Briceno Noriega et al., 2022, Song et al., 2021).

Diabetes mellitus is associated with the organism's oxidative and anti-oxidative status (Khalili et al., 2022). Free radicals and oxidative stress (OS) play a major role in the development and progression of diabetic complications (Bala et al., 2021, Moridi et al., 2015, Deng et al., 2021, Tsai et al., 2021). Oxidative stress (OS), a pathological condition, is associated with the overproduction of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which reduces the scavenging capacity of antioxidant systems (Ma et al., 2022, El-Masry and Mahmoud, 2021, Parcheta et al., 2021, Hajam et al., 2022). Enhanced oxidation of lipids, proteins, and DNA, which has been observed in DM patients from the early stages, may result in organ damage (Asgharpour and Alirezaei, 2021, Michalak, 2022). Under normal conditions, oxidative stress is a major component of the innate immune system, which is part of the body's defense mechanisms against pathogens (Wang et al., 2021). On the other hand, oxidative stress contributes to the development of a number of non-communicable complications (chronic diseases) (Okdahl and Brock, 2021). Over the time the DM patients are suffering from elevation of lipid profile, and this leads to accumulation of cholesterol on the arteries and plaque formation (Mirończuk-Chodakowska et al., 2018, Charlton et al., 2020, Deng et al., 2021). The purpose of the study is to determine the state of AGEs, OS, and antioxidants in sera of type II diabetic patients and find the correlations between AGE with oxidative stress, antioxidants and lipid profile. The parameters involved in the estimation include Carboxymethyl-lysine (CML), Carboxyethyl-lysine (CEL), Pyrraline, Malondialdehyde (MDA), Nitric Oxide (NO), 8-Hydroxydeoxyguanosine (8-OHdG), Catalase (CAT), Glutathione (GSH), Superoxide Dismutase SOD, Glutathione peroxidase (GSH-Px), Total cholesterol, Triglyceride (TG), High-density lipoprotein (HDL), Low-density lipoprotein (LDL), and Very low-density lipoprotein (VLDL).

2.Materials and Methods

The study was designed to investigate Advanced Glycation End Products and other biochemical parameters such as oxidative stress, antioxidants, and lipid profile in Diabetes Mellitus patients and healthy group. For this study, blood samples of 82 individuals with type II diabetes mellitus patients at Hawler Diabetic Center and Koya-Shahid Doctor Khalid Hospital were collected. The study consisted of 50 patients (25 males and 25 females) who had (HbA1C $\geq$ 7) Diabetes mellitus as the patient group. Although, blood samples of 32 individuals (16 males and 16 females) as a healthy group were obtained who had no diabetes. The patients and healthy groups ranged in age from 38 to 78. The blood sample collection started in October 2021 and was completed in November 2021. A venous blood sample of approximately (8 ml) was obtained from both patients and healthy individuals. After 15 minutes of letting the blood clot at room temperature in a yellow clot activator tube, the samples were centrifuged at 1500 rpm for 10 minutes to separate the serum, which was

then separated into small parts and refrigerated until further examination. Furthermore, a meeting interview was used to fill in a questionnaire that was designated for matching the study's needs. The interviews were conducted face to face by a questionnaire that included personal information, health and medical history (age, weight, height, gender, family history of DM, medications, and other diseases in relation to diabetes mellitus). All biochemical parameters AGEs, antioxidants, and oxidative stress were determined by using (SUNLONGBIOTECH) ELISA kits. The serum lipid profile determination was performed using a Cobas Integra 400 analyzer (Roche Diagnostics System, Mannheim, Germany). This study is performed at the Research Center of Koya University and Novella Lab for Medical Analysis, Erbil.

2.1Statistical Analysis

In the current study, statistical analysis was carried out by Graph pad-prism (version 9). The data were expressed as mean ± standard deviation (mean ± SD). The differences between groups are tested by the Student t-test and Pearson correlation which were utilized to assess relationships between the parameters. The level of P-value ($P<0.05$) level of significance is deemed to be statistically significant. Additionally, the area under the curve (AUC) for diagnostic accuracy in diabetic patients was evaluated by applying the Receiver Operating Characteristic analysis (ROC) curve.

3.Results and Discussion

Diabetes Mellitus plays a crucial role in formation of advanced glycation end products induce oxidative stress. This study shows that the mean serum levels of CML, CEL, and Pyrraline in DM patients are 609.3±23.09 ng/ml, 77.53±2.873 ng/ml, and 286.7±11.43 ng/ml, respectively. However, the control group 458.5±13.45 ng/ml, 66.85±2.150 ng/ml, and 224.2±11.08 ng/ml. The P-values are <0.0001, 0.0035, and 0.0004, as presented in **Figure 1**. These results exhibit that the mean level of CML, CEL, and pyralline are significantly higher than those of the control group. These results are consistent with some previous report investigations which reported that the serum level of AGEs are significantly higher in DM patients as compared with the control group (Wang et al., 2019, Sun et al., 2020, Ramasamy et al., 2016). Recently a similar pattern of data has been obtained, about a significant increase in CML, CEL, and Pyralline serum levels in DM patients (Nakano et al., 2020, El Jellas et al., 2022, Fan et al., 2021). Based on our data, we hypothesize that persistent hyperglycemia increases the generation of reactive oxygen species (ROS) from a variety of sources in diabetic individuals. Therefore, the rate of AGE generation in DM patients increase.

The current study illustrates that the median serum level of MDA is 186.0 (160.6, 219.4) ng/ml, and the mean serum levels of NO, and 8-OHdG in DM patients are 82.73±2.453 ng/ml, and 1468±59.20 ng/ml, respectively, while in the healthy group are 153.8 (131.9, 189.8) ng/ml, 101.7±3.153 ng/ml, and 1229±39.99 ng/ml, correspondingly, as shown in **Figure 1**. The P-values are 0.0025, <0.0001, and 0.0009. These data show that the serum levels of MDA and 8-OHdG in DM patients are significantly higher compared to the healthy group. Although, NO in DM patients is significantly lower compared to the healthy group. These results are similar to other results which reported the lipid peroxidation level represented by serum MDA and 8-OHdG in DM patients were significantly higher, compared to the controlled group (Ummaiya et al., Amiri et al., 2011). Recently similar patterns of data have been obtained, about a significant increase in MDA and 8-OHdG serum levels in DM patients (Li et al., 2019, Dai et al., 2019). These are due to that Diabetes Mellitus is associated with enhanced oxidative stress, and supposed that this might lead to the development and progression of CVD. Furthermore, another study displayed that the serum level of NO is lower in DM patients as compared to the control group (Gheibi et al., 2020). NO bioavailability has been shown to be decreased in type II diabetes. Hyperglycemia contributes to endothelial dysfunction and leads to a decrease in NO bioavailability by inhibiting basal levels of eNOS expression/activity or increased NO quenching (increased NO oxidation). Moreover, it has been demonstrated that uncoupling of NOS, led to decreased availability/transport of L-arginine, and an increase in arginase activity resulted in reduced NO generation.

Our study shows that the mean serum levels of CAT, GSH, SOD, and median levels GSH-Px in DM patients are 3.866±0.07617 ng/ml, 11.64±0.4492 ng/ml, 5.437±0.3838 ng/ml, and 9.484 (8.779, 10.92) ng/ml, while in contrast in the healthy group are 4.070±0.09036 ng/ml, 13.69±0.5886 ng/ml, 6.056±0.3667 ng/ml, and 10.78 (9.609, 12.24) ng/ml, sequentially. The P-values are 0.0951, 0.0165, 0.2695, and 0.0065. These results exhibit that the mean levels of GSH and GSH-Px in DM patients are significantly lower compared to the healthy group. Whereas, the mean levels of CAT and SOD in DM patients are not significantly lower compared to the healthy group. These results are consistent with some previous report investigations which exhibited that the serum levels CAT, GSH, SOD, and GSH-Px are lower in DM patients as compared to the control group (Arpaci et al., 2020, Dworzański et al., 2020, Arribas et al., 2016). However, the results of this study are in disagreement with the results of a previous study that demonstrated the CAT level in serum DM patients is significantly higher than in the healthy group (Zarei et al., 2018). Recently similar patterns of data have been obtained, about a decrease in CAT, GSH, SOD, and GSH-Px serum levels in DM patients (Feng et al., 2020, Onyibe et al., 2021, Ling et al., 2020). Antioxidants are natural substances that may inhibit or delay certain types of cell damage. Furthermore, they play a vital role in antioxidant defense and may serve as oxidative stress biomarkers (Jebur et al., 2016). Based on our research, we postulated that excessive ROS accumulation, due to CAT, GSH, SOD, and GSH-Px deficiency, inhibits gene expression or the protein production of key transcriptional factors, lowers islet β cell mass, insulin synthesis, and insulin secretion thus resulting in DM.

The present study demonstrates that the mean serum levels of Cholesterol, HDL-Cholesterol, and LDL-Cholesterol in DM patients are 153.4±5.358 mg/dl, 29.79±1.114 mg/dl, and 91.94±4.477 mg/dl, respectively, whereas in the control group are 164.7±8.866 mg/dl, 34.07±1.397 mg/dl, and 107.5±7.055 mg/dl. Furthermore, the median levels of TG and VLDL in DM patients are 207.0 (133.0, 291.3) and 41.40 (26.60, 58.25). While in the control group are 155.0 (118.3, 211.5) and 31.00 (23.65, 42.30), as shown in **Figure 2.** The P-values are 0.2482, 0.0188, 0.0534, 0.0607 and 0.0558. These results illustrate that the serum levels of Cholesterol and LDL in DM patients are not significantly lower compared to the healthy group. The serum levels of TG and VLDL in DM patients are not significantly higher compared to the healthy group. Although, the serum level of HDL in DM patients is significantly lower as compared to the healthy group. These results are consistent with some previous report investigations which reported that the serum level of TG is higher in DM patients as compared to the control group. However, the serum levels of cholesterol, HDL, and LDL in diabetic patients are significantly lower than in the healthy group (Cui et al., 2016). In contrast, another study showed a non-significant decrease in serum TG level in cases with DM rather than in the control group (Artha et al., 2019). Dyslipidemia is an important problem maker for chronic non-infectious diseases (Panahi et al., 2017, Islam et al., 2019, Bhambhani et al., 2015). There is a high incidence of dyslipidemia in both T1DM and T2DM patients [72]. Therefore, in addition to hemoglobin HbA1c control, it is necessary to examine the serum lipid profile of DM patients and take appropriate action based on age and type of disorder.

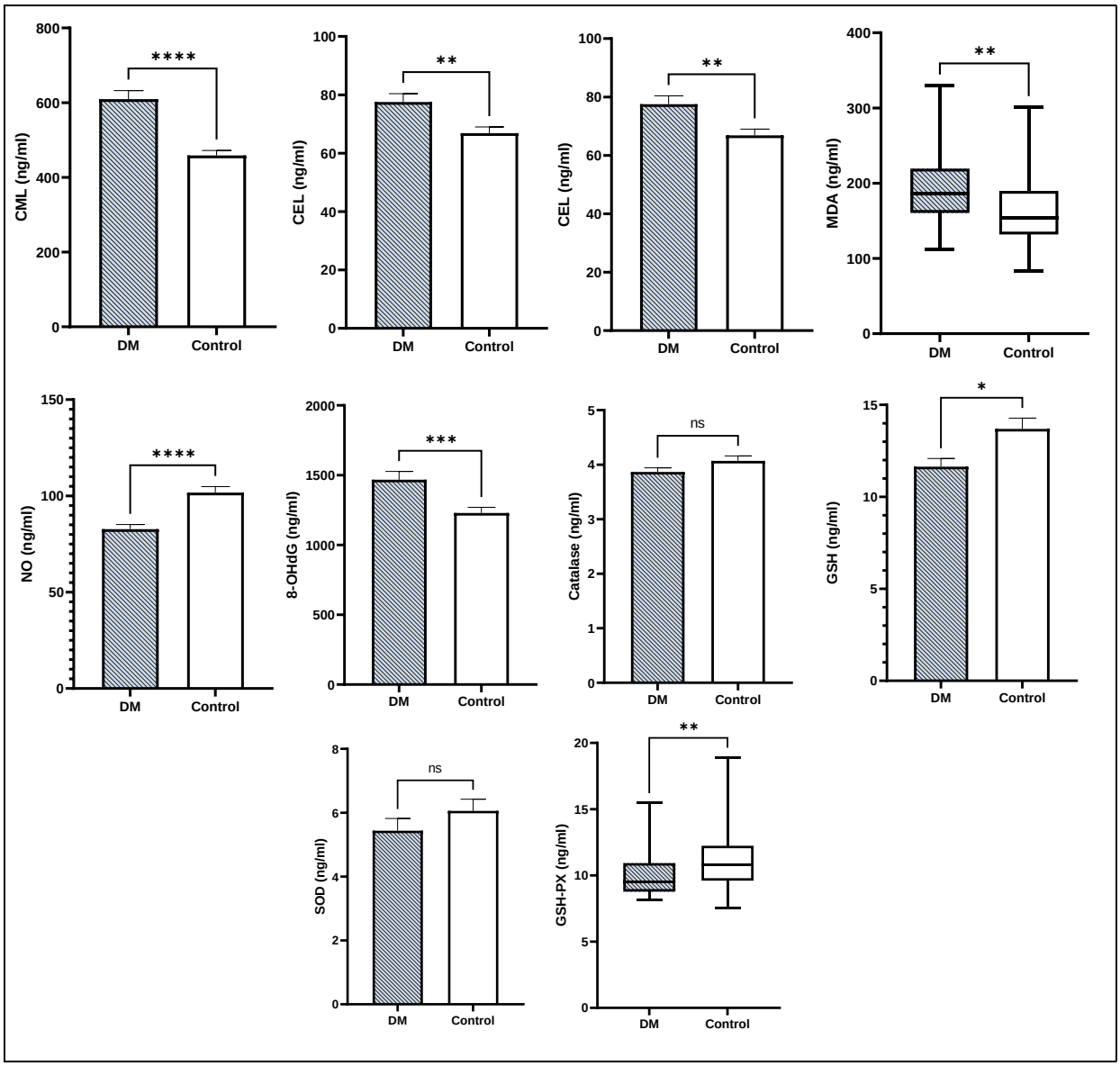

Figure 1: Serum levels of CML, CEL, Pyralline, MDA, NO, 8-OHdG, CAT, GSH, SOD, and GSH-Px in DM patients and healthy group.

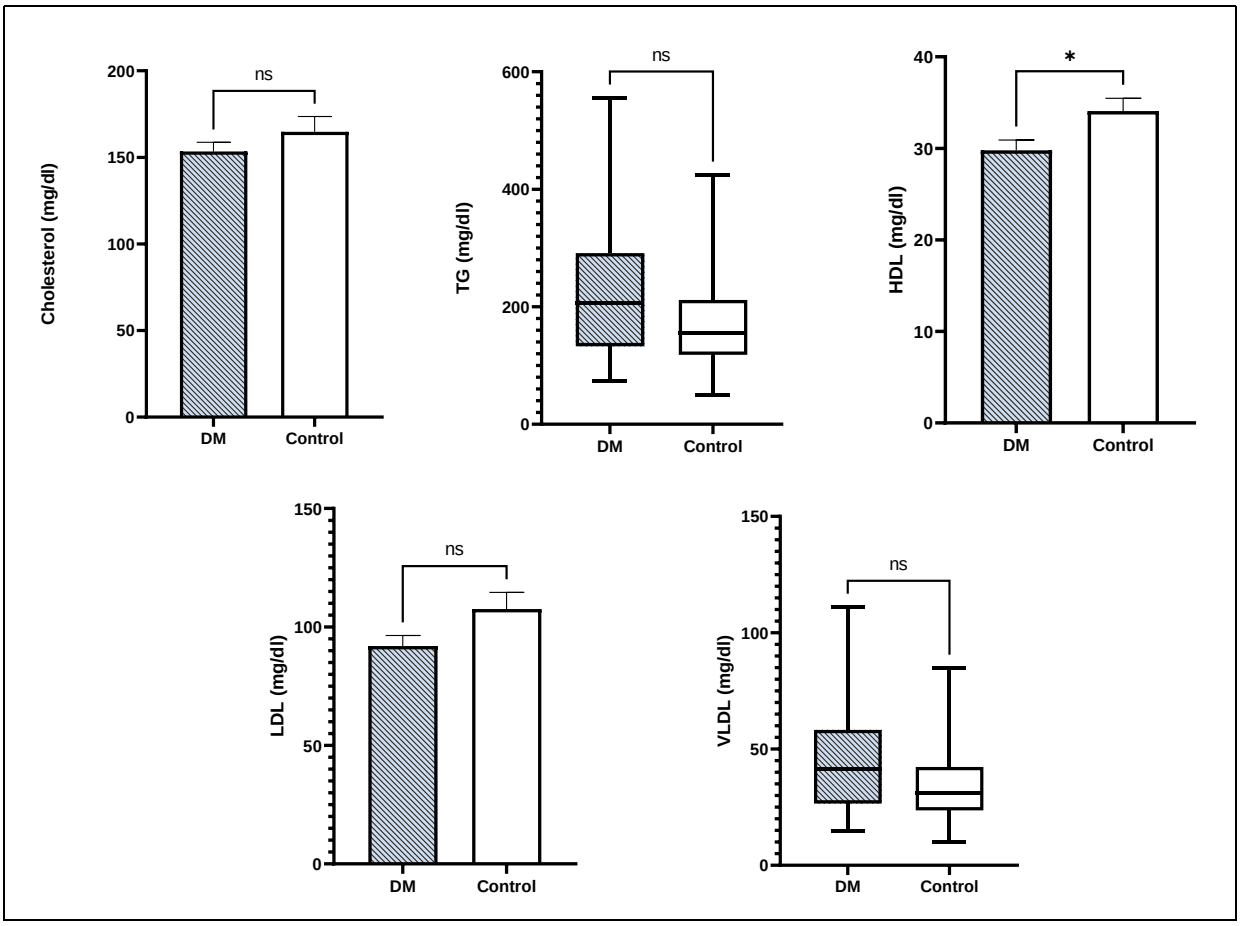

Figure 2: Serum levels of Cholesterol, TG, HDL, LDL, and VLDL in DM patients and healthy group.

The correlation analysis was performed to find the relationship between CML with MDA, NO, 8-OHdG, CAT, GSH, SOD, and GSH-Px. The results of this study show there is positive non-significant correlation between CML and 8-OHdG, CAT, GSH, SOD, and GSH-Px. The Correlation coefficient (r) for 8-OHdG (0.1876), CAT (0.08392), GSH (0.1087), SOD (0.09062), and GSH-Px (0.2287). And there is a negative non-significant correlation between serum CML and NO which is a Correlation coefficient (r) for NO (-0.1012). Although, there is a positive and significant correlation between CML and MDA with the Correlation coefficient (r) (0.3896), as shown in **Figure 3**. These findings are in agreement with a previous report study, which reported that there is a non-significant and moderate correlation between CML and SOD (Legiawati et al., 2020). Furthermore, another study reported that there is a negative moderate correlation between CML and NO (Mogale et al., 2019).

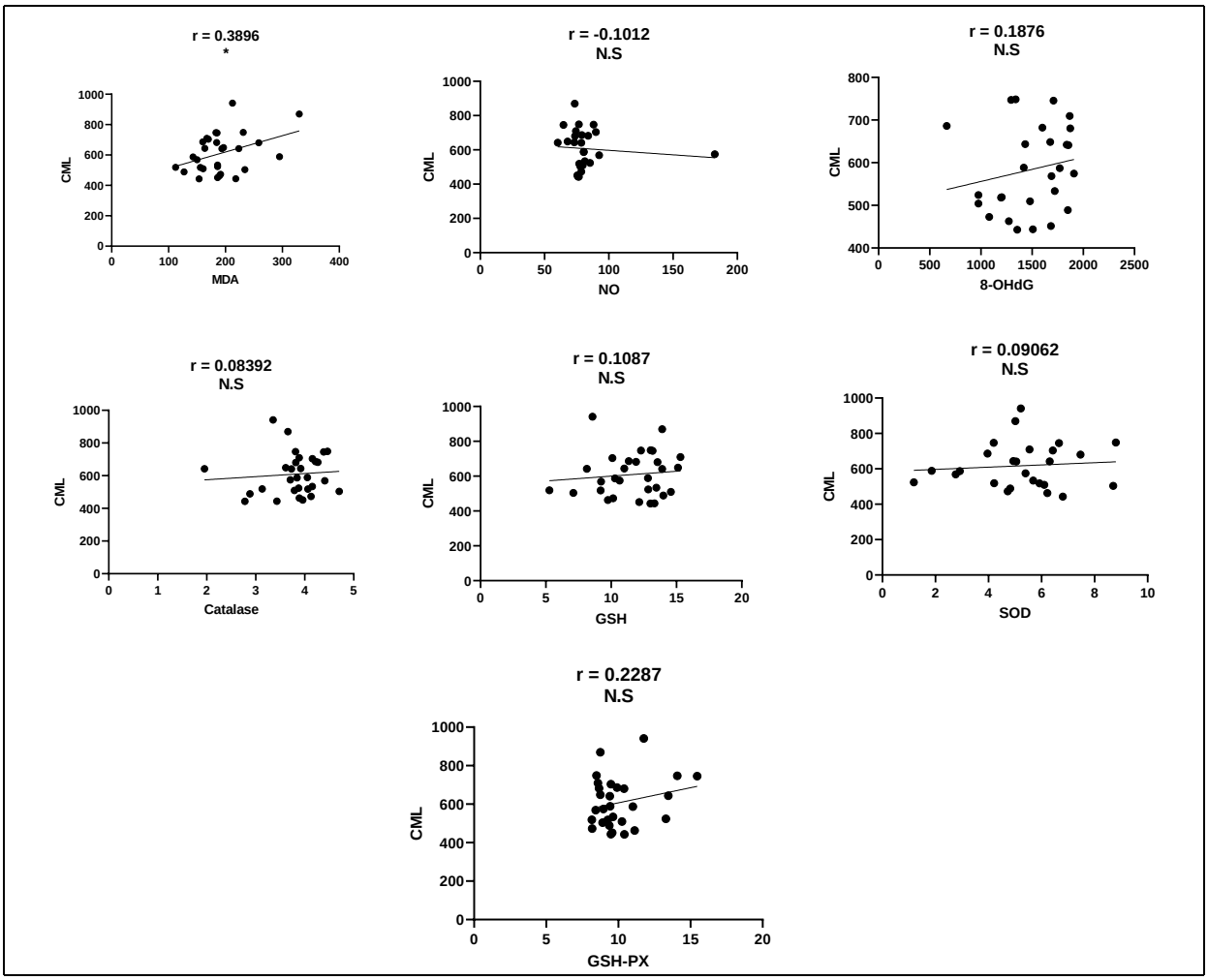

Figure 3: Correlation analysis between CML with MDA, NO, 8-OHdG, CAT, GSH, SOD, and GSH-Px.

In correlation between CEL with MDA, NO, 8-OHdG, CAT, GSH, SOD, and GSH-Px. The data shows that there is a positive non-significant correlation between CEL and MDA, 8-OHdG, GSH, SOD, and GSH-Px. The Correlation coefficient (r) for MDA (0.1167), 8-OHdG (0.3665), GSH (0.1563), SOD (0.1099), and GSH-PX (0.1992). While, there is a non-significant negative correlation between CEL with NO and CAT with Correlation coefficient (r) (-0.07032) and (-0.04570), respectively, as shown in **Figure 4**. These findings are in the same line with the previous observation which reported that there are positive and non-significant correlations between CEL and MDA in diabetic patients (Tan et al., 2018). Additionally, another study reported that there is a positive correlation between CEL with SOD and GSH-Px (Li et al., 2022).

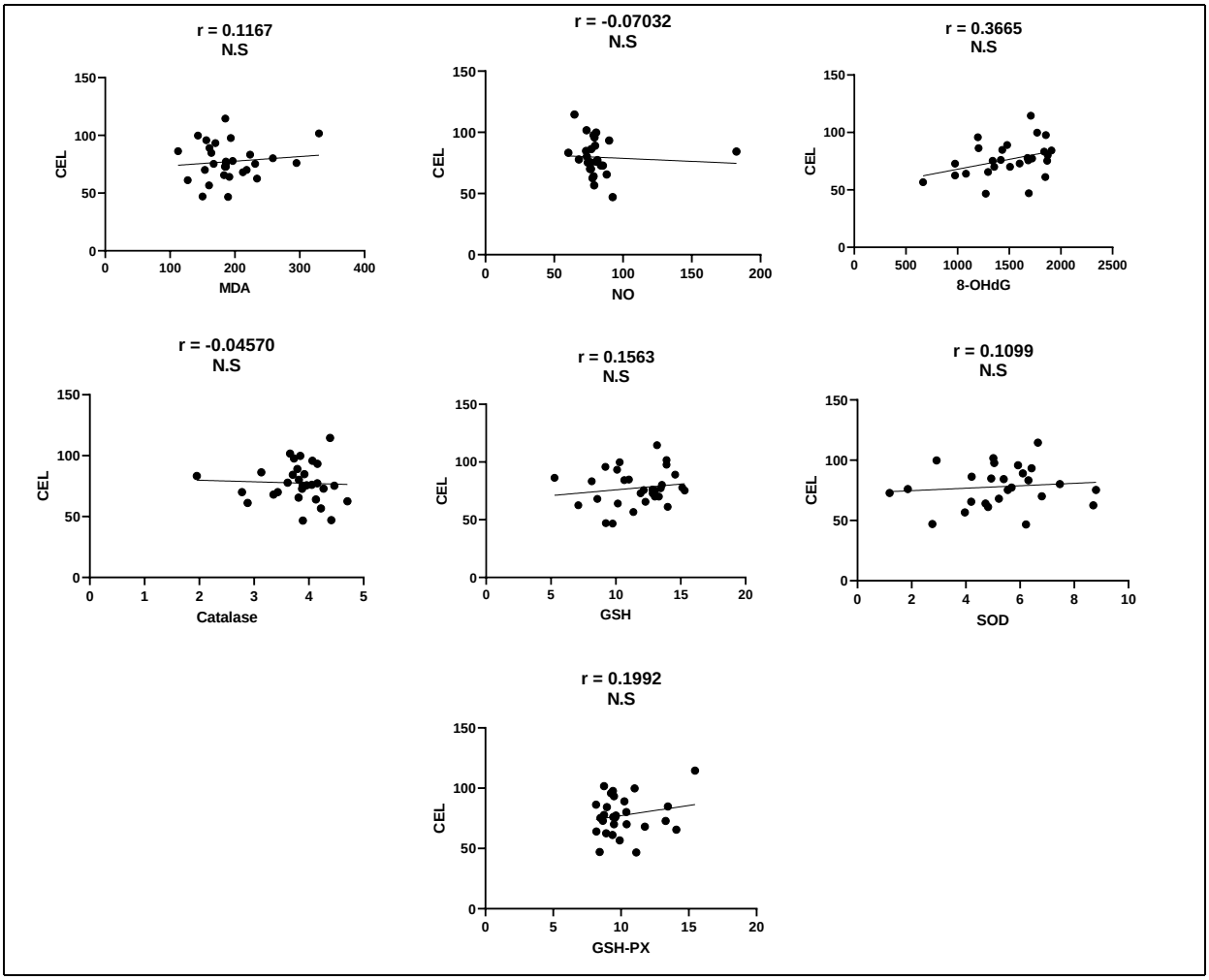

Figure 4: Correlation analysis between CEL with MDA, NO, 8-OHdG, CAT, GSH, SOD, and GSH-Px.

The correlation between Pyralline with MDA, NO, 8-OHdG, CAT, GSH, SOD, and GSH-Px shows that there is a positive non-significant correlation between Pyralline and MDA, 8-OHdG, CAT, GSH, and GSH-Px. The Correlation coefficient (r) for MDA (0.2911), 8-OHdG (0.009893), CAT (0.01233), GSH (0.1148), and GSH-Px (0.3324). However, there is a non-significant negative correlation between Pyralline with NO and SOD with Correlation coefficient (r) (-0.1225) and (-0.1813), sequentially, as presented in **Figure 5**. These findings are consistent with foremost studies, which reported that there is a non-significant correlation between AGEs parameters with these biomarkers (Reyaz et al., 2020).

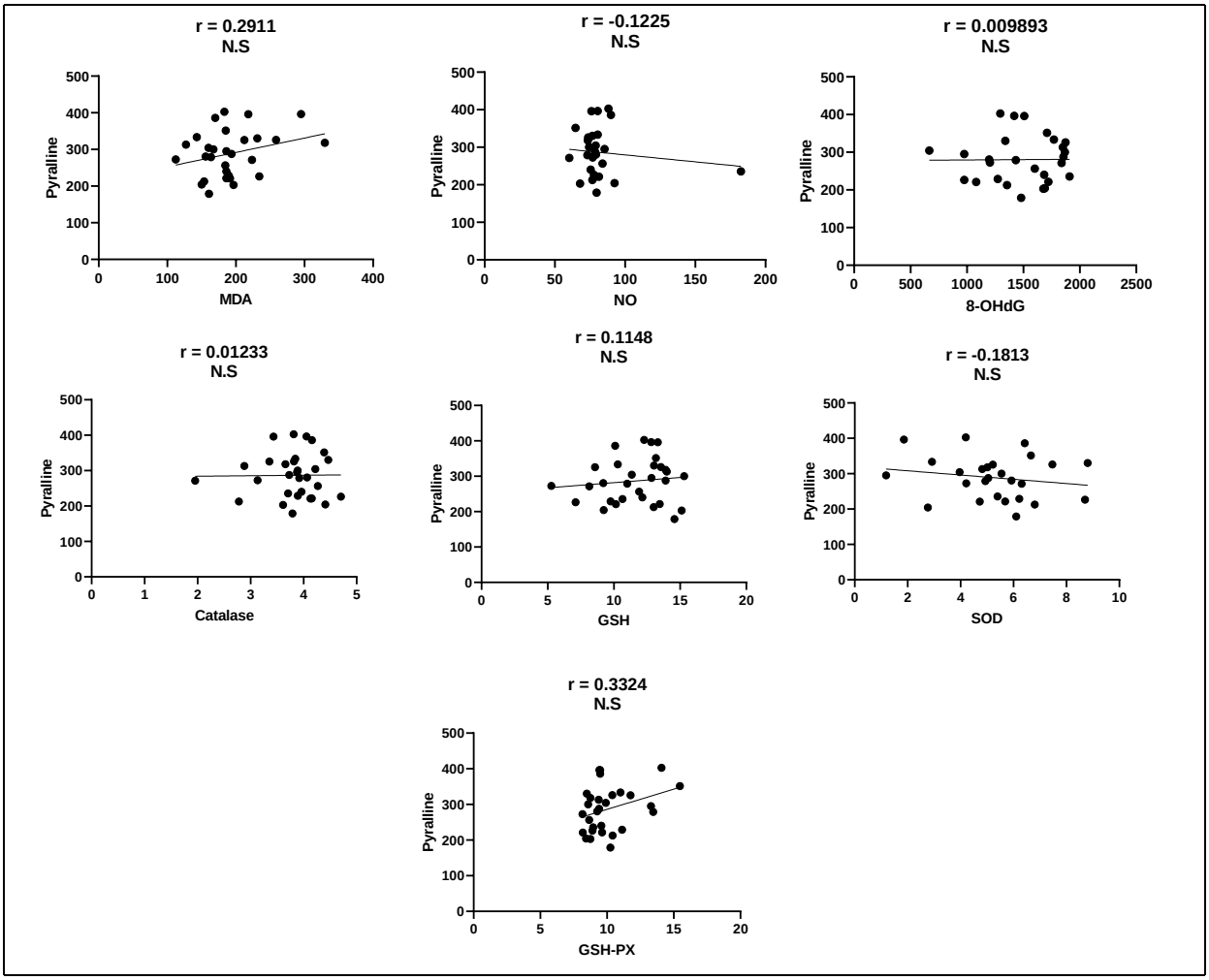

Figure 5: Correlation analysis between Pyralline with MDA, NO, 8-OHdG, CAT, GSH, SOD, and GSH-Px.

ROC curve analysis is performed for determining the diagnostic accuracy of serum CML, CEL, Pyralline, MDA, NO, and 8-OHdG. The AUC value in serum CML is 0.8707 also S.E and 95 Cl% values are 0.03916, 0.7939 to 0.9474, and (p <0.0001) respectively. While, the AUC value in serum CEL is 0.6883 also S.E and 95 Cl% values are 0.06141, 0.5679 to 0.8087, and (p=0.0055), as shown in **Figure 6**. The results exhibit that the serum CML is certainly good biomarker for DM. The AUC value in serum Pyralline is 0.7286 also S.E and 95 Cl% values are 0.05624, 0.05624, and (p=0.0007). As well as, the AUC value in serum MDA is 0.7014 also S.E and 95 Cl% values are 0.05914, 0.5855 to 0.8173, and (p=0.0028). Whereas, the AUC value in serum NO is 0.8862 also S.E and 95 Cl% values are 0.03719, 0.8133 to 0.9591, and (p=<0.0001) correspondingly. These data display that the serum NO is an excellent biomarker for diagnostic accuracy of DM, due to the high levels of AUC. On the other hand, the AUC value in serum 8-OHdG is 0.7154, S.E has been identified with a value of 0.06444 and the 95%Cl value is 0.5891 to 0.8417 (p=0.0022). These data show that the serum 8-OHdG is a good biomarker for DM.

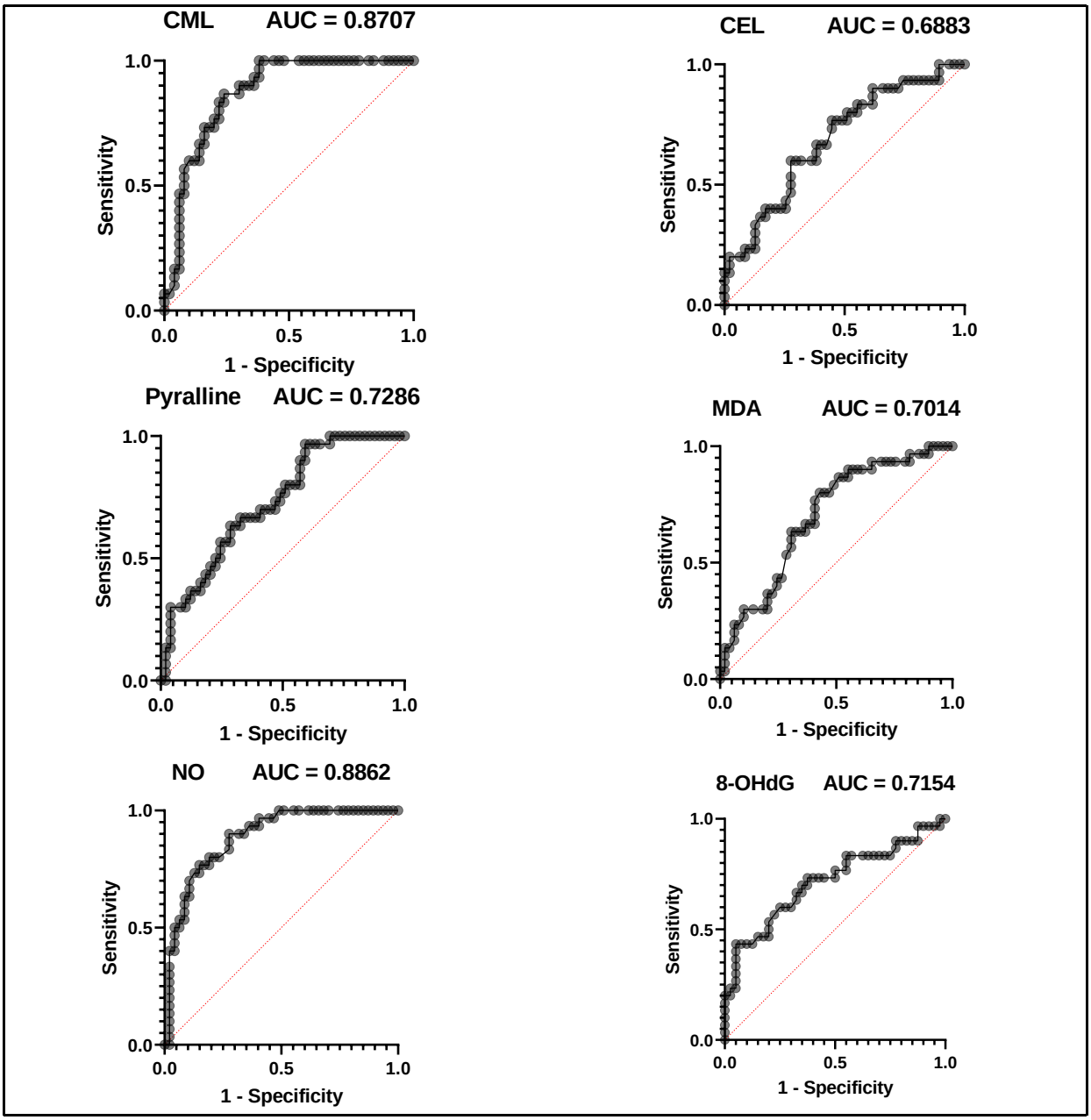

Figure 6: ROC curve analysis for the serum levels of AGEs and oxidative stress parameters in DM patients and control group.

4.Conclusion

The present study reveals that serum levels of CML, CEL, Pyralline, MDA, and 8-OHdGH were significantly elevated in DM patients compared with the healthy group. The mean serum levels of GSH, GSH-Px, and NO were significantly lowered in patients with DM rather than in the healthy group. Whereas, the serum levels of CAT and SOD were non-significantly lowered in DM patients. Furthermore, the serum level of Cholesterol and LDL were non-significantly lowered in DM patients compared with the healthy group, due to the administration of different kinds of medicine by DM patients. While the serum level of HDL significantly lowered in DM patients. The serum levels of TG and VLDL were non-significantly elevated in DM patients compared with the healthy group. NO and CML have turned out to be potential biomarkers for DM. Further researches are required to confirm the relation between all used parameters (AGEs, OS, Antioxidants, and Lipid profile) and diabetes type II, as well as using more parameters, of microRNA and genetic studies in all cities of Kurdistan. Our studied parameters can be an easy

and less expensive way to confirm most chronic diseases such as DM, Cancer, cardiovascular diseases and Alzheimer's.

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