## Original Article

# *Relation between Hemodialysis and Oxidative Stress Markers' blood levels in End Stage Renal Disease on Regular Dialysis*

***Menna Hossam Arafat*[1], Mohamed Shawky Khater[1] , Tamer Wahid Elsaid[2], Mohamad Ahmad Alsadany[1], Mennatallah Safwat Sayed Elaraby.[1]***

*1Geriatrics Medicine Department ,Faculty of Medicine, Ain Shams University*
*2Internal Medicine and Nephrology Department, Faculty of Medicine ,Ain Shams University*

## ABSTRACT

***Background:*** Chronic kidney disease (CKD) is a common medical problem in elderly. The progressive worsening of renal function in CKD induces numerous biological and clinical dysfunctions including augmentation of synthesis of inflammation and oxidative stress mediators.
***Aim of the Work:*** The aim was to study relation between frequency of hemodialysis and oxidative stress markers' blood levels in end stage renal disease (ESRD) patients on regular dialysis.
***Patients and Methods:*** This is a cross-sectional study that was done on a convenience sample of 80 cases of elderly patients,60years and older, who had ESRD and on regular dialysis. The study was conducted in the hemodialysis unit at Ain Shams University Hospital (El-Demerdash).The study period was from the first of May 2021to the end ofNovember2021.
***Results:*** We found a statistically significant positive correlation between hemodialysis related factors, namely duration of hemodialysis, number of sessions, and duration of each session and the blood levels of oxidative stress markers.
***Conclusion:*** Patients with ESRD on regular hemodialysis are at increased risk of oxidative stress risks as they are shown to have higher oxidative stress biological markers which are directly related to duration of being on hemodialysis, number of hemodialysis sessions and the duration of each session.
***Keywords:*** *Oxidative stress markers, Hemodialysis, Chronic kidney disease, ESRD.*

## INTRODUCTION

Chronic kidney disease (CKD) is a substantial concern in the elderly with both an increasing incidence of treated kidney failure with dialysis and a high prevalence of earlier stages of CKD. Given the high load of risk factors for CKD, the high prevalence of CKD in the elderly is not surprising. With the rise in obesity, diabetes and hypertension in middle-aged adults further increases in CKD prevalence among the elderly[1].
End stage renal disease(ESRD)is defined as permanent decrease in

kidney function that is severe enough to be fatal in the absence of dialysis or transplantation[2].

ESRD is included under stage5 of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative classification of chronic kidney disease, where it refers to persons with an estimated glomerular filtration rate less than 15mLper minute per1.73m$^2$ body surface are requiring dialysis irrespective of glomerular filtration rate[3].

Impairment of renal function leads to a host of maladaptive changes, including fluid retention (extracellular volume overload), anaemia, and disturbances of bone and mineral density, hyperlipidaemia ,and malnutrition[4].

In Egypt, the predictable annual incidence of ESRD was around 74 per million and the total prevalence of patients on dialysis is 264 per million[5].The prevalence of dialysis patients is supposed to be increasing and the main causes of ESRD in Egypt are not limited to diabetic nephropathy but also include hypertensive kidney disease, chronic glomerulonephritis(GN),chronic pyelonephritis, and obstructive uropathy[6].

Oxidative stress is known to be involved in many pathological processes, such as hypertension, atherosclerosis ,and neurological disorders with much evidences that CKD is also associated with increased oxidant production and decreased antioxidant protection[7].

ESRD patients on peritoneal dialysis (PD) have an increased oxidative stress when compared to non-dialyzed uremic patients, but was found lower, when compared to hemodialysis (HD) patients[8].

Patients with CKD typically have harshly reduced anti oxidative systems, which worsen gradually with the degree of renal failure. Oxidative stress is a critical defense mechanism against infections but if not properly regulated they may start a number of harmful effects such as cytokine overproduction and an increase in oxidative stress mediators[9].

Oxidative stress results from the inequity between the production of reactive oxygen species (ROS) and the ability to counteract them. The diversity between excessive reactive molecules and weak endogenous protection leads to damage to cell structures and molecules such as lipids, proteins, and DNA; eventually contributing to the pathogenesis of a wide range of diseases[10].

Oxidative stress appears in early stages of chronic kidney disease (CKD), advances along with worsening of renal failure, and is further exacerbated by the HD process per session . HD patients manifest excessive OS status due to retention of a plethora of toxins, subsidized under uremia, nutrition lacking antioxidants and turn-over of antioxidants, loss of antioxidants during renal replacement therapy, and leukocyte activation that leads to accumulation of oxidative products. Duration of dialysis therapy, iron infusion, anemia, presence of central venous catheter, and bioincompatible dialyzers are several factors triggering the development of OS[11]

The current study aimed to find the relation between hemodialysis and

oxidative stress markers' blood levels in ESRD patients on regular hemodialysis.

## PATIENTS AND METHODS

**Type of Study**: A cross-sectional study.

**Study Setting:** The haemodialysis unit in Ain Shams University Hospital(El-Demerdash).

**Study Period:** Seven months; from May 1st, 2021, to November 30th,2021.

**Study Population :**The participants were recruited from patients coming to hemodialysis unit in Ain shams university Hospital.

**Inclusion Criteria:**

1- Sex: Males and females.

2- Age: 60 years and above.

3- Patients with ESRD on regular hemodialysis.

**Exclusion Criteria:**

1- Patients who refused to participate in the study.

2- Patients younger than 60 years old.

3- Patients not on regular hemodialysis.

4- Patients on peritoneal dialysis.

**Sample Size:**

A sample size of 80 cases achieves 81% power to detect a statistically significant Pearson correlation coefficient of at least 0.50 when the null hypothesis correlation of 0.00 and the alternative theory correlation of 0.50 using a two-sided theory test with a meaning level of 0.05.

**Sampling Method:** Consecutive sampling method.

**Ethical Considerations:** Approval from Ain Shams University Ethical Committee was obtained [Approval Number 000017585]. An informed written consent was obtained from every participant. Those who were unable to read or write for whatever cause; the study aim and procedure was elaborated to them and the consent signed by a proxy. Permission to carry out this study was obtained from the dialysis unit.This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

**Study Procedures:** Recruited patients underwent the following assessment:

1. **Comprehensive geriatric assessment** including personal data, demographic data, relevant history, socioeconomic status, hemodialysis related factors (years of dialysis, number of sessions per week, duration of session in hours.)
2. **Blood sampling (1.5ml) to be withdrawn once before dialysis to** measure the oxidative stress markers, namely Malondialdehyde (MDA), Total antioxidant capacity (TAC),and Glutathione peroxidase (GPX). All blood samples were collected in the morning before a dialysis session. Following the collection of blood, the serum was separated immediately. Samples were centrifuged and the

supernatant is removed and stored -70 ºC until the analysis.

## RESULTS

A descriptive analysis for the study sample was done as seen in **table (1)** that showedthat 41 participants were males and 39 were females,their ages ranged from 60 to 81 years (mean 66.875 years). The mean number of co-morbidities was 4.300 ± 0.906, with Charlson comorbidity index mean at 6.01± 0.70.25 % of the participants (n=57) were married, and 28.75% (n=23) were widow/widower. 88.75 % of the participants (n=71) were hypertensive, while 62.50% (n=50) were diabetic. 60% of the participants (n=48) had a history of receiving nephrotoxic drugs.

As regards the data for hemodialysis, the mean duration of hemodialysis was 9.175 ± 4.684 (range 1- 21yrs), number of sessions/weeks ranged from 2-3, and duration of session in hrs. ranged from 2-4 hrs. with mean 3.188 ± 0.597.

| Demographic & general characteristics | | | |
|---|---|---|---|
| Age | | 60 – 81 years | |
| | | 66.875 ± 5.085 | |
| Sex | | Males 41 (51.2 5%) | |
| | | Females 39 (48.75 %) | |
| Charlson comorbidity index | | 4 – 7 | |
| | | 6.013 ± 0.703 | |
| Marital status | | Married 57 (71.25 %) | |
| | | Widow 23 (28.75 %) | |
| Special habits | | Smoker 57 (71.25 %) | |
| | | Nonsmoker 23 (28.75 %) | |
| History of nephrotoxic drugs | | 48 (60%) | |
| Co-morbidities | HTN[1] | 71 (88.75 %) | |
| | DM[2] | 50 (62.5%) | |
| Hemodialysis | Duration | Range | 1 – 21 years |
| | | Mean ±SD | 9.175 ±4.684 |
| | Number of sessions/weeks | Range | 2 – 3 sessions |
| | | Mean ±SD | 2.738 ±0.443 |
| | Average session duration (in hours) | Range | 2 – 4 hours |
| | | Mean ±SD | 3.188 ±0.597 |

A correlation study was done in **table (2)** that showed that GPX blood level had a significant positive correlation with duration of hemodialysis sessions. TAC blood level had a significant positive correlation with both duration of hemodialysis & sessions duration in hours, while MDA blood levels had a significant negative correlation with number of sessions/ weeks.

[1] hypertension
[2] Diabetes mellitus

**Table (2): Correlation between hemodialysis-related factors and blood levels of oxidative stress markers**

| | GPX | | TAC | | MDA | |
|---|---|---|---|---|---|---|
| | **R** | **P-value** | **r** | **P-value** | **r** | **P-value** |
| Duration of hemodialysis | 0.183 | 0.105 | **0.314** | **0.005*** | -0.190 | 0.092 |
| No of session/week | 0.118 | 0.295 | 0.201 | 0.074 | **-0.222** | **0.048*** |
| Duration of session in hrs. | **0.231** | **0.039*** | **0.344** | **0.002*** | -0.192 | 0.089 |

GPX: Malondialdehyde, TAC: Total antioxidant capacity, GPX: Glutathione peroxidase.

## DISCUSSION

Chronic kidney disease (CKD) is a major public health problem and its main consequences include loss of renal function leading to ESRD, increased risk of cardiovascular disease ,major increase in morbidity and death and a decrease in health-related quality of life[12].

With chronic kidney disease the gradual decline of kidney function induces several biological and clinical dysfunctions, including augmentation of synthesis of inflammation and oxidative stress mediators[13]

Oxidative stress has been associated with the creation of highly reactive intermediates during inflammation. On the other hand, reactive oxygen species (ROS) can further increase the inflammatory response by activating pro-inflammatory mediators.[14]numerous markers of oxidative stress such as malondialdehyde (MDA)have significantly elevated levels in circulating blood and tissue in CKD patients.[15]

The current study aimed to determine the relation between hemodialysis and its related factors and the levels of oxidative stress markers in ESRD on regular dialysis. A descriptive analysis for the hemodialysis related factors was done and it showed that the mean duration of hemodialysis was 9.175 ± 4.684 (ranging from 1 year to 21 years with number of sessions per week ranging from 2 to 3 sessions per week and the duration of each session in hours ranging from 2 to 4 hours with mean of 3.2 ± 0.6 hours. Our study also revealed that there was a direct relation between oxidative stress markers (GPX, TAC and MDA) and above-mentioned hemodialysis related factors.

There is diversity of results; In our study, we found that the (GPX)as an oxidative stress marker showed a statistically significant positive association with duration in hours spent in each HD session per week, this finding also agreed with ***Roxborough et al.,1999*** whose study aimed to detect the level of glutathione peroxidase in hemodialysis patients. Their study revealed that concentrations remained normal unchangeable after the hemodialysis session.[16]

This is opposed by El-Far and his colleagues by their study conducted in

2005 on 12 patients with nephrotic syndrome (NS), 48 patients with renal impairment (RI), and 50 patients with chronic renal failure on maintenance hemodialysis (HD); before and after dialysis), and in 50 healthy volunteers who were as controls. His results showed that in comparison to healthy controls, GPX activity was decreased in the HD group and the RI group, whereas the NS group showed no significant transformation from the control. Although they didn't investigate the correlation between the duration of each HD session, they found that the HD group showed a higher decrease in GPx (reduced to 36.6% of the mean control value) than the RI group (reduced to 61.8% of the mean control value). Further investigation of the RI group showed a highly significant negative correlation between GPx activity and serum creatinine level.[17]

In contrast to our study, ***Lucchiet al., 2005***, whose study was to measure the content of glutathione in ESRD during hemodialysis session, found that there was no significant changes observed in glutathione during the HD session[18].Though his study was done on a group of end-stage chronic renal failure (CRF) patients conducted on 15patients, with mean duration of the dialysis treatment was 61.7 ± 56.5 months (ranging from 10 to 142 months) and they were dialyzed three times a week with each session lasting 4 hours.

We found that there was no relation between GPX and duration of hemodialysis and this goes in accordance with ***Valentini et al.,2008***, whose study revealed that there was no correlation between GPX and the duration of hemodialysis[19].

In contrary to our study was the study done by ***Barrosoet al., 2020***to evaluate the association between the time of hemodialysis, nutritional selenium status and glutathione peroxidase activity (GPx), a case-control study of 75 individuals aged 18 to 88 years. It found that the patients who had undergone hemodialysis for 60 months or more had lower GPX activity than those who had undergone the treatment for less than 60 months.[20] Though, these findings were not significant after adjusting with age and gender .This could be explained by the significant role played by the GPX in the reduction of lipid and hydrogen peroxides. If GPX activity is decreased, more hydrogen peroxide is found, which leads to direct tissue injury and establishment of inflammatory pathways.

Our study also discovered a statistically significant positive correlation between TAC and the duration of hemodialysis measured by years and the duration of each session measured by hours.

This was opposed by ***Zargari et al.,2015***who also found that The TAC is significantly lower (21.8%) in pre-HD than in controls and also decreases after HD (27.9%), which agrees with previous studies[21].

One study done by ***Malliarakiet al.,2003*** supported our results as regard the time of hemodialysis session as measured by hours. In his study they

have consecutively measured TAC and corrected TAC (cTAC: after subtraction of the interactions due to endogenous uric acid, bilirubin and albumin) in 10 patients before the onset of the dialysis session, 10 min, 30 min, 1 h, 2 h and 3 h into the process and after achievement of the session. Their results showed that TAC decreases, reaching the least levels at 2 h.[22]

This also agrees with what ***Toboreket al.,1992***who studied the effect of hemodialysis on lipid peroxidation and antioxidant system in ESRD. During their case-control study the mean duration of hemodialysis was 56 +/- 11 months for the cases. Their results found that the total TAC was increased in hemodialysis. The explanation for this could be attributed to either hemoconcentration ,adaptation or to a possible exchange of antioxidants between the lipid and aqueous phases.[23]The reason for this elevation in TAC according to ***Bergesioet al.,1998***colleaguesis likely to be dependent on increased uric acid levels and does not seem to induce an efficient protection in vivo from oxidative stress, thus TAC does not appear to be a reliable method for assessing the oxidative susceptibility of CRF patients.[24]

Our research results showed that there was no relation between MDA and duration of hemodialysis. In contrast to our results was the study conducted by ***Valentini et al., 2008***who studied the effect of the hemodialysis treatment time under oxidative stress biomarkers in chronic renal failure patients, a study in which MDA was measured into two different groups of HD patients: recent treatment ($n$ = 36; HD duration: 17.7 ± 1.71 months),with 51 +/- 11.6 years of age (ranging between 29 and 75 years and longtime of treatment ($n$ = 26; HD duration: 82.2 ± 6.32 months), and in a control group ($n$ = 40). They showed that the plasmatic MDA levels were significantly more in patients with long time of HD treatment in comparison with patients with recent time of HD treatment.[25]

The increase in enzyme level may be correlated to an overproduction of free radicals, which can be confirmed by an increase in MDA production. The difference between our study and this previous study was due to the difference in the sample size used in it and the range of age group.

***Yavuz et al.,2004*** studied the effect of hemodialysis on oxidative stress markers. He studied 40 long-term dialysis patients, and 20 age-matched healthy controls were joined into the study. Serum malondialdehyde (MDA) activity was determined before and after hemodialysis. Their research revealed that the plasma MDA levels were augmented in groups on longer periods of HD treatment and MDA levels were even higher than the pre-dialysis period for the same group[26].

This study's results were opposite to our results due to the difference in the study group and the study method.

Another cross-sectional study done by***Yilmaz et al., 2006*** to investigate the association between levels of oxidative stress markers in patients with chronic

kidney disease of 159 patients (28 to 36 patients in each of the CKD stages 1 to 5) and compared their results with 30 healthy controls. Their research results showed a progressive rise in the levels of oxidative stress marker MDA among HD patients. And that was associated more with the increase in the severity of renal failure as compared to control group.[27] , this study used a wide range of age group, also it excluded all comorbidities in the used sample either cases or control groups and this explained the difference between their results and our results.

Our study results found that there was a statistically significant negative correlation between MDA and frequency of hemodialysis as presented by number of sessions per week. These finding were opposed by other researchers such as ***Purwati et al., 2022*** who studied the relation between MDA and frequency of hemodialysis. They conducted an observational clinical study with a cross sectional design. They studied 49 patients with diagnosis of CKD with GFR less than 60 ml/min per 1.73 m2, persisting for at least 3 months and they found that there was a statistically significant increase in serum malondialdehyde MDA when compared to patients before hemodialysis and it was in direct relation with frequency of dialysis, these results obtained from HD patients after one dialysis session show that values of both antioxidant and pro-oxidant markers improve after HD. The increase in enzyme level may be related to an overproduction of free radicals, which can be confirmed by an increase in MDA production. Increased oxidative stress status in the hemodialysis patients specifically because of reduced dietary intake of the exogenous antioxidants, accumulation the oxidative products, and also loss of antioxidant throughout HD[28]. , the difference in results may be due to difference in age group in which this study was applying the research on 2 different groups a group above 50 years old and a group below 50 years old , but our study age group was 60 years old and above.

Limitations to our study were its relatively smaller sample size, and we did not include those patients with CKD who did not start dialysis yet. So, we think that further studies on a larger scale are required to confirm our finding.

## CONCLUSION

We concluded that patients with ESRD on regular hemodialysis are at increased risk of oxidative stress risks as they are shown to have higher oxidative stress biological markers which are directly related to period of being on hemodialysis, number of hemodialysis sessions and the duration of each session

## REFERRENCES

[1]Levey, A. S., Stevens, L. A., Schmid, C. H., Zhang, Y., Castro III, A. F., Feldman, H. I., ... & CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration)*. (2009). A new equation to estimate glomerular filtration rate. Annals of internal medicine, 150(9), 604-612.

[2]BouChebl, R., Tamim, H., AbouDagher, G., Sadat, M., Ghamdi, G., Itani, A., ... & Arabi, Y. M. (2021). Sepsis in end-stage renal disease patients: are they at an increased risk of mortality?. Annals of Medicine, 53(1), 1737-1743.

[3]Stevens, L. A., Coresh, J., Greene, T., & Levey, A. S. (2006). Assessing kidney function—measured and estimated glomerular filtration rate. New England Journal of Medicine, 354(23), 2473-2483.
[4]Abbasi, M. A., Chertow, G. M., & Hall, Y. N. (2010). End-stage renal disease. BMJ clinical evidence, 2010.

[5]El-Arbagy, A. R., Yassin, Y. S., &Boshra, B. N. (2016). Study of prevalence of end-stage renal disease in Assiut governorate, upper Egypt. Menoufia Medical Journal, 29(2), 222.
[6]Barsoum, R. S. (2006). Chronic kidney disease in the developing world. New England Journal of Medicine, 354(10), 997-999.
[7]Tylicki, L., Rutkowski, B., &Hörl, W. H. (2003). Antioxidants: a possible role in kidney protection. Kidney and Blood Pressure Research, 26(5-6), 303-314.

[8]Liakopoulos, V., Roumeliotis, S., Gorny, X., Dounousi, E., & Mertens, P. R. (2017). Oxidative stress in hemodialysis patients: a review of the literature. Oxidative medicine and cellular longevity, 2017.

[9]Syed-Ahmed, M., & Narayanan, M. (2019). Immune dysfunction and risk of infection in chronic kidney disease. Advances in chronic kidney disease, 26(1), 8-15.
[10]Popolo, A., Autore, G., Pinto, A., & Marzocco, S. (2013). Oxidative stress in patients with cardiovascular disease and chronic renal failure. Free radical research, 47(5), 346-356.

[11] Vassilios Liakopoulos, Stefanos Roumeliotis, Xenia Gorny, Evangelia Dounousi, Peter R. Mertens, "Oxidative Stress in Hemodialysis Patients: A Review of the Literature", Oxidative Medicine and Cellular Longevity, vol. 2017, Article ID 3081856, 22 pages, 2017.

[12]Fried, L. F., Shlipak, M. G., Crump, C., Kronmal, R. A., Bleyer, A. J., Gottdiener, J. S., ... & Newman, A. B. (2003). Renal insufficiency as a predictor of cardiovascular outcomes and mortality in elderly individuals. Journal of the American College of Cardiology, 41(8), 1364-1372.

[13]Russa, D. L., Pellegrino, D., Montesanto, A., Gigliotti, P., Perri, A., Russa, A. L., &Bonofiglio, R. (2019). Oxidative balance and inflammation in hemodialysis patients: biomarkers of cardiovascular risk?. Oxidative Medicine and Cellular Longevity, 2019.
[14]Simone, S., Rascio, F., Castellano, G., Divella, C., Ditonno, P., Battaglia, M., ... &Grandaliano, G. (2014). Complement-dependent NADPH oxidase enzyme activation in renal ischemia/reperfusion injury. Free Radical Biology and Medicine, 74, 263-273.

[15]Kinugasa, E. (2011). Markers and possible uremic toxins: Japanese experiences. Hemodiafiltration-A New Era, 168, 134-138.
[16]Roxborough, H. E., Mercer, C., McMaster, D., Maxwell, A. P., & Young, I. S. (1999). Plasma glutathione peroxidase activity is reduced in haemodialysis patients. Nephron, 81(3), 278-283.

[17] El-Far MA, Bakr MA, Farahat SE, Abd El-Fattah EA. Glutathione peroxidase activity in patients with renal disorders. Clin Exp Nephrol. 2005 Jun;9(2):127-31. doi: 10.1007/s10157-005-0343-1. PMID: 15980946.

[18]Lucchi L, Bergamini S, Iannone A, Perrone S, Stipo L, Olmeda F, et al. Erythrocyte susceptibility to oxidative stress in chronic renal failure patients under different substitutive treatments. Artif Organs 2005;29(1): 67e72.

[19]Valentini, J., Grotto, D., Paniz, C., Roehrs, M., Burg, G., & Garcia, S. C. (2008). The influence of the hemodialysis treatment time under oxidative stress biomarkers in chronic renal failure patients. Biomedicine & pharmacotherapy, 62(6), 378-382.

[20]*Barroso, C. F., Pires, L. V., Santos, L. B., Henriques, G. S., Pessoa, P. P., de Araújo, G. N., ... & Maia, C. S. C. (2021). Selenium nutritional status and glutathione peroxidase activity and its relationship with hemodialysis time in individuals living in a brazilian region with selenium-rich soil. Biological Trace Element Research, 199, 2535-2542.*

[21]*Zargari M, Sedighi O. Influence of Hemodialysis on Lipid Peroxidation, Enzymatic and Non-Enzymatic Antioxidant Capacity in Chronic Renal Failure Patients. Nephrourol Mon. 2015 Jul 29;7(4):e28526. doi: 10.5812/numonthly.28526. PMID: 26539417; PMCID: PMC4628136.*

[22]*Malliaraki, N., Mpliamplias, D., Kampa, M., Perakis, K., Margioris, A. N., & Castanas, E. (2003). Total and corrected antioxidant capacity in hemodialyzed patients. BMC nephrology, 4(1), 1-8.*

[23]*Toborek, M., Wasik, T., Drózdz, M., Klin, M., Magner-Wróbel, K., &Kopieczna-Grzebieniak, E. (1992). Effect of hemodialysis on lipid peroxidation and antioxidant system in patients with chronic renal failure. Metabolism, 41(11), 1229-1232.*

[24]*Bergesio, F., Monzani, G., Ciuti, R., Pinzani, P., Fiaschi, N., Priami, F., ... & Salvadori, M. (1998). Total antioxidant capacity (TAC): is it an effective method to evaluate the oxidative stress in uraemia?.*

[25]*Valentini, J., Grotto, D., Paniz, C., Roehrs, M., Burg, G., & Garcia, S. C. (2008). The influence of the hemodialysis treatment time under oxidative stress biomarkers in chronic renal failure patients. Biomedicine & pharmacotherapy, 62(6), 378-382.*

[26]*Yavuz, O., Bicik, Z., Cinar, Y., Guney, Y., &Guler, S. (2004). The effect of different dialysis membranes on oxidative stress and selenium status. ClinicaChimicaActa, 346(2), 153-160.*

[27]*Yilmaz, M. I., Saglam, M., Caglar, K., Cakir, E., Sonmez, A., Ozgurtas, T., ... & Zoccali, C. (2006). The determinants of endothelial dysfunction in CKD: oxidative stress and asymmetric dimethylarginine. American Journal of Kidney Diseases, 47(1), 42-50.*

[28]*Purwati, D. D., Mustika, A., Hakim, L., &Thaha, M. (2022). Correlation of Serum Nitric Oxide and Urine Malondialdehyde Levels in Non-Hemodialysis Chronic Kidney Disease Patients. Molecular and Cellular Biomedical Sciences, 6(1), 43-9.*