folia medica

Folia Medica 62(4): 838-42
DOI: 10.3897/folmed.62.e51457

Short Communication

Does Chronic Low-grade Systemic Inflammation Change Tumor Markers Levels in Patients on Hemodialysis?

Gilmar Pereira Silva[1], Vítor Pereira Xavier Grangeiro[2], Carmelita Félix Dantas de Oliveira[2]

[1] *University of Brasilia, Federal District of Brasilia, Brazil*

[2] *Academic of the Medical Course of the Faculty of Medical Sciences, João Pessoa, Paraíba, Brazil*

Corresponding author: Gilmar Pereira Silva, Hotel Sector North, Block D, Apartment 1716, Fusion Building, Postal Code: 70701- 040, Brasilia, Federal District, Brazil; E-mail: gilpsilva2006@gmail.com; Tel.: +5561 3051-7400

Received: 25 Feb 2020 ♦ **Accepted:** 12 May 2020 ♦ **Published:** 31 Dec 2020

Citation: Silva GP, Grangeiro VPX, de Oliveira CFD. Does chronic low-grade systemic inflammation change tumor markers levels in patients on hemodialysis? Folia Med (Plovdiv) 2020;62(4):838-42. doi: 10.3897/folmed.62.e51457.

Abstract

Introduction: End-stage renal disease (ESRD) patients are known to have a high risk of developing cancer-related inflammation. Elevated serum levels of tumor markers in ESRD/hemodialysis patients makes analysis and interpretation difficult.

Aim: To verify the possible relationship between chronic low-grade systemic inflammation serum levels determined by C-reactive protein (CRP) and the tumor biomarkers in patients on hemodialysis.

Materials and methods: A prospective study of prevalence was conducted in the Hemodialysis Sector of the University Hospital of the University of Brasília between July 2016 and December 2016 in men aged 18 to 60 years without clinically detectable cancer. We assessed inflammation by serum high-sensitivity CRP test (hs-CRP) and serum tumor in the case groups and controls. The hemodialysis group was split into two subgroups: group 1: patients with inflammation (CRP > 5 mg/L, n=27), and group 2: patients without inflammation (CRP ≤5 mg/L, n=33).

Results: There was no significant difference in age mean levels between case groups and controls (44.00±08.00 vs. 41.00±07.00, p=0.08). There was no difference or correlation (p>0.05) between tumor markers levels and patients with and without inflammation.

Conclusions: The results of this study suggest that chronic low-grade systemic inflammation defined by C-reactive protein serum levels does not promote elevated serum PSA levels in chronic hemodialysis patients.

Keywords

cancer-related inflammation, cancer biomarker, c-reactive protein, chronic kidney disease, systemic inflammation

INTRODUCTION

Different studies in the past have shown that the risk of cancer development is increased in end-stage renal disease (ESRD) patients, whether on dialysis or not, when compared with the general population.[1,2] Lin et al.[2] checked in dialysis (hemodialysis and peritoneal dialysis) group a significantly higher 7-year cancer incidence rate (6.4%) than did the control group and by multivariable analyses confirmed the association between long-term dialysis and cancer and concluded that dialysis is associated with a higher risk of cancer in patients with ESRD. Identification of specific cancer risks is crucial in the cancer screening of these patients.

On the other hand, the presence of elevated serum levels of tumor markers in ESRD/ hemodialysis patients makes analysis and interpretation difficult. Considering the real risk of cancer and the false positive in that can raise the concentration of tumor markers in the absence of cancer by several causes with methodological, physiological or pathological.[3] False positives with a methodological origin include water permeability (low flux or high flux) and principle of hemodialysis involves the clearance of solutes across a semi-permeable membrane (diffusion, convection, adsorption and ultrafiltration mechanisms).[3] False positives with a pathological origin include alterations that increase marker release due to the alterations that reduce its elimination (such as kidney or liver failure), necrosis or inflammation.[3]

The chronic low-grade systemic inflammation (CLGSI) is regarded as a common comorbid condition in chronic kidney disease (CKD)[4] and a confounding factor in the interpretation and analysis of elevated serum levels of tumor markers of ESRD/hemodialysis patients by the prevalence of high inflammatory factor in this group of patients.[5] Low-grade chronic systemic inflammation in CKD may cause elevated levels of tumor markers due to a likely link between chronic inflammation and development of neoplasia.[6]

In this context, it was decided to verify the possible relationship between CLGSI serum level determined by C-reactive protein (CRP) and tumor biomarkers in patients on haemodialysis.

MATERIALS AND METHODS

A prospective study of prevalence realized in the Hemodialysis Sector of the University Hospital of the University of Brasília, between July 2016 and December 2016, after approval by the Research Ethics Committee of the Faculty of Health Sciences of the University of Brasília (No 53172316.9.0000.0030). We assessed inflammation via serum high-sensitivity CRP (hs-CRP) measurements in the group case and control. Patients in hemodialysis group were classified into two subgroups: group 1: with inflammation (CRP > 5 mg/L, n=27), group 2: without inflammation (CRP ≤5 mg/L, n=33) based on the recommendation of the National Kidney Foundation.[7] The control group (group 3, n=20) were subjects from the health promotion general outpatient clinic of the same hospital who had normal glomerular filtration rate and 90 ml/min/1.73 m^2. CRP value of ≤1 mg/L is considered normal for healthy patients.[8]

The patients included in the study were aged 18-60 years, without clinically detectable cancer. The case group was undergoing hemodialysis for >6 months, received high-flux hemodialysis three 4-h dialysis weekly sessions, using fistula as vascular access.

Exclusion criteria were chronic inflammation due to positive serology for hepatitis B, C, or HIV. Patients with acute or chronic liver disease, rectal examination in the previous week, prostate biopsy in the previous 4 months, cystoscopy, history of urinary tract infection, clinical signs of acute or chronic infection/inflammation, vascular access infection, leukocytosis, fever, or hypoproteinemia were not included in the study.

Blood samples were collected for analysis at the same time, between 8:00 a.m. and 10:00 a.m. in the clinical laboratory of the same hospital. The samples were taken from the arteriovenous fistula immediately before the first weekly hemodialysis session in the case group and on a previously scheduled day in the control group. Five millilitres of blood were collected via arm venoclysis without anticoagulant administration. The blood was centrifuged at 3500×g for 20 min, and the supernatant was collected in a centrifuge tube and maintained at -20°C until tumor markers (alpha-fetoprotein, cancer antigen 19-9, carcinoembryonic antigen, lactate dehydrogenase) and CRP measurements.

Serum CRP levels were measured using turbidimetry in the automatic analyzer BN II (Dade Berhing, kit Dade Berhing, USA). Tumor markers levels were measured via enzyme immunochemoluminescence by using automatic analyzer Immulite 2000/Siemens. Specific kits in addition to calibrators and controls recommended by the manufacturer were used to quantify measurements. All statistical analyses were performed using SPSS® for Windows, version 24.0.

After analyzing the sample distribution by using the Shapiro-Wilk or Kolmogorov-Smirnov normality test, differences between three independent quantitative variables were evaluated using the Kruskal-Wallis test when abnormal distribution curve was presented. Those between three independent quantitative variables with normal distribution curve were evaluated using one-way ANOVA test. Statistical significance was set at $p<0.05$ to reject the null hypothesis.

RESULTS

There was no significant difference in age mean levels between case and control groups (44.00±08.00 vs. 41.00±07.00, p=0.08). There was no difference (p>0.05) between tumor markers levels of patients with inflammation (CRP > 5 mg/L) and patients without inflammation (CRP ≤5 mg/L). CRP serum levels have no correlation with tumor markers (p>0.05) **(Table 1)**.

DISCUSSION

The present study has its relevance because it is one of the first to verify the possible effect of chronic systemic inflammation prevalent in these patients on the biomarkers levels, helping in the analysis and interpretation of these levels above normal limits.

Despite the evidence key component of cancer-related inflammation[6,9], this seems to be ignored in most biomar-

Table 1. Correlational evaluation between serum C-reactive protein (mg/L) and tumor markers (ng/mL) levels in case groups

Variable	Case groups		Spearman's test	
			r	*p*
C-reactive protein serum levels versus tumor makers	Group 1 N=27	Alpha fetoprotein	0.110	0.615
		Cancer antigen 19-9	-0.097	0.630
		Carcinoembryonic antigen	0.257	0.195
		Lactate dehydrogenase	-0.103	0.608
	Group 2 N=33	Alpha fetoprotein	-0.095	0.591
		Cancer antigen 19-9	0.005	0.980
		Carcinoembryonic antigen	-0.033	0.855
		Lactate dehydrogenase	-0.244	0.171

ker studies with confounding conditions. The prevalence of signs of inflammation are inversely related to the level of kidney function and positively associated with the magnitude of proteinuria.[4,10] The etiology of inflammation in CKD is multifactorial, triggering orchestra action to produce key mediators molecules (cytokines and acute-phase proteins) of the inflammatory process as well as markers of inflammation.[4]

The similar age between the groups studied ($p>0.05$) ensures greater reliability in the interpretation of the results and comparative statistical analysis of the impact of age on outcome variables.

Our results show that CRP serum levels do not significantly influence to increase (comparative evaluation ($p>0.05$) **(Table 2)** or maintain correlation (correlational evaluation, $p>0.05$) **(Table 1)** with the tumor markers analyzed in patients undergoing hemodialysis. These results can be explained, in part, by the high-flux type of membranes used in the hemodialysis. These membranes are known to be capable of removing moderate-size molecules between 10000 to 15000 Dalton, including many of the inflammatory proteins, tumor markers, ß$_2$ macroglobulin, lipoproteins and a wide spectrum of uremic toxins.[11,12] As result, in theory, high-flow hemodialysis would have a direct effect on the inflammatory cytokines and/or serum levels of tumor markers.

In the absence of cancer, the increase in the plasma concentration of a tumour marker above the upper reference limit established for healthy individuals is considered a false positive. There are different types of false positives which can be classified as methodological, physiological or pathological.[3] Methodological false positives are attributed to the measuring system; they arise due to the lack of specificity of the antibody, crossed reactions with other molecules, or due to the presence of heterophil antibodies.[3] The pathological false positives include alterations that increase marker release due to necrosis or inflammation, and the alterations that reduce its elimination (such as kidney or liver failure).[13]

The physiopathological processes that link the increase of plasma concentrations of tumor markers to CLGSI is not understood; however, it has been hypothesized that inflam-

Table 2. Comparative evaluation of tumor markers (ng/mL) according to C-reactive protein serum levels in case/control groups

Variables			N	Mean	Median	Standard deviation	p-value*
Tumor markers according to C-reactive protein serum levels	Alpha fetoprotein*	Group 1	27	01.93	01.80	00.59	0.71
		Group 2	33	01.84	01.78	00.47	
		Group 3	20	01.96	01.85	00.66	
	Cancer antigen 19-9**	Group 1	27	09.84	10.00	05.01	0.28
		Group 2	33	07.85	08.00	03.15	
		Group 3	20	07.69	06.35	04.21	
	Carcinoembryonic antigen*	Group 1	27	02.94	03.03	00.44	0.82
		Group 2	33	03.01	03.00	00.48	
		Group 3	20	02.96	03.00	00.41	
	Lactate dehydrogenase*	Group 1	27	181.15	178.00	40.10	0.06
		Group 2	33	177.45	168.00	32.68	
		Group 3	20	213.50	189.50	93.59	

* One-way ANOVA test; ** Kruskal-Wallis test

mation may play a role in cancer development or cancer may cause an inflammatory response and influence measured biomarker levels.[14] This vicious circle of events generates cancer-promoting local and systemic inflammatory microenvironment[14,15] and may be a confounding factor for analysis and interpretation of the serum levels of tumor markers.[16]

For Thompson et al.[14] it is this chronically inflamed state, a pro-inflammatory state sustains the release of cytokines and chemokines with the capability of causing progressive alterations in the cellular and molecular composition of the microenvironment. This leads to elevated levels of promutagenic reactive oxygen and reactive nitrogen species, alterations in the vasculature (e.g. vascular hyperpermeability, neovascularization, and angiogenesis), disturbances in mitochondrial function, and, most importantly, the disruption of normal cell-cell signalling/cross-talk such as recruitment of macrophages with suppressive function to disable T cell-mediated tumor immunity.

Alternatively, molecular, cellular and tissue alterations caused by the chronic inflammation can induce the synthesis and secretion of tumor markers.[13]

The limitations of the present study are the use of CRP as a non-specific marker of inflammation and the reduced number of sample and tumor markers. However, the CRP is a serological marker of inflammation that can be used to investigate the association between inflammation and risk of cancer practically at low cost.[17]

CONCLUSIONS

The results of this study suggest that the chronic low-grade systemic inflammation defined by C-reactive protein serum levels does not promote elevated serum PSA levels in chronic hemodialysis patients.

Abbreviations

ESKD: end-stage kidney disease;
CLGSI: chronic low-grade systemic inflammation;
CKD: chronic kidney disease;
hs-CRP: high-sensitivity CRP-C-reactive protein

REFERENCES

1. Cheung CY, Chan GC, Chan SK, et al. Cancer incidence and mortality in chronic dialysis population: a multicenter cohort study. Am J Nephrol 2016; 43(3):153–9.
2. Lin MY, Kuo MC, Hung CC, et al. Association of dialysis with the risks of cancers. PLoS One 2015; 10(4):e0122856.
3. Trapé J, Filella X, Alsina-Donadeu M, et al. Increased plasma concentrations of tumour markers in the absence of neoplasia. Clin Chem Lab Med 2011; 49(10):1605-20.
4. Raj DS, Pecoits-Filho R, Kimmel PL. Inflammation in chronic kidney disease. In: Kimmel PL, Rosenberg ME, editors. Chronic Renal Disease. Elsevier; 2020: 355–73.
5. Kowalewska M, Nowak R, Chechlinska M. Implications of cancer-associated systemic inflammation for biomarker studies. Biochimica et Biophysica Acta (BBA)-Reviews on Cancer. 2010; 1806(2):163–71.
6. Greten FR, Grivennikov SI. Inflammation and cancer: triggers, mechanisms, and consequences. Immunity 2019; 51(1):27–41.
7. KDOQI, Foundation NK. KDOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease. Am J Kidney Dis 2006; 47(5 Suppl 3):S11-145.
8. Ridker PM. High-sensitivity C-reactive protein, inflammation, and cardiovascular risk: from concept to clinical practice to clinical benefit. Am Heart J 2004; 148(1 Suppl):S19–26.
9. Murata M. Inflammation and cancer. Environ Health Prev Med 2018; 23(1):50.
10. Amiri M. Aggravation of chronic kidney disease by inflammatory factors; a narrative review on current concepts. J Renal Endocrinol 2016; 2:e05.
11. Akoglu H, Dede F, Piskinpasa S, et al. Impact of low- or high-flux haemodialysis and online haemodiafiltration on inflammatory markers and lipid profile in chronic haemodialysis patients. Blood Purif 2013; 35(4):258–64.
12. Ronco C, Clark WR. Haemodialysis membranes. Nat Rev Nephrol 2018; 14(6):394–410.
13. Liu XX, Shen XF, Liu F-J. Screening targeted testis-specific genes for molecular assessment of aberrant sperm quality. Mol Med Rep 2016; 14(2):1594–600.
14. Thompson PA, Khatami M, Baglole CJ, et al. Environmental immune disruptors, inflammation and cancer risk. Carcinogenesis 2015; 36 Suppl 1:S232–53.
15. Chai EZ, Siveen KS, Shanmugam MK, et al. Analysis of the intricate relationship between chronic inflammation and cancer. Biochem J 2015; 468(1):1–15.
16. Chechlinska M, Kowalewska M, Nowak R. Systemic inflammation as a confounding factor in cancer biomarker discovery and validation. Nat Rev Cancer 2010; 10(1):2–3.
17. Guo YZ, Pan L, Du CJ, et al. Association between C-reactive protein and risk of cancer: a meta-analysis of prospective cohort studies. Asian Pac J Cancer Prev 2013; 14(1):243–8.

Меняет ли хроническое системное воспаление низкой степени уровень опухолевых маркеров у пациентов, находящихся на гемодиализе?

Гилмар Перейра Силва[1], Витор Перейра Хавиер Грангейро[2], Кармелита Феликс Дантас де Оливейра[2]

[1] *Университет Бразилии, Федеральный округ Бразилия, Бразилия*

[2] *Преподаватель по специальности „Медицина", Факультет медицинских наук, Жуан-Песоа, Параиба, Бразилия*

Адрес для корреспонденции: Гилмар Перейра Силва, Гостиничный сектор Север, Корпус Д, Номер 1716, Строение „Фьюжен", П.к. 70701-040, Федеральный округ Бразилия, Бразилия; E-mail: gilpsilva2006@gmail.com; Тел.: +5561 3051-7400

Дата получения: 25 февраля 2020 ♦ **Дата приемки:** 12 мая 2020 ♦ **Дата публикации:** 31 декабря 2020

Образец цитирования: Silva GP, Grangeiro VPX, de Oliveira CFD. Does chronic low-grade systemic inflammation change tumor markers levels in patients on hemodialysis? Folia Med (Plovdiv) 2020;62(4):838-42. doi: 10.3897/folmed.62.e51457.

Резюме

Введение: Безусловно установлено, что пациенты с терминальной стадией почечной недостаточности имеют высокий риск развития воспаления, связанного с раком. Повышенные уровни опухолевых маркеров у пациентов с терминальной стадией почечной недостаточности или гемодиализа затрудняют анализ и интерпретацию.

Цель: Проверить вероятную взаимосвязь между уровнями в сыворотке крови при хроническом системном воспалении низкой степени, которые определяются С-реактивным белком (CRP) и опухолевыми биомаркерами у пациентов, находящихся на гемодиализе.

Материалы и методы: Проспективное частотное исследование проводилось в Центре гемодиализа при университетской больнице университета Бразилии с июля по декабрь 2016 года среди мужчин в возрасте от 18 до 60 лет без клинически установленного рака. Мы оценивали воспаление с помощью высокочувствительного теста на CRP в сыворотке (hs-CRP) и опухоли в сыворотке в экспериментальной и контрольной группах. Группа гемодиализа была разделена на две подгруппы: группа 1: пациенты с воспалением (CRP > 5 мг/L, n=27) и группа 2: пациенты без воспаления (CRP ≤5 мг/L, n=33).

Результаты: Мы не обнаружили существенной разницы в средних возрастных уровнях между группами случаев и контрольной группой (44,00 ± 08,00 против 41,00 ± 07,00, p=0.08). Не было никакой разницы или корреляции (p>0.05) между уровнями опухолевых маркеров и пациентами с воспалением и без него.

Заключение: Результаты этого исследования показали, что хроническое системное воспаление низкой степени, определяемое уровнями С-реактивного белка в сыворотке, не увеличивало уровень PSA в сыворотке у пациентов, находящихся на хроническом гемодиализе.

Ключевые слова

связанное с раком воспаление, биомаркер рака, с-реактивный белок, хроническое заболевание почек, системное воспаление