ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

DOI: 10.5336/dermato.2020-75109

Assessment of Serum Creatinine, Cystatin C and Neutrophil Gelatinase-associated Lipocalin Levels in Rosacea: A Case-Control Study

Rozasea Hastalarında Serum Kreatinin, Sistatin C ve Nötrofil Jelatinaz İlişkili Lipokalin Düzeylerinin Değerlendirilmesi: Bir Vaka-Kontrol Çalışması

Ezgi AKTAŞ KARABAY[a], Emre KARABAY[b], Özlem UNAY DEMİREL[c], Nejdet KARŞIYAKALI[d]

[a]Bahçeşehir University Faculty of Medicine, Department of Dermatology and Venereology, İstanbul, TURKEY
[b]Haydarpaşa Numune Training and Research Hospital, Department of Urology, İstanbul, TURKEY
[c]Bahçeşehir University Faculty of Medicine, Department of Biochemistry, İstanbul, TURKEY
[d]Acıbadem Hospital, Department of Urology, İstanbul, TURKEY

ABSTRACT Objective: Rosacea, a chronic inflammatory skin disease, is known to be associated with various systemic disorders. However, limited data are available on the association between rosacea and renal diseases. The objective of this study was to evaluate serum creatinine, cystatin C and neutrophil gelatinase-associated lipocalin (NGAL) levels in patients with rosacea without any systemic diseases. **Material and Methods:** A prospective, case-control study was planned to investigate the relationship between rosacea and renal involvement by evaluating serum creatinine, cystatin C and NGAL levels. **Results:** A total of 38 patients with rosacea and 45 healthy controls were included. Statistically significant differences in serum creatinine and cystatin C levels were noted between the patient and control groups (respectively p=0.012, p<0.001). No statistically significant difference was shown in the values of NGAL between the two groups (p=0.235). A positive correlation was noted between serum creatinine and serum cystatin C levels (r=0.434; p<0.001). The serum levels of cystatin C were positively correlated with disease duration (r=0.511, p<0.001). **Conclusion:** Serum creatinine and cystatin C levels may provide early detection of renal dysfunction in rosacea.

Keywords: Creatinine; cystatin C; inflammation; neutrophil gelatinase-associated lipocalin; renal disease; rosacea

ÖZET Amaç: Rozasea, pek çok sistemik hastalıkla ilişkili olduğu bilinen kronik, inflamatuar bir deri hastalığıdır. Bununla birlikte rozasea ve renal hastalıklar arasındaki ilişkiyle ilgili bilgi sınırlıdır. Bu çalışmanın amacı, hiçbir sistemik hastalığı olmayan rozasea hastalarında, serum kreatinin, sistatin C ve nötrofil jelatinaz ilişkili lipokalin (NGAL) düzeylerini değerlendirmektir. **Gereç ve Yöntemler:** Rozasea ve renal tutulum arasındaki ilişkiyi araştırmak için serum kreatinin, sistatin C ve NGAL düzeylerini değerlendiren prospektif, vaka-kontrollü çalışma planlanmıştır. **Bulgular:** Toplam 38 rozasea hastası ve 45 sağlıklı kontrol çalışmaya dâhil edilmiştir. Serum kreatinin ve sistatin C düzeylerinde hasta ve kontrol grubu arasında istatistiksel olarak anlamlı fark bulunmuştur (sırasıyla p=0,012, p<0,001). NGAL değerlerinde, 2 grup arasında anlamlı bir fark bulunmamıştır (p=0,235). Serum kreatinin ve serum sistatin C düzeyleri arasında pozitif bir korelasyon izlenmiştir (r=0,434; p<0,001). Serum sistatin C düzeyleri hastalık süresiyle pozitif korelasyon göstermiştir (r=0,511, p<0,001). **Sonuç:** Serum kreatinin ve sistatin C düzeyleri rozasea hastalarında renal disfonksiyonun erken bir belirteci olabilir.

Anahtar Kelimeler: Kreatinin; sistatin C; inflamasyon; nötrofil jelatinaz ilişkili lipokalin; renal hastalık; rozasea

Rosacea is a common, chronic inflammatory skin disease that presents with relapses and remissions on the central face.[1] It is known that chronic inflammation plays a prominent role in the development of systemic diseases. Recent data have shown that rosacea is associated with systemic comorbidities that may affect morbidity and mortality.[2] In a recent nationwide population-based study, it was reported that rosacea is an independent risk factor for chronic kidney diseases (CKD). Chronic inflamma-

Correspondence: Ezgi AKTAŞ KARABAY
Bahçeşehir University Medicine of Faculty, Department of Dermatology and Venereology, İstanbul, TURKEY/TÜRKİYE
E-mail: ezgi.aktaskarabay@med.bau.edu.tr

Peer review under responsibility of Turkiye Klinikleri Journal of Dermatology.

Received: 28 May 2020 ***Received in revised form:*** 07 Jun 2020 ***Accepted:*** 09 Jun 2020 ***Available online:*** 21 Sep 2020

tion and oxidative stress are suggested as the link between rosacea and kidney diseases as they contribute in the pathogenesis of both diseases.[3]

Serum creatinine is a well-known, relatively inexpensive and accessible marker used for the assessment of renal function, which can be influenced by several variables, including diet and age.[4] Cystatin C is a protease inhibitor and also a marker of kidney dysfunction that can be detected earlier than plasma creatinine and is not affected by age, gender, diet or muscle bulk.[4] It has been shown to be an accurate predictor of renal disease-related morbidity and mortality.[4] Neutrophil gelatinase-associated lipocalin (NGAL), a lipocalin protein, is produced by renal tubular cells in response to epithelial damage. Plasma and urine NGAL are reported to be reliable biomarkers for the early prediction of acute kidney injury following various clinical presentations, such as cardiopulmonary bypass,contrast administration, kidney transplantation,or emergency settings.[5-8] Both NGAL and cystatin C are accepted as sensitive and early biomarkers of renal injury.[4]

In the present study, we measured serum creatinine, cystatin C and NGAL levels in patients with rosacea who have no other diseases or risk factors of renal disease to determine the renal functions in patients with rosacea.

MATERIALS AND METHODS

STUDY POPULATION AND PROTOCOLS

The study was reviewed and approved by the local ethics committee (protocol number: 22481095-020-1261; date of approval: 26/06/2018), and written informed consents were obtained from all participants. The study was conducted in accordance with the principles in the Declaration of Helsinki.

A prospective, case-control study was planned to investigate the relationship between the levels of serum creatinine, cystatin C, NGAL and rosacea. Thirty-eight rosacea patients and 45 healthy controls were enrolled in the study. The sample size was calculated using G Power version. A confidence level of 95% ($p < 0.05$) and power of 80% were used.

Thirty-eight patients diagnosed with rosacea by clinical examination were enrolled from a dermatology outpatient clinic. Forty-five age- and gender-matched healthy subjects without rosacea or any other inflammatory skin disease were included as the control group. Only those with normal body mass index (BMI) (18.5–25 kg/m^2) were included. Patients with a history of any systemic treatment, including non-steroidal anti-inflammatory drugs, and immunosuppressants, within six months of the study and any systemic diseases, such as hypertension (defined as either resting systolic or diastolic blood pressure of ≥140/90 mmHg on two occasions or the current use of antihypertensive medication); diabetes mellitus; cardiovascular disease; dyslipidemia; vascular disease; renal or liver disease; any inflammatory, autoimmune diseases; malignancy were excluded.[9] Currently pregnant or lactating females and smokers were also excluded. At the time of admission, the arterial blood pressure (BP) of the participants was measured using an automated blood pressure cuff on the left arm. The subjects with higher than 140/90 mmHg of BP were not included.

The data on baseline demographics, clinical characteristics and blood test results were obtained on the same day.

Rosacea is classified as erythematotelangiectatic rosacea (ETR), papulopustular rosacea (PPR), phymatous rosacea, ocular rosacea and variant granulomatous rosacea, according to the American National Rosacea Society (NRS) Expert Committee classification and staging system, which also acts as a diagnostic tool.[1]

LABORATORY ANALYSIS

Fasting venous blood samples were used to assess the levels of serum creatinine, cystatin C and NGAL. The samples were collected from the participants in the morning following a 12-hour fasting period. The creatinine levels were measured by the kinetic alkaline picrate method, and cystatin C was measured by the immunoturbidimetric method (particle-enhanced turbidimetric immunoassay). The cystatin C and creatinine levels of the serum samples were measured by Abbott Architect ci8200 autoanalyzer (Abbott Diagnostics, Abbott Park, Illinois, USA). NGAL was

measured by the enzyme-linked immunosorbent assay (ELISA) method.

STATISTICAL ANALYSIS

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 22.0 software (IBM Corp., Armonk, NY, USA). The data were statistically described in terms of median (min-max), number and frequency. The Kolmogorov-Smirnov test, Shapiro-Wilk test, and graphic analysis were applied to assess the normality of data for quantitative variables. The Mann-Whitney U test was used to compare two groups of quantitative variables showing abnormal distribution. The Pearson chi-square test and Fisher's exact test were used to compare the qualitative data. The Kruskal-Wallis test was performed for the subgroup analyses, and a *post-hoc* analysis was carried out by the Dunn-Bonferroni test to analyze statistical significance. In addition, the Mann-Whitney U test was also used for pairwise comparisons when the Dunn-Bonferroni test could not determine the statistical significance in the *post-hoc* analyses. The correlations between the biochemical parameters and age, gender, BMI and disease duration were identified by the Spearman's correlation analysis. P values less than or equal to 0.05 were considered statistically significant.

RESULTS

A total of 38 patients with rosacea and 45 healthy control subjects were included in the study. The rosacea group comprised of 26 (68.4%) patients with ETR and 12 (31.57%) patients with PPR.

No significant differences were observed in the gender ratio or age between the patients with rosacea and healthy controls (p=0.756 and p=0.711, respectively). All participants' BMI values were in the normal range.

None of the subjects had any accompanying disease. The median disease duration was 12 (2-120) months among the rosacea patients.

A statistically significant difference in serum creatinine levels was observed between the patient and control groups (0.79 mg/dL vs 0.72 mg/dL, p= 0.012, respectively).

A statistically significant difference was also observed in terms of cystatin C levels between rosacea patients and controls (0.99 mg/L vs 0.84 g/dL, p<0.001, respectively).

No statistically significant difference was shown in the values of NGAL between the two groups (56.03 ng/mL vs 58.6 ng/mL, p=0.235, respectively). The demographic data and the clinical characteristics of the study group are shown in Table 1.

When the healthy controls and the patients with rosacea were evaluated according to disease subtype (ETR and PPR), the serum creatinine levels and serum cystatin C levels were statistically significantly different between the groups (p=0.038 and p < 0.001, respectively).

In the *post-hoc* analyses, statistically significant higher serum cystatin C levels were observed in the patients with ETR and in the patients with PPR when compared to the healthy controls (1.01 vs 0.84 p < 0.001 and 0.98 vs 0.84 p=0.001). In the pairwise comparisons, statistically significant higher serum creatinine levels were observed in the patients with ETR when compared to the healthy controls (0.76 mg/dL vs 0.72 mg/dL, p=0.032). The subgroup

TABLE 1: Demographic characteristics serum creatinine, cystatin C and NGAL values in rosacea patients and healthy controls.

Variables		Rosacea patients (n, %) (38, 45.8)	Healthy controls (n, %) (45, 54.2)	p-value
Gender; n(%)	Female	29 (46.8%)	33 (53.2%)	[a]0.756
	Male	9 (42.9%)	12 (7.1%)	
Age; years med (min-max)		34 (19-68)	35 (24-58)	[b]0.711
BMI med (min-max)		23.7 (20.1-26.7)	23.4 (20.1-24.8)	[b]0.464
Disease duration (months) med (min-max)		12 (2-120)	-	
Creatinine med (min-max)		0.79 (0.63-1.25)	0.72 (0.58-1.03)	[b]0.012*
Cystatin C med (min-max)		0.99 (0.69-1.60)	0.84 (0.65-1.09)	[b]<0.001*
NGAL med (min-max)		56.03 (28.65-65.96)	58.60 (24.59-110.60)	[b]0.235

[a]Chi-Square test, [b]Mann-Whitney U test, * p<0.05
BMI: Body Mass Index, NGAL: Neutrophil gelatinase-associated lipocalin.

TABLE 2: Evaluation of serum creatinine, cystatin C and NGAL levels in subgroups of rosacea patients and healthy controls.

Variables	ETR (n, %) (26, 31.3%)	PPR (n, %) (12, 14.5%)	Healthy controls (n, %) (45, 54.2)	p-value
Gender; n (%) Female	22 (35.5%)	7 (11.3%)	33 (53.2%)	[a]0.212
Male	4 (19.0%)	5 (23.8%)	12 (57.1%)	
Age; years med (min-max)	34 (19-68)	35 (23-65)	35 (24-58)	[b]0.918
BMI med (min-max)	23.8 (20.1-26.7)	23.4 (20.2-24.7)	23.4 (20.1-24.8)	[b]0.748
Disease duration (months) med (min-max)	12 (2-120)	12 (6-60)	-	
Creatinine	0.76 (0.63-1.14)	0.82 (0.63-1.25)	0.72 (0.58-1.03)	[b]0.038*
Cystatin C	1.01 (0.79-1.30)	0.98 (0.69-160)	0.84 (0.65-1.09)	[b]<0.001*
NGAL	57.02 (28.65-65.96)	46.11 (29.56-65.78)	58.60 (24.59-110.60)	[b]0.453

[a]Chi-square test, [b]Kruskal Wallis test, *p<0.05.
BMI: Body Mass Index, NGAL: Neutrophil gelatinase-associated lipocalin.
ETR: Erythematotelangiectatic rosacea, PPR: Papulopustular rosacea.

analysis between ETR, PPR and healthy controls are shown in Table 2.

A positive correlation was noted between the serum creatinine and serum cystatin C levels ($r= 0.434$; $p < 0.001$). The serum levels of cystatin C were positively correlated with disease duration ($r=0.511$, $p < 0.001$).

DISCUSSION

The present study demonstrated that rosacea patients had higher levels of serum creatinine and cystatin C than the healthy controls, suggesting that rosacea patients may be followed-up in case of possible kidney dysfunction development.

Although rosacea was defined as a skin disorder, recent research suggests that there might be an association between rosacea and systemic disorders.[2,10] In a recent systemic review, the association of rosacea with systemic comorbidities was emphasized and a possible correlation between the severity of skin diseases and their incidence was suggested.[2] The associations between cardiovascular diseases (CVD), gastrointestinal, neurologic, psychiatric disorders and rosacea have been well documented. Cardiovascular risk factors, such as hypertension, dyslipidemia, high total cholesterol, low-density lipoprotein, and C-reactive protein levels, were demonstrated to be more common in rosacea patients compared with controls.[11]

Limited data are available on the association between rosacea and kidney diseases. Some systemic disorders that have been reported to be associated with rosacea, such as dyslipidemia, hypertension, metabolic diseases, alcohol consumption, smoking and cardiovascular diseases, are also known to be related to CKD.[2,3,10-15] In the literature, one study presented an evaluation of the risk of CKD development in patients with rosacea. In the population-based study, rosacea was reported to be an independent risk factor for CKD development, and the severity of rosacea and older age were also found to be associated with the increased risk.[3]

Chronic inflammation and metabolic, immune and endocrine changes caused by the skin disease were suggested as the pathophysiologic link between systemic disease and rosacea.[2] Some researchers have reported elevated inflammatory markers and oxidative stress in rosacea patients, supporting the presence of systemic inflammation that could contribute to the development of comorbidities.[3,10,11] Similarly, inflammatory pathways and oxidative stress may contribute in renal diseases.[16-18]

The production of pro-inflammatory cytokines, including interleukin (IL)-1 β, IL-6, IL-8 and tumor necrosis factor-α (which contribute to development of rosacea), and inflammasome-related genes (CASP-1 and NALP-3) are reported to be increased in the skin of rosacea patients.[18,19] These inflammatory mediators are also thought to contribute to CKD development.[3,20] Chiu et al.[3] reported a correlation between the development of CKD and the severity of rosacea, suggesting that the similar inflammatory mediators are involved in the pathogenesis of both CKD and rosacea.[3]

Although shared pathologic mechanisms in the development of rosacea and renal diseases and the

presence of the same comorbidities accompanying both diseases are known, the link between renal functions and rosacea has not been established yet. We conducted this study to investigate renal functions in rosacea by measuring serum creatinine, cystatin C and NGAL levels, which are easily accessible markers. The present study demonstrated that rosacea patients had higher levels of serum creatinine and cystatin C than the healthy controls, suggesting that rosacea patients may have kidney dysfunction even when a renal disease is not diagnosed.

Creatinine is the commonly used biomarker in the evaluation of renal functions; however, it has a delayed increase after kidney injury and is heavily dependent on age, sex, muscle mass and nutritional status.[4]

Cystatin C is produced by all the nucleated cells of the body. It is not affected by gender, race, weight, changes of muscle mass and nutrition. Serum cystatin C may demonstrate acute renal injury with more accuracy than creatinine.[4] The serum cystatin C levels at 24 hours were shown to be more efficient than creatinine in predicting CKD development at a 1-year follow-up.[21] Cystatin C is known as a useful marker in determining the glomerular filtration rate (GFR) and renal function.[4] Additionally, cystatin C has been demonstrated as a predictor of CVD.[22,23] Priorly, it was proposed that cystatin C is associated with cardiovascular outcomes due to its sensitivity in detecting early renal dysfunctioning.[24] But now cystatin C is considered both as a marker of GFR and also correlated with inflammation and oxidative stress in CVD.[25] Interestingly, cystatin C levels were also reported to be associated with cardiometabolic risk factors, including hypertension, dyslipidemia and diabetes,[26-28] which are also known to accompany rosacea.[2]

In the present study, the higher cystatin C levels in the rosacea patients and the correlation between the serum levels of cystatin C and creatinine suggest the possibility of renal disease development in disease/symptom-free rosacea patients. Still, it should be considered that the inflammatory nature of rosacea and the possible cardiovascular comorbidities that may accompany rosacea may be the cause of the elevated cystatin C levels. Moreover, renal impairment, is itself an important cardiovascular risk factor.[29] Elevated cystatin C levels may reflect the risk of cardiovascular and renal disease development in rosacea. The serum cystatin C levels did not show significant differences between rosacea subgroups, which may be due to the small sample size. However, the serum cystatin C levels were positively correlated with disease duration, indicating that the longer rosacea persists, the more renal functions may be impaired. Although there was a statistically significant difference in terms of serum creatinine levels between rosacea patients and healthy subjects, the difference was not significant clinically. The small sample size may be an explanation as well the lack of severe forms of rosacea. Or maybe levels of creatinine may not be related with the presence of rosacea.

The levels of NGAL, a small molecule of the lipocalin family of proteins that is found on renal tubular cells, are increased in kidney injuries.[30] NGAL is produced by neutrophils, macrophages, epithelial cells, smooth muscle cells, hepatocytes, adipocytes and neurons.[31] Elevated levels of serum NGAL were demonstrated in response to epithelial injuries in the gastrointestinal tract, respiratory tract or renal tubules.[32] NGAL has been introduced as a diagnostic and prognostic biomarker for acute or chronic kidney disease, sepsis and acute pancreatitis, as well as for gastric, colorectal, pancreatic and biliary cancer.[33-35]

The present study revealed higher levels of serum creatinine and cystatin C in patients with rosacea than in healthy controls, which may be an indicator of subclinical renal dysfunctioning in rosacea. Still it should be noted that both serum creatinine and cystatin C levels were within the normal limits in both groups. But it should be kept in mind that the subjects included were at a relatively young age and none of them had any systemic diseases or were under any treatment that could affect the renal functions. So it may be hypothesized that the higher levels of serum creatinine and cystatin C in rosacea patients even within the normal limits might be very early predictors of renal dysfunctioning. Although the NGAL levels did not statistically differ

between two groups, future studies are necessary to make conclusions.

Although the biomarkers evaluated in the study are considered sensitive tools in determination of renal dysfunction, the lack of GFR measurement is an important limitation of this study. The small sample size and the variations of subgroup numbers are also limitations. The sample size was decided according to the G Power version of power analysis. The results of this study might be confirmed in further studies with larger groups.

CONCLUSION

We believe that rosacea-induced inflammation and oxidative stress may cause renal injury. Nevertheless, more data are necessary to confirm this hypothesis. In this study, the serum creatinine and cystatin C levels were demonstrated to be higher in disease- and symptom-free rosacea patients. Although rosacea is not a life-threatening condition, the early detection of possible comorbidities may be life extending. It may be proposed that patients with rosacea should be screened for renal disorders.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and/or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Ezgi Aktaş Karabay, Emre Karabay;* ***Design:*** *Ezgi Aktaş Karabay, Emre Karabay, Özlem Unay Demirel, Nejdet Karşıyakalı;* ***Control/Supervision:*** *Ezgi Aktaş Karabay;* ***Data Collection and/or Processing:*** *Ezgi Aktaş Karabay, Emre Karabay, Özlem Unay Demirel;* ***Analysis and/or Interpretation:*** *Emre Karabay, Nejdet Karşıyakalı;* ***Literature Review:*** *Ezgi Aktaş Karabay, Emre Karabay;* ***Writing the Article:*** *Ezgi Aktaş Karabay;* ***Critical Review:*** *Emre Karabay;* ***References and Fundings:*** *Ezgi Aktaş Karabay, Özlem Unay Demirel.*

REFERENCES

1. Wilkin J, Dahl M, Detmar M, Drake L, Liang MH, Odom R, et al. Standard grading system for rosacea: report of the National Rosacea Society Expert Committee on the classification and staging of rosacea. J Am Acad Dermatol. 2004;50(6):907-12. [Crossref] [PubMed]
2. Haber R, El Gemayel M. Comorbidities in rosacea: a systematic review and update. J Am Acad Dermatol. 2018;78(4):786-92. [Crossref] [PubMed]
3. Chiu HY, Huang WY, Ho CH, Wang JJ, Lin SJ, Hsu YW, et al. Increased risk of chronic kidney disease in patients with rosacea: a nationwide population-based matched cohort study. PLoS One. 2017;2;12(10):e0180446. [Crossref] [PubMed] [PMC]
4. George JA, Gounden V. Novel glomerular filtration markers. Adv Clin Chem. 2019;88:91-119. [Crossref] [PubMed]
5. Mishra J, Dent C, Tarabishi R, Mitsnefes MM, Ma Q, Kelly C, et al. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. Lancet. 2005;2-8;365(9466):1231-8. [Crossref]
6. Bachorzewska-Gajewska H, Malyszko J, Sitniewska E, Malyszko JS, Dobrzycki S. Neutrophil-gelatinase-associated lipocalin and renal function after percutaneous coronary interventions. Am J Nephrol. 2006;26(3):287-92. [Crossref] [PubMed]
7. Parikh CR, Jani A, Mishra J, Ma Q, Kelly C, Barasch J, et al. Urine NGAL and IL-18 are predictive biomarkers for delayed graft function following kidney transplantation. Am J Transplant. 2006;6(7):1639-45. [Crossref] [PubMed]
8. Nickolas TL, O'Rourke MJ, Yang J, Sise ME, Canetta PA, Barasch N, et al. Sensitivity and specificity of a single emergency department measurement of urinary neutrophil gelatinase-associated lipocalin for diagnosing acute kidney injury. Ann Intern Med. 2008;3;148(11):810-9. [Crossref] [PubMed] [PMC]
9. de la Sierra A. New American and European hypertension guidelines, reconciling the differences. Cardiol Ther. 2019;8(2):157-66. [Crossref] [PubMed] [PMC]
10. Holmes AD, Spoendlin J, Chien AL, Baldwin H, Chang ALS. Evidence-based update on rosacea comorbidities and their common physiologic pathways. J Am Acad Dermatol. 2018;78(1):156-66. [Crossref] [PubMed]
11. Duman N, Ersoy Evans S, Atakan N. Rosacea and cardiovascular risk factors: a case control study. J Eur Acad Dermatol Venereol. 2014;28(9):1165-9. [Crossref] [PubMed]
12. Hua TC, Chung PI, Chen YJ, Wu LC, Chen YD, Hwang CY, et al. Cardiovascular comorbidities in patients with rosacea: a nationwide case-control study from Taiwan. J Am Acad Dermatol. 2015;73(2):249-54. [Crossref] [PubMed]
13. Shankar A, Klein R, Klein BEK. The association among smoking, heavy drinking, and chronic kidney disease. Am J Epidemiol. 2006;1;164(3):263-71. [Crossref] [PubMed]
14. Kawaguchi Y, Mine T, Kawana I, Yasuzaki H, Kokuho T, Toya Y, et al. Gastroesophageal reflux disease in chronic renal failure patients: evaluation by endoscopic examination. Tokai J Exp Clin Med. 2009;20;34(3):80-3.

15. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American heart association councils on kidney in cardiovascular disease, high blood pressure research, clinical cardiology, and epidemiology and prevention. Hypertension. 2003;42(5):1050-65. [Crossref] [PubMed]

16. Kang HT, Kim JK, Shim JY, Lee HR, Linton JA, Lee YJ, et al. Low-grade inflammation, metabolic syndrome and the risk of chronic kidney disease: the 2005 Korean National Health and Nutrition Examination Survey. J Korean Med Sci. 2012;27(6):630-5. [Crossref] [PubMed] [PMC]

17. Kaysen GA, Eiserich JP. The role of oxidative stress-altered lipoprotein structure and function and microinflammation on cardiovascular risk in patients with minor renal dysfunction. J Am Soc Nephrol. 2004;15(3):538-48. [Crossref] [PubMed]

18. Small DM, Coombes JS, Bennett N, Johnson DW, Gobe GC. Oxidative stress, anti-oxidant therapies and chronic kidney disease. Nephrology (Carlton). 2012;17(4):311-21. [Crossref] [PubMed]

19. Buhl T, Sulk M, Nowak P, Buddenkotte J, McDonald I, Aubert J, et al. Molecular and morphological characterization of inflammatory infiltrate in rosacea reveals activation of Th1/Th17 pathways. J Invest Dermatol. 2015;135(9):2198-2208. [Crossref] [PubMed]

20. Granata S, Masola V, Zoratti E, Scupoli MT, Baruzzi A, Messa M, et al. NLRP3 inflammasome activation in dialyzed chronic kidney disease patients. PLoS One. 2015;23;10(3): e0122272. [Crossref] [PubMed] [PMC]

21. Lahoud Y, Hussein O, Shalabi A, Nativ O, Awad H, Khamaisi M, et al. Effects of phosphodiesterase-5 inhibitor on ischemic kidney injury during nephron sparing surgery: quantitative assessment by NGAL and KIM-1. World J Urol. 2015;33(12):2053-62. [Crossref] [PubMed]

22. Jernberg T, Lindahl B, James S, Larsson A, Hansson LO, Wallentin L, et al. Cystatin C: a novel predictor of outcome in suspected or confirmed non-ST-elevation acute coronary syndrome. Circulation. 2004;19;110(16):2342-8. [Crossref] [PubMed]

23. Åkerblom A, Wallentin L, Larsson A, Siegbahn A, Becker RC, Budaj A, et al. Cystatin C- and creatinine-based estimates of renal function and their value for risk prediction in patients with acute coronary syndrome: Results from the PLATelet inhibition and patient outcomes (PLATO) study. Clin Chem. 2013;59(9):1369-75. [Crossref] [PubMed]

24. Correa S, Morrow DA, Braunwald E, Davies RY, Goodrich EL, Murphy SA, et al. Cystatin C for risk stratification in patients after an acute coronary syndrome. J Am Heart Assoc. 2018;16;7(20):e009077. [Crossref]

25. Smith ER. Cystatin C- More than a filtration marker? Atherosclerosis. 2013;230(1):73-5. [Crossref] [PubMed]

26. Okura T, Jotoku M, Irita J, Enomoto D, Nagao T, Desilva VR, et al. Association between cystatin C and inflammation in patients with essential hypertension. Clin Exp Nephrol. 2010;14(6):584-8. [Crossref] [PubMed]

27. Salgado JV, Souza FL, Salgado BJ. How to understand the association between cystatin C levels and cardiovascular disease: imbalance, counterbalance, or consequence? J Cardiol. 2013;62(6):331-5. [Crossref] [PubMed]

28. Magnusson M, Molvin J, Engström G, Svensson-Färbom P, Persson M, Christensson A, et al. Cystatin C and risk of diabetes and the metabolic syndrome - biomarker and genotype association analyses. PLoS One. 2016;24;11(5):e0155735. [Crossref] [PubMed] [PMC]

29. Taglieri N, Koenig W, Kaski JC. Cystatin C and cardiovascular risk. Clin Chem. 2009;55(11):1932-43. [Crossref] [PubMed]

30. Bolignano D, Donato V, Coppolino G, Campo S, Buemi A, Lacquaniti A, et al. Neutrophil gelatinase-associated lipocalin (NGAL) as a marker of kidney damage. Am J Kidney Dis. 2008;52(3):595-605. [Crossref] [PubMed]

31. Janas RM, Ochocińska A, Śnitko R, Dudka D, Kierkuś J, Teisseyre M, et al. Neutrophil gelatinase-associated lipocalin in blood in children with inflammatory bowel disease. J Gastroenterol Hepatol. 2014;29(11):1883-9. [Crossref] [PubMed]

32. Nielsen BS, Borregaard N, Bundgaard JR, Timshel S, Sehested M, Kjeldsen L, et al. Induction of NGAL synthesis in epithelial cells of human colorectal neoplasia and inflammatory bowel diseases. Gut. 1996;38(3):414-20. [Crossref] [PubMed] [PMC]

33. Mårtensson J, Bell M, Xu S, Bottai M, Ravn B, Venge P, et al. Association of plasma neutrophil gelatinase-associated lipocalin (NGAL) with sepsis and acute kidney dysfunction. Biomarkers. 2013;18(4):349-56. [Crossref] [PubMed]

34. Budzynska A, Nowakowska-Dulawa E, Marek T, Boldys H, Nowak A, Hartleb M, et al. Differentiation of pancreatobiliary cancer from benign biliary strictures using neutrophil gelatinase-associated lipocalin. J Physiol Pharmacol. 2013;64(1):109-14.

35. Yan L, Borregaard N, Kjeldsen L, Moses MA. The high molecular weight urinary matrix metalloproteinase (MMP) activity is a complex of gelatinase B/MMP-9 and neutrophil gelatinase-associated lipocalin (NGAL): modulation of MMP-9 activity by NGAL. J Biol Chem. 2001;5;276(40):37258-65. [Crossref] [PubMed]