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Evaluation of Pathological Relationship between Oxidative Stress, Inflammation and Malnutrition in Patients with Renal Failure

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ABSTRACT

Background: The current study shows the effects of oxidative stress, including inflammation, malnourishment, and a weakened antioxidant defence system, on individuals with chronic kidney disease (CKD) and its cogent implications over a 38-month follow-up period.

Methods: Risk factors such as malnutrition, inflammation, and oxidative deterioration of lipids diminished the activity of anti-oxidative enzymes, such as Paraoxonase (PON-1) and rarely found (PON-3). Diazoxonase (DZOase) activity developed cardiovascular diseases (CVDs) in all studied groups of CKDs usually observed in hemodialysis (HD) patients.

Results: A non-parametric analysis-survival function investigates the time-to-death relationship, especially in hemodialysis patients. Kaplan Meir curve analysis showed a high risk of death assessment and different degrees of risk factors in all studied groups of patients. After 8 to 10 months of research, the combined impact of two risk factors- oxidative stress and inflammation- was displayed, although 85% of survival function was seen. The survival function drops to 30% as the disease worsens, and this is because there is only one risk factor- malnutrition, which causes the concatenation of CVD events in patients with chronic kidney disease.

Conclusion: This study found that among long-term hemodialysis patients, malnutrition, inflammation, and oxidative lipid degradation are linked to an increased risk of death. Malnutrition is the only risk factor for high mortality in hemodialysis patients at the end stage of CKD.

Key-words: Malnutrition, Inflammation, Oxidative stress, Paraoxonase-1, Chronic kidney disease stage

INTRODUCTION

Most health-related mortality issues have been attributed to the development in the burden of infectious diseases over the past few decades, and worries about morbidity have expanded globally. Accordingly, over time, the prevalence of instances of chronic renal illness has progressively increased.

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A person with CKD is said to have reached many critical stages, and most patients are reported to have passed away before reaching the final stage of the disease. Many patients with chronic stages of kidney disease have cardiovascular disease events as their primary cause of occurrence [1]. Traditional risk factors for CVDs, such as diabetes mellitus, dyslipidemia, and hypertension, are what cause the ageing mortality rate. Aside from this, in the modern world, non-traditional risk factors such as oxidative stress and inflammation greatly increase the prevalence of CVDs in patients with chronic kidney disease [2]. Lipid abnormalities are commonly observed in CKD patients. This condition is called dyslipidemia, and it is characterised by hypertriglyceridemia, a high level of very low-density lipoprotein cholesterol (VLDL-C)-a chemical formula of C27H46O-a decreased level of high-density lipoprotein cholesterol (HDL-C), and a normal

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concentration of low-density lipoprotein cholesterol (LDL-C). A patient's oxidative stress environment may be exacerbated by increased oxidant concentration, mostly caused by inflammation and dialysis. Malnutrition events also significantly weaken the antioxidant defence system.

The primary purpose of antioxidant enzymes like Paraoxonase (PON), which is linked to HDL particles, is to shield the LDL particles from lipid oxidation. These enzymes are more prone to change in an oxidative stress environment [3]. PON-1, PON-2, and PON-3 are the three members of this antioxidant enzyme family; PON-1 and PON-3 are human-made enzymes that are primarily created in the liver and primarily affixed to high-density lipoprotein-cholesterol (HDL-C) in the bloodstream. Both enzymes' main job is to control inflammation and oxidative stress to prevent atherosclerosis in renal disease patients. According to recent data, people with CKD typically have lower levels of PON-1 activity [4].

On the other hand, no information is available on PON-3 presence in CKD patients. Nonetheless, oxidative stress, inflammation, and malnutrition may change these individuals' lipoproteins' redox state [5]. The current study aims to examine a 38-month follow-up period to illustrate the influence of stressors such as inflammation, starvation, and a weakened antioxidant defence system on patients with CKD and its coherent implications.

MATERIALS AND METHODS

This study included 176 patients with CKDs (aged 49±20 years, 96 males and 80 females) in the Dialysis measurements were started in the Department of Nephrology, MLB Medical College, Jhansi April 2011 to September 2012 during the 18-month study.

Exclusion criteria- Patients suffering from autoimmune disease, rheumatoid arthritis, and diabetes mellitus complications are not included in this study. Those patients underwent for <3 Months of HD and those undertaking the lipid-lowering therapy were not a part of this study.

Inclusion criteria- This study only considered individuals who received hemodialysis for over three months. It did not administer any drugs or hyperactive substances known to impact the stress state of any of the participants.

Methodology- The primary cause of CKDs in patients is chronic glomerulonephritis (n=12 in kidney transplant (T_k) patients, n=11, have chronic kidney disease, n=9 underwent hemodialysis), chronic pyelonephritis (n=19, n=0 in kidney transplant (T_k) patients, n=7, have chronic kidney disease, n=12 underwent for hemodialysis), nephrosclerosis (n=32, n=8 in kidney transplant (T_k) patients, n=10, have CKD, n=14 underwent for hemodialysis), polycystic kidney disease (n=22, n=6 kidney transplant (T_k) patients, n=4, have chronic kidney disease, n=12 underwent for hemodialysis), systemic diseases (n=22, in n=2 kidney transplant (T_k) patients, n=11, have CKD, n=9 underwent for hemodialysis), urological malformation (n=8, n=1 kidney transplant (T_k) patients, n=4, have chronic kidney disease, n=3 underwent for hemodialysis), and unknown (n=2, in n=0 kidney transplant (T_k) patients, n=1, have chronic kidney disease, n=1 underwent for hemodialysis). Every patient with CKD received three modest doses of corticosteroids or another immunosuppressive medication for 4 to 5 hrs each day, closely adhering to clinical standard guidelines. While no patients had received the hypolipidemic medications externally, the anaemia patients with CKDs advised to employ recombinant proteins such as erythropoietin. For this study, 39 healthy people served as controls. Following an all-night fast, whole blood samples were taken. Blood serum and EDTA were separated by ultracentrifugation at 1500 g for 10 min at 4^{o}C, and the aliquots were fractioned before being stored at -80^{o}C for additional analysis. The local institution committee has approved and evaluated the study protocol, and informed consent was obtained from all the patients before the execution of the study.

Lipid status determination- Triglycerides (TG), HDL-C, and total cholesterol (TC) were measured with an ILAB-600 bioassay analyzer and conventional laboratory procedures. On the other hand, CKD patients' LDL-C concentration was assessed using the Friedewald formula [6].

Enzymatic determination of PON-1- Using paraoxon and diazoxon as substrates, the rate of PON-1 enzyme activity in the patient blood serum was measured. Utilising the Sandwich-ELISA-kit acquired from the Bioassay Technology Laboratory, the serum's interleukin (IL-6) amount was determined.

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Statistical analysis- Minitab (version-19, National Bureau of Statistics) software was used to analyse the research data. The student-t-test, chi-square (χ^2), and two-way ANOVA tests were used to compare the study's variables. Time-death measured in months is the dependent variable. Examining risk factors considered in this study is predicated on inflammation, oxidative stress, and malnutrition. The significance threshold was determined statistically at the two-tailed P<0.05 level. According to Kirushnan *et al.* [7] and Hwang *et al.* [8], risk factor-like malnutrition was identified in patients whose albumin level was below average values (<38g/L) when compared to the total study population. It was also recognised in patients whose BMI was below the previously recorded BMI (22 kg/m^2). Acute-phase proteins are produced at the site of inflammation when the total number of patients under consideration has an IL-6 concentration of more than 5 pg/ml. It was observed that the decline in lipids happened when the concentration of the antioxidant enzymes Paraoxonase (>122 U/L) and Doxonase (5966 U/L) in the blood serum of the patients was less than normal.

Ethics approval and consent to participate- The above study was approved by the Human Ethical Committee of the Institute and informed consent was obtained from the patients before the study.

RESULTS

The four groups' demographic and clinical characteristics studies were outlined in Tables 1 and 2. Older patients were more significantly at risk of CKDs than control p<0.01, so age factor analysis should be done. Data on factors such as gender disparities, body mass index, cigarette smoking status and blood pressure were comparable in both the groups studied. In addition, Parameters like hemodialysis study duration and sub-categorical disease occurrence in CKD patients' data are presented in Table 1.

Table 1: Representation of parameters like hemodialysis study duration and sub-categorical disease occurrence in CKD patients

Group Parameters	Control groups (n=39)	(CKDs) Kidney Patients (n=48)	Kidney Transplanted (T_k=29)	Hemodialysis Patients (n=60)
Age in Yrs	51.7±14	37.5±13.8	42±11.64	54.87±11.55
Gender, **M/F	45/49	25/23	19/10	29/31
CKDs/HD study duration in months, *BMI (Kg/m^2)	-	42.9±23.76	33.8±85.7	111±78

**BMI=Body mass Index; **M/F=Males/Females*

As compared to other groups, hemodialysis patients significantly had a higher activity of PON-1 presented in Table 2 (Control vs hemodialysis patients, Kidney transplanted (T_k) patients; CKDs χ^2=32.34 at a p<0.001 and hemodialysis vs CKDs, (T_k) χ^2=27.12 at a p<0.001).

Table 2: General-biochemical parameters analysis, antioxidant enzyme PON-1 status, and the inflammatory-markers level in CKDs, kidney transplanted HD patients and control groups.

Group Parameters	Control groups (n=94)	(CKDs) Kidney Patients (n=48)	Kidney Transplanted patients (T_k=29)	Hemodialysis Patients (n=60)
BMI(Kg/m^2)	29.4±5.69	23.19±4.63$^{\alpha}$	23.19±4.66$^{\alpha}$	21.91±3.99$^{\alpha,\beta,\gamma}$
Albumin (g/L)	42.6±3.81	41.4±6.23	41.6±3.16	40.8±3.09$^{\alpha,\gamma}$
Urea(mmol/L)	4.66±1.46	19.7±9.22$^{\alpha\alpha\alpha}$	11.2±5.66$^{\alpha\alpha\alpha,\ \beta}$	21.3±3.46$^{\alpha\alpha\alpha,\ \beta,\gamma}$

Creatinine (µmol/L)	65.5±13.68	323.6±245.88^{ααα}	185.4±163.58^{ααα,ββ}	877±166^{ααα,βββ,γγγ}
GFR (mL/min/1.73m^2)	Nil	31.8±25.7^{ααα}	38.8±14.0^{ααα}	<6^{ααα,βββ,γγγ}
TC(mmol/L)	5.32±1.10	5.57±1.35	5.52±1.05	4.71±1.1^{αα,ββ,γγγ}
TG (mmol/L)	1.55±0.864	2.33±0.072^{ααα}	1.97±0.958^{β}	2.13±1.300^{ααα,γ}
LDL-C (mmol/L)	3.59±1.09	3.64±1.244	3.45±0.934	2.81±0.894^{ααα,βββ,γγγ}
HDL-C (mmol/L)	1.22±0.345	1.19±0.246^{α}	1.32±0.357^{β}	1.09±0.313^{ααα,γγγ}
hs-CRP (mg/L*)	1.18(0.877–1.49)	0.88(0.374–1.760)	1.31 (0.767 - 1.928)^{β}	3.18(2.293–4.565)^{ααα,βββ,γγ}
IL-6(pg/mL)	1.58 (1.251–1.984)	2.37(1.867–3.356)^{α}	4.11(3.340–4.830)^{αα,β}	3.83(3.150–4.734)^{ααα,β}
POase activity, (U/L*)	361 (301–489)	339(267–501)	232 (191–292)^{αα,β}	241 (201–310)^{αα,β}
DZOase activity, (U/L*)	9877 (8829–12,013)	13,998 (10,890–15,738)^{α}	14,128 (12,651–15,979)^{αα}	7159 (6566-8152)^{α,βββ,γγγ}

*^{α}Group differences from control group, ^{β}group differences from CKS, ^{γ}group differences from T_k based on one way-ANOVA, Tukey's post-hoc-test. Chronic kidney stage (CKS). *Geometric mean and Confidential Interval (CI) for mean; were measured significantly at different levels of p-value: *p>0.05; **p>0.01; ***p>0.001. POase=Peroxonase; DZOase= Diazoxonase; GFR= Glomerular-filtration rate; IL=Interleukin; TC= Total cholesterol; TG= Triglycerides*

Non-parametric analysis-survival functions in hemodialysis patients- An outcome of this 38-month study duration investigated that, of these 16 patients, the majority of them, 15 hemodialysis patients, have died, and one patient underwent kidney transplantation. The main reason behind the death of 15 HD patients was due to the cardiovascular diseases (cardiac arrest, myocardial infarction (MI), thrombotic and hemorrhagic strokes) noticed in 10/15 (66.66%), malignancy in 3/15 (0.20%), and unknown information in rest of the 2/15 (0.14%). Fig. 1 survival plot showed the cumulative risk factors increment in patients with renal disease was more prone to risk of death. It illustrated the number of risk factors (log rank=12.03 at p<0.007) and explained that death risk is higher in patients who increment in risk factors number.

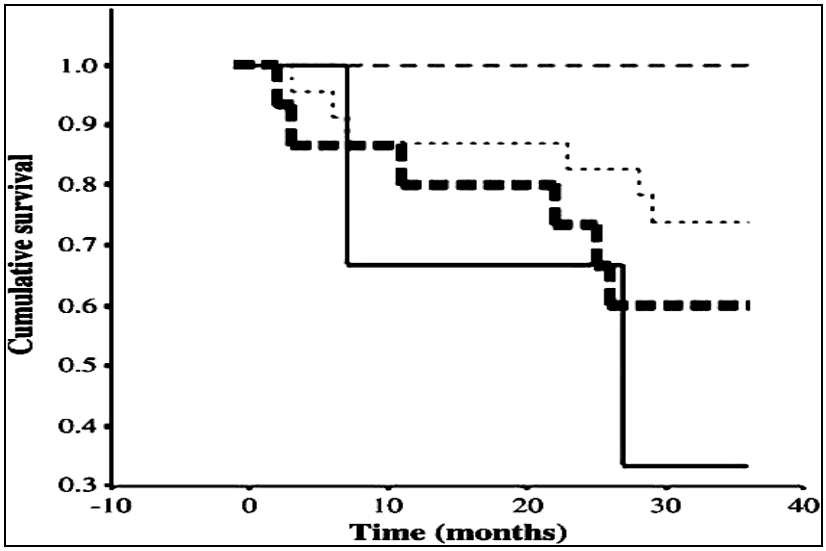

Fig. 1: Different degrees of risk factors involved in CKD patients during the 38 months of the study (Kaplan-Meir curve): Well-nourished denoted as control, Risk factors such as Malnutrition; inflammation, and Oxidative lipids deterioration

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DISCUSSION

Albumin level and BMI value were used to diagnose malnutrition; it was shown that HD patients had the highest levels of both albumin and BMI. Studies [9] reported a significant increase in hs-CRP and IL-6 indicators in patients with CKD at the severe malnutrition and inflammation stage. TC and TG were lower in HD patients, indicating that they also had inflammation and oxidative stress risk factors. This was corroborated by Hopewell *et al*. [10], who observed that because of lipid abnormalities, HDL-C enrichment in serum enhanced the clearance of apolipoprotein A-1 (Apo-1), which causes a decrease in HDL-C level and lowered the activity of lecithin-cholesterol acyl-transferase (LCAT), reduces the HDL level, and stops HDL-C maturation [11]. However, compared to control subject groups, hemodialysis patients' oxidised and altered protein products had significantly higher anti-oxidative potential because of decreased superoxide dismutase (SOD) activity and less total sulphydryl groups (-SH) present in between the intra-chain of the altered protein products. Interleukin (IL-6) levels were significantly higher in CKD patients and kidney transplant recipients; however, they were not as high as in hemodialysis patients. [12]. Additionally, it was found that, in comparison to the healthy control group, the level of ferric-reducing ability of plasma (FRAP) dropped in HD patients and that inflammatory indicators such as serum malondialdehyde (MDA) and heat shock-C-reactive protein (hs-CRP) had increased in HD patients' blood. According to Kirushnan *et al.* [7], oxidative stress is a likely cause of malnutrition, inflammation, and CVDs, particularly in individuals with chronic kidney disease.

However, some studies have investigated the fact that PON and glutathione peroxidase enzyme activity imparts HDL-C antioxidant and anti-inflammatory properties, especially observed at the latter stages of renal disease [13]. It was also evident that increased activity of PON-1 and DZOase (ApoA-1) presence in HDL-C [14] protects the LDL from oxidation by killer cells like macrophages and stimulates the macrophage-cholesterol efflux. Still, in this study, PON-1 activity was higher in hemodialysis patients, meaning they are not in a stage of kidney failure compared to the healthy control groups. We have already discussed the previous studies [15], which clearly emphasize the other complications, such as the concurrent series of atherosclerosis development, especially in renal patients, because of conventional and non-traditional risk factors for cardiovascular disease.

Patients with albumin levels <38g/L and BMI rates <22 kg/m^2 were diagnosed with malnutrition; IL-6 concentrations >5 pg/ml were found in all patients investigated; antioxidant enzyme concentrations for Paraoxonase (>122U/L) and Doxonase (DZOase) activity (5966U/L), respectively, were also found to be lowered. Furthermore, a substantial negative connection [16] was seen between PON-1 and Lipid fraction, mostly very-low-density lipoprotein (VLDL), which was documented in previous investigations, particularly in patients with renal impairment. The VLDL component cannot be disregarded because it is the primary precursor for LDL synthesis and essential to atherosclerotic processes [17]. After ten months of research, the combined impact of two risk factors- oxidative stress and inflammation displayed, although 85% of survival function was seen. During the study's final phase, it was discovered that oxidative stress and malnutrition combined negatively impact hemodialysis patients' survival rate, as shown in earlier research [18,19]. Malnutrition is the single risk factor that contributes to the progression of CVD events and shifts towards a critical stage of renal failure when only 30% of patients survive. This stage of renal dysfunction is particularly noticeable in HD patients. This study shows that reduced antioxidant potential was present in all patient groups examined. However, it was most evident in HD patients. Increased levels of hs-CRP and IL-6 during the mid-phase of kidney disease indicate oxidative stress and inflammation, as supported by previously published studies [20,21].

CONCLUSIONS

The present study concludes that malnutrition, inflammation and oxidative deterioration of lipids are all correlated to a higher risk of mortality in long-term hemodialysis patients. At the last stage of chronic kidney disease, only the malnutrition risk factor is responsible for high mortality in hemodialysis patients. However, in this study, reported numbers of subject groups were limited. It was a preliminary study. Highlighted risk factors promote complications like cardiovascular disease events in renal patients. Thus, future research emphasizes nutritional studies or antioxidant therapies to combat the risk of CKD patients.

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CONTRIBUTION OF AUTHORS

Research concept- Nivedita Saxena, S P Singh
Research design- Nivedita Saxena, S P Singh
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Data analysis and Interpretation- S P Singh
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Critical review- S P Singh
Article editing- Nivedita Saxena, S P Singh
Final approval- S P Singh

REFERENCES

[1] Subbiah AK, Chhabra YK, Mahajan S. Cardiovascular disease in patients with chronic kidney disease: a neglected subgroup. Heart Asia, 2016; 8(2): 56–61. doi: 10.1136/heartasia-2016-010809.

[2] Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. Lancet, 2013; 382(9829): 339-52.

[3] Chistiakov DA, Melnichenko AA, Orekhov AN, Bobryshev YV. Paraoxonase and atherosclerosis-related cardiovascular diseases. Biochim., 2017; 132: 19-27.

[4] Gugliucci A, Kotani K, Kimura S. Paraoxonase-1 in chronic kidney failure. J Lipids, 2012; 2012: 726048.

[5] Ungurianu A, Margina D, Gradinaru D, Bacanu C, Ilie M, et al. Lipoprotein redox status evaluation as a marker of cardiovascular disease risk in patients with inflammatory disease. Molec Med Rep., 2017; 15(1): 256-62.

[6] Seth S, Martin MJ, Mohamed BB, Elshazly BEA, Toth PP, et al. Friedewald-estimated versus directly measured low-density lipoprotein cholesterol and treatment implications J Am Coll Cardiol., 2013; 62(8): 732-39. doi: 10.1016/j.jacc.2013.01.079.

[7] Kirushnan BB, Rao BS, Annigeri R, Balasubramanian, S, Seshadri, R, et al. Impact of Malnutrition, Inflammation, and Atherosclerosis on the Outcome in Hemodialysis Patients. Indian J Nephrol., 2017; 27(4): 277-83. doi: 10.4103/0971-4065.202830.

[8] Hwang JH, Ryu J, An JN, Kim CT, Kim H, et al. Pretransplant malnutrition, inflammation, and atherosclerosis affect cardiovascular outcomes after kidney transplantation. BMC Nephro., 2015; 16(1): 109. doi 10.1186/s12882-015-0108-3.

[9] Jagadeswaran D, Indhumathi E, Hemamalini AJ, Sivakumar V, Soundararajan P, et al. Inflammation and nutritional status assessment by malnutrition inflammation score and its outcome in pre-dialysis chronic kidney disease patients. Clin Nutr., 2018. doi: 10.1016/j.clnu.2018.01.001.

[10] Hopewell JC, Haynes R, Baigent C. The role of lipoprotein (a) in chronic kidney disease. J. Lipid Res., 2018; 59(4): 577–85. doi: 10.1194/jlr.r083626 .

[11] Moradi H, Vaziri ND, Kashyap ML, Said HM, Kalantar-Zadeh K. Role of HDL dysfunction in end-stage renal disease: a double-edged sword. J Ren Nutr., 2013; 23: 203–06.

[12] Lakshmi BS, Devi NH, Suchitrab MM, Srinivasa PV, Raob LN, et al. Changes in the inflammatory and oxidative stress markers during a single hemodialysis session in patients with chronic kidney disease. Renal fail., 2018; 40(1): 534–40. doi: 10.1080/0886022X.2018.1487857.

[13] Epstein M, Vaziri ND. Statins in the management of dyslipidemia associated with chronic kidney disease. Nat Rev. Nephrol., 2012; 8: 214–23.

[14] Holzer M, Schilcher G, Curcic S, Trieb M, Ljubojevic S, et al. Dialysis modalities and HDL composition and function. J Am Soc Nephrol., 2015; 26(9): 2267-76.

[15] Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, Jafar TH, Heerspink HJ, et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. Lancet, 2013; 382(9829): 339-52.

[16] Samouilidou E, Kostopoulos V, Liaouri A, Kioussi E, Vassiliou K, et al. Association of lipid profile with serum PON1 concentration in patients with chronic kidney disease. Ren Fail., 2016; 38(10): 1601-06.

[17] Mikolasevic I, Zutelija M, Mavrinac V, Orlic L. Dyslipidemia in patients with chronic kidney disease: etiology and management. Int. J. Nephrol Renovasc Dis., 2017; 10: 35-45.

[18] Kotur-Stevuljevic J, Bogavac-Stanojevic N, Jelic-Ivanovic Z, Stefanovic A, Gojkovic T, Joksic, J, et al. Oxidative stress and paraoxonase-1 status in acute ischemic stroke patients. Atherosclerosis, 2015; 241(1): 192-98. doi: 10.1016/j.atherosclerosis. 2015.05.016.

DOI: 10.21276/SSR-IIJLS.2023.9.6.13

[19] Robson ES, Ana CSS, Aline SM, Patrícia BIJ, Maísa RPL, et al. Potential Role of Nutrient Intake and Malnutrition as Predictors of Uremic Oxidative Toxicity in Patients with End-Stage Renal Disease. Oxid Med Cell Longev., 2019; 2019: 7463412. doi: 10.1155/2019/7463412.

[20] Kaptoge S, Seshasai SR, Gao P. Inflammatory cytokines and risk of coronary heart disease: new prospective study and updated meta-analysis. Eur Heart J., 35, 2014: 578–89.

[21] Briasoulis A, Bakris GL. Chronic kidney disease as a coronary artery disease risk equivalent. Curr Cardiol Rep., 2013; 15: 340.