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ENDOCAN: A RELIABLE BIOMARKER FOR RENAL IMPAIRMENT IN PSORIASIS VULGARIS PATIENTS

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Abstract

Background: Endocan may play a possible indicator for vascular endothelial related pathologies. Severe psoriasis is a risk factor for chronic kidney disease. Endocan may predict renal impairment in psoriatic patients. **Aim(s):** To assess risk of renal impairment in patients having psoriasis and to investigate the role of serum endocan in renal impairment in these patients. **Methods:** We have estimated glomerular filtration rate (eGFR) and examined serum endocan level in normotensive non-diabetic psoriasis patients (n=70) controlled to age- and gender- matched volunteers (n=60). Psoriasis area severity index (PASI) score was used to assess psoriasis severity. **Results:** eGFR was significantly low in psoriasis patients than controls ($p = 0.02$), and in sever than moderate psoriasis ($p = 0.02$). Endocan serum level showed a significant elevation among psoriatic cases than controls ($p < 0.001$), and was correlated positively with psoriasis severity ($r=0.83$, $p < 0.001$), and negatively with eGFR ($r= - 0.43$, $P < 0.001$). Severe psoriasis patients had odds ratio (OR) of 2.5 getting renal impairment compared to moderate psoriasis. The best cutoff of endocan was 507.23 pg/mL for detection of early kidney impairment in psoriasis patients (sensitivity =87.5%, specificity=82.3%, accuracy=82.9%) with area under the curve of 0.79. Psoriasis patients with high serum endocan had 2.3 OR of getting renal impairment. **Conclusion**: Serum endocan is associated with psoriasis severity and may be a sensitive and accurate predictive biomarker for early detection of renal impairment in psoriasis patients. Renal impairment has OR of 2.5 in severe psoriasis and of 2.3 in psoriasis patients with high endocan.

KEYWORDS: psoriasis, renal impairment, eGFR, endocan, biomarker.

What's known?

- Psoriasis was suggested to have increased risk of kidney dysfunction that may be attributed to chronic inflammation.
- Endocan is a unique endothelial dysfunction marker that has an important role in many inflammatory conditions.

What's new?

- Endocan has an active role in the pathogenic mechanism shared between psoriasis and renal impairment.
- Circulating endocan is an early indicator for renal affection in psoriasis cases.

INTRODUCTION

Psoriasis is a chronic immune-mediated inflammatory disease that requires a life-long treatment. It affects 2-4% of the population all-over the world.[1,2] It has unique pathological features such as vascular hyperplasia, increased keratinocytes proliferation and mononuclear inflammatory infiltration of the dermis and epidermis. Keratinocytes hyperproliferation is associated with activation of cellular immune response involving T cells, dendritic cells, as well as many chemokines and cytokines.[3]

Immunogenetic changes reported to explain immune-pathogenesis of psoriasis disease have shifted modern concepts on psoriasis from distinct skin disease to a systemic immune mediated inflammatory state equivalent to other well-known immune- inflammatory disorders such as cardiovascular disease,[4] Moreover,

epidemiological studies showed that in patients with psoriasis, associated disorders may occur more frequently than expected. Such comorbidities include, among others, psoriatic arthritis, inflammatory bowel disease, obesity, diabetes, cardiovascular disease, cancer, gastrointestinal diseases, chronic obstructive pulmonary diseases and depression.[5,6]

It has been shown that, independently to traditional risk factors to renal impairment, psoriatic patients, with moderate and severe disease forms, have an increased risk for chronic kidney disease (CKD)[7, 8], indicating severe psoriasis as a risk factor for CKD and end stage CKD.[9] The association between psoriasis and kidney disease remains mostly unclear. Renal impairment in psoriasis patients could be explained by immune-pathologic entities such as inflammatory disorders and CKD.[15] Moreover, in psoriasis, endocan was proposed as a biomarker of both psoriasis activity and psoriasis associated cardiovascular disease risk.[16]

Therefore, through this study we aimed to examine the risk of renal impairment in psoriasis patients having moderate and severe disease forms, in addition to validating the role of serum endocan as a diagnostic biomarker for development of renal impairment in psoriatic patients.

MATERIALS AND METHODS

Our current case control study got approved by the Committee of Human Rights of Research in Menoufia University in accordance with the revised Helsinki Declaration. We have enrolled patients with variable degrees of psoriasis vulgaris severity (n=70) referenced to age and sex matched healthy volunteers (n=60) as a control group in this study, who were selected from Dermatology outpatient clinic, Menoufia University Hospital during the period from June 2015 to April 2016. Prior to participation and study initiation, everyone has signed an informed consent form prior. Inclusion criteria for psoriasis patients include both sexes, being over 18 years old, and not receiving any topical (two weeks) or systemic (1 month) treatment for psoriasis prior to examination in this study. Exclusion criteria include presence of any immune-inflammatory disorders other than psoriasis, hypertension, diabetes, dermatologic disorders e.g. dermatitis, metabolic syndrome, fever and/or smoking.

Physical examination was performed for all participants**;** including evaluation of vital signs such as blood pressure, and temperature**.** Psoriasis Area and Severity Index (PASI) was used to assess severity of psoriasis.[17] A PASI score < 7 was defined as mild, used.

Descriptive statistics included percentage (%), mean (x) and standard deviation (SD). The analytic ones included a student t-test that was used to compare normally distributed quantitative variables in two groups and a mediated renal damage as well as treatment induced nephrotoxicity such as cyclosporin and methotrexate.[10] However, other studies found no association between psoriasis and renal impairment.[11] Nonetheless, the exact mechanisms explicate the link between psoriasis and renal dysfunction remains unclear.[12]

Endocan, was called endothelial cell-specific molecule-1, is a soluble chondroitin/ dermatan sulfate proteoglycan.[13] It is secreted by vascular endothelial cells in different body organs including skin and epithelial cells lining renal distal tubules.[14] It was suggested that endocan has a pivotal role in the regulation of cell adhesion, inflammatory disorders and tumor progression, and was of prognostic value in various
from 7 to 12 as moderate and > 12 as severe disease.[18] Fasting and postprandial blood sugar, glycosylated hemoglobin (HbA1c), and lipid profile were performed to exclude any patient with DM and/or dyslipidemia.

Estimated glomerular filtration rate (eGFR)

For every participant, collected 24 hour urine was obtained. e-GFR was calculated in mL/min/1.73 m^2 based upon urine volume (mL), urine flow rate (mL/ min) and creatinine levels in serum and urine in mg/dL. eGFR was estimated using 2009 Chronic Kidney Disease Epidemiology Collaboration equation[19], as follows; eGFR =141 x $\min(S_{Cr}/\kappa, 1)^{\alpha}$ x $\max(S_{Cr}/\kappa, 1)^{-1.209}$ x 0.993^{Age} x 1.018 [if female] x1.159 [if Black]. Abbreviations/ units are as follow; S_{Cr} (standardized serum creatinine) = mg/dL. κ = 0.7 (females) or 0.9 (males), α = -0.329 (females) or -0.411 (males), min = indicates the minimum of S_{Cr}/κ or 1, max = indicates the maximum of S_{Cr}/κ or 1, age = years.

Endocan serum level examination:

Briefly, venous blood (2 mL) was withdrawn, under aseptic condition, kept in a serum separating tube, left to complete clotting, then centrifuged at 4000 r.p.m for 10 min. harvested sera were stored at -80°C till timing for batch testing. Endocan serum level was measured according to the manufacturer's instructions using PicoKine™ ELISA Kit, catalog # EK0752, for human ESM1/Endocan (Boster Biological Technology Co., Ltd., CA, USA).[20] This assay's was sensitive to < 10 pg/ mL, with detection range of 31.2 to 2000 pg/ mL.

Statistical Methods

Data were tabulated and statistically analyzed by an IBM personal computer using statistical package for social science (SPSS version 20) (Chicago, IL, USA). Descriptive and analytic statistics were

Mann Whitney U test that was used for non-normally distributed variables. To study association between two qualitative variables, a Chi-square test (χ^2) was performed. Pearson's correlation coefficient (r) investigates how variables or rank orders are related. The receiver operating characteristic (ROC) curve

analysis was carried out for endocan serum level to assess its validity as a diagnostic marker for renal affection in psoriasis patients. A P-value of ≤ 0.05 was reflected as statistically significant.

RESULTS

Demographic and clinical characteristics of studied psoriasis patients (n=70) and control group (n=60) were demonstrated in Table 1. Patients were age and gender matched with their healthy volunteer group (Table 1). Age of onset of psoriasis, duration and severity of psoriasis were presented as mean +/- SD in Table 1. PASI score, stability and progress of psoriasis were presented in Table 1 for all patients.

Patients had low significant eGFR (mL/min) levels compared to control group (98.20 ± 8.45 vs 101.63 ± 7.74 mL/ min, p=0.02, Table 2). Low eGFR was noticed in sever vs moderate psoriasis (95.95 ± 7.47 vs 100.87 ± 8.88 mL/min, p = 0.02, Fig. 1a). Moreover, 8/70 (11.4%, Table 2) patients showed abnormal low eGFR levels, 2/32 had moderate disease and 6/38 has severe psoriasis. The odds ratio of renal impairment in severe psoriasis patient group compared to moderate ones was 2.5.

Interestingly, psoriasis patients had a significant higher level of serum endocan compared to patients in the control group (p<0.001, Table 2). Supplementary figure 1 showed comparison of serum endocan levels in male versus female psoriasis patients sub-classified according to psoriasis disease activity into moderate and severe sub-groups. Endocan was associated with severity of psoriasis (p<0.001) and was not related to a patient's gender.

In psoriasis patients, low eGFR was observed in males (8/8, 100%) who were older patients (p=0.003) with delayed onset of psoriasis (p=0.01). Most importantly, psoriasis patients having abnormal eGFR showed significant higher endocan serum levels versus those with normal eGFR (533.8 ± 147.6 pg/mL vs 365.7 ± 120.9 pg/mL, p =0.007, Table 3). Endocan serum levels were significantly high in psoriasis patients than controls (384.91 ± 134.27 pg/mL vs 122.39 ± 42.07 pg/mL, p <0.001, Table 2). This high endocan level was more significantly observed in severe (n=38, 482.63 ± 99.19 pg/mL) versus moderate (n=32, 268.87 ± 52.77 pg/mL, p<0.001) form of psoriasis (Fig. 1b).

In the psoriasis patient group, serum endocan levels were positively correlated with age of psoriasis onset (r=0.30, P=0.01), its duration (r=0.53, P<0.001) and severity (PASI score) (r=0.83, P<0.001), as well as the patients' age (r=0.44, P<0.001), and was negatively correlated with eGFR (r=-0.43, P<0.001) (Figure 2).

A linear regression model for an independent predictor of endocan levels among psoriasis patients revealed that the severity of psoriasis (PASI score) was an independent predictor for endocan serum levels (P<0.001, 95%CI=19.43–28.3, Table 4). Moreover, regression analysis for independent risk factors of renal impairment among psoriatic patients revealed that endocan is the independent risk factor for renal impairment (P=0.02, with odds ratio 2.33 and 95%CI=1.87–8.92, Table 5).

Furthermore, a receiver operating characteristics (ROC) curve to assess endocan as an early biomarker of renal affection in psoriatic patients demonstrated an area under the curve (AUC) of 0.79, and revealed that endocan serum level is a relatively accurate and sensitive (accuracy=82.9%; sensitivity=87.5%) test for predicting renal affection in psoriasis, with a level of 507.23 pg/mL as the best cutoff point level (Figure 3).

Figure legends:

Figure 1: eGFR (A) and endocan level (B) in relation to psoriasis severity.

Figure 2: Correlation between serum endocan level and other studied parameters:
(A) Age of psoriasis onset (r=0.30, p = 0.01).
(B) Duration of psoriasis (r=0.53, p < 0.001).
(C) PASI score (r=0.83, P<0.001).
(D) The patients' age (r=0.44, P<0.001).
(E) eGFR (r=-0.43, P<0.001).

Figure 3: Receiver operating characteristics (ROC) curve for endocan as a diagnostic marker of renal affection among psoriatic patients.

Table 1: Socio-demographic and clinical character of the studied patients and controls.

	Psoriatic patients N = 70	Control N = 60	Test	P value
Age (years) X±SD Range	 42.54±10.89 18 – 65	 41.25±11.65 18 – 60	t-test 0.65	0.52
Sex Male Female	 40 (57.1) 30 (42.9)	 37 (61.7) 23 (38.3)	χ^2 0.27	0.60
Age of onset/year				

X±SD Range	34.66±10.21 12 – 55			
Duration /year X±SD Range	 7.86±3.10 3 – 15			
PASI X±SD Range	 12.85±4.97 8 – 31.2			
Severity Moderate Sever	No % 32 45.7 38 54.3			
Stability Stable Progressive	No % 48 68.6 22 31.4			
Family history Yes No	No % 4 5.7 66 94.3			

PASI: Psoriasis Area and Severity Index; t-test: student t-test.; χ^2: Chi-square test ; * P value < 0.05 is considered statistically significant.

Table 2: Endocan level and eGFR among cases and control group.

	The studied groups		Test	P value
	Cases N = 70	**Control N = 60**		
eGFR (mL/min) X±SD Range	 98.20±8.45 85 – 116	 101.63±7.74 90 – 115	t-test 2.40	**0.02***
eGFR(mL/min) normal decreased **(renal affection)**	 62 (88.6) 8 (11.4)	 60 (100) 0 (0.0)	FE 7.31	**0.007***
Endocan(pg/mL) X±SD Range	 384.91 ± 134.27 200.93 – 565.41	 122.39 ± 42.07 54.87 – 184.66	U 9.81	**<0.001***

t-test; student t-test.; FE, Fisher Exact test; U, Mann Whitney U test; * P value < 0.05 is considered statistically significant.

Table 3: Association between renal affection with different studied parameters

	e GFR among psoriatic cases N = 70		**Test**	**P value**
	Normal N = 62	**Abnormal N = 8**		
Age (years) X±SD Range	 41.2±10.4 16 – 60	 53.0±10.0 39 – 65	3.0	**0.003***
Sex Male Female	 32 (51.6) 30 (48.4)	 8 (100) 0 (0.0)	FE 6.77	**0.009***
Age of onset/year X±SD Range	 33.6±10.2 12 – 55	 42.8±6.1 34 – 50	2.48	0.01*
Duration /year X±SD Range	 7.5±2.9 3 – 13	 10.3±4.0 5 – 15	1.86	0.06
PASI X±SD Range	 12.3±3.9 8 – 24.6	 17.5±9.1 8 – 31.2	1.18	0.24
Severity Moderate Sever	 30 (48.4) 32 (51.6)	 2 (25.0) 6 (75.0)	FE 1.56	0.28

Stability Stable Progressive	 44 (71.0) 18 (29.0)	 4 (50.0) 4 (50.0)	FE 1.45	0.25
Family history Yes No	 4 (6.5) 58 (93.5)	 0 (0.0) 8 (0.0)	FE 0.55	1.0
Endocan X±SD Range	 365.7±120.9 200.93 – 639.92	 533.8±147.6 200.93 – 656.41	U 2.7	**0.007***

* P value < 0.05 is considered statistically significant.

Table 4: Linear regression analysis model for independent risk predictors for Endocan level.

	Multivariate linear regression analysis				
	r	**SE**	**P value**	**95% CI**	
				Lower	Upper
Age	0.004	1.88	0.92	-3.44	2.65
Age of onset	0.03	1.21	0.70	-1.96	2.88
Duration	0.05	4.21	0.96	-8.62	8.22
PASI	**0.88**	2.22	**<0.001***	**19.43**	**28.3**
eGFR	0.03	1.38	0.75	-.233	3.20

r= coefficient of variation, SE = standard error, CI = confidence interval * P value < 0.05 is considered statistically significant.

Table 5: Multivariate regression analysis for independent risk factors for renal impairment in psoriatic patients

Parameters	**SE**	**P value**	**Odds ratio**	**95% CI**	
				Lower	Upper
Age	0.68	0.11	0.98	0.18	1.55
Sex	0.98	0.23	1.09	0.68	2.33
Age of onset	0.99	0.08	1.38	0.77	2.99
Endocan	**0.14**	**0.02***	**2.33**	**1.87**	**8.92**

SE = standard error, CI = confidence interval, * P value < 0.05 is considered statistically significant.

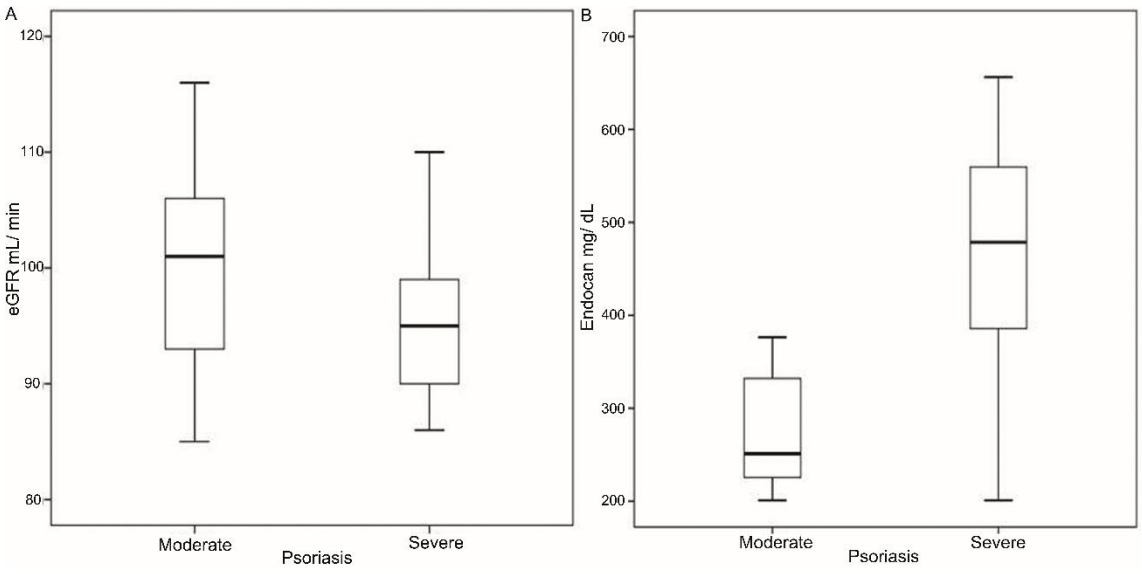
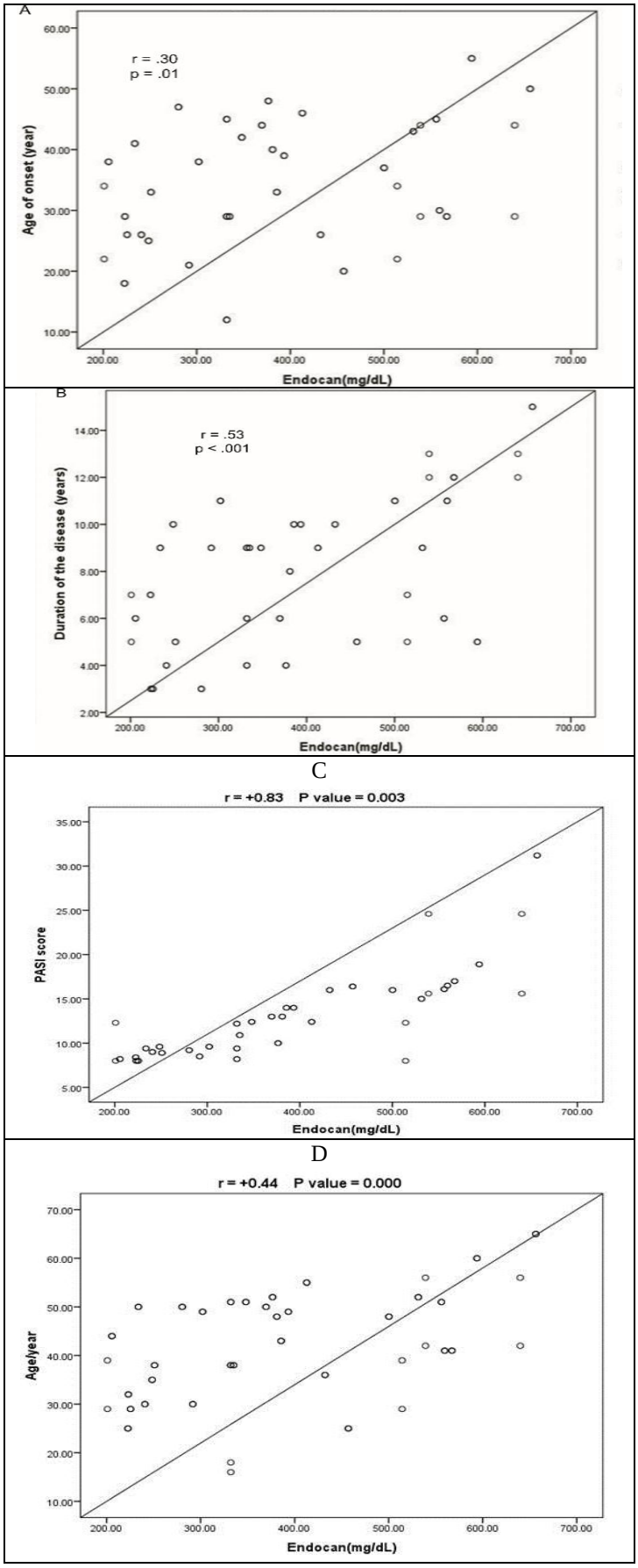
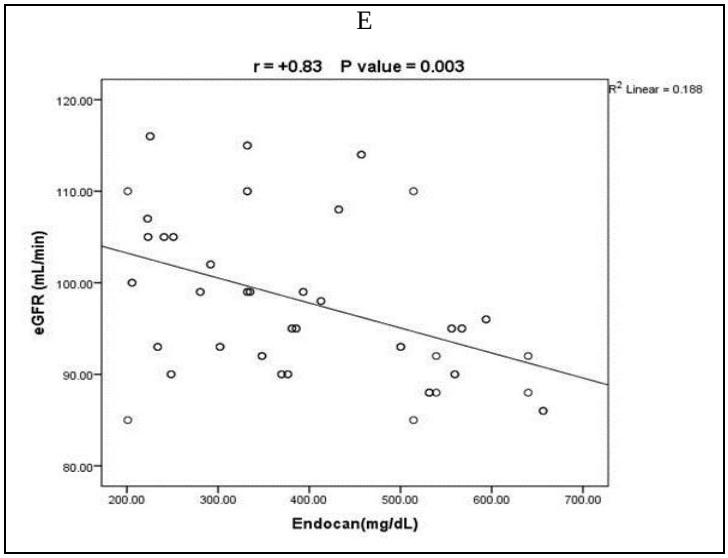


Figure 1.

Figure 2.


A
r = .30
p = .01
Age of onset (year)
Endocan(mg/dL)
B
r = .53
p < .001
Duration of the disease (years)
Endocan(mg/dL)
C
r = +0.83 P value = 0.003
PASI score
Endocan(mg/dL)
D
r = +0.44 P value = 0.000
Age/year
Endocan(mg/dL)



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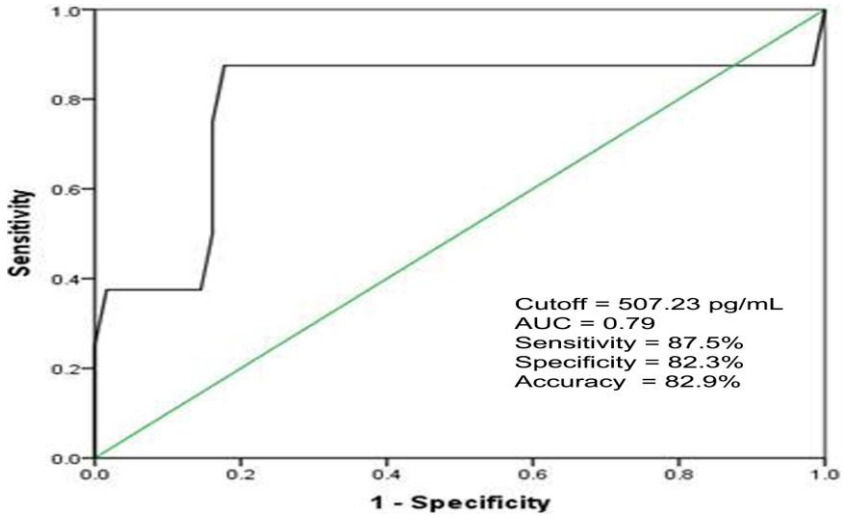
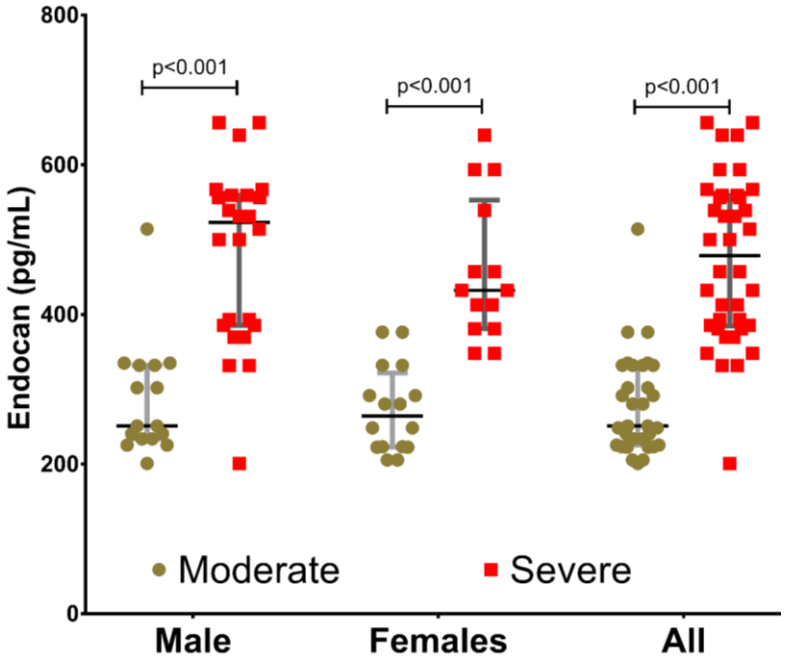


Figure 3.



Supplemental Figure 1

DISCUSSION

Early stage of renal disease is clinically silent and is associated with both morbidity and mortality. Better laboratory tests are required for its detection especially in psoriasis patients. GFR is generally considered the best index of renal function in health and disease population.[21] As evidenced with decreased eGFR, our findings demonstrated that patients with psoriasis without any clinically evident or risk factor for kidney dysfunction have a high prevalence of renal impairment, particularly in those with severe disease. Severe psoriasis patients have an OR of 2.5 getting renal impairment. Psoriasis patients with high endocan levels have 2.3 OR for getting renal impairment. The best serum Endocan cutoff level was 507 pg/mL, turns into a sensitive (87.5%), specific (82.3%) and an accurate (82.9%).

In harmony, Wan et al. (2013), reported that moderate to severe psoriasis is associated with increased risk of moderate to advanced chronic kidney disease (CKD) in their population-based cohort, reviewed in Wan and Gelfand (2016).[7-8] However, Chi et al (2015) found that only sever psoriasis patients carry this risk and they were twice more likely to have CKD and thrice more likely to develop end stage renal disease compared to healthy controls.[9] Additionally, the presence of psoriatic arthritis and concomitant NSAIDs use further increases the risk of CKD in patients having psoriasis.[22] Recently, Coimbra et al (2017) also revealed low renal function in their psoriatic cases. In their study, although the decreased eGFR was insignificant, it was correlated to disease severity and inflammatory markers in their investigated patients, even after successful treatment.[12]

Moreover, when psoriasis patients were categorized according to evaluated eGFR, we observed that old age, male patients, those having delayed onset of psoriasis, and to a less extent, those with long disease duration, represented a more high risk group for renal affection among our studied patients, along with cases having severe disease, who may need closer observation.

It was confirmed that inflammation, the hallmark of psoriasis, seems to be a significant element for renal function deterioration.[12] In psoriasis, inflammation of major vessels has been characterized[23] as a comorbidity of sever psoriasis, and the inflammation of smaller vessels in the kidney may occur.[9] The adhesion cascade involving the rolling, tethering, adherence, and consequently leukocyte transmigration through the endothelium is the initial step in vascular inflammation, with subsequent formation of psoriatic plaque.[24] This recruitment and accumulation of leukocytes to the endothelium is mediated through up regulation of adhesion molecules such as ICAM-1 and VCAM-1[25] that are increased in patients having CKD.[26] Yet, how the inflammation contributed to renal dysfunction remains enigmatic and needs to be clarified. So our aim was extended to investigate if endocan has any possible role in the molecular mechanism linking development of renal impairment in psoriasis.

In line with Balta et al. we have observed significant increase in endocan serum level in psoriasis patients than their matched peers, and this elevated level showed significant positive correlation not only with severity of psoriasis[27], but also with its age of onset and duration as well as the age of patients. Moreover, the PASI score was the only independent predictor for endocan serum level. This suggests an active role of endocan in aetiopathogenesis of psoriasis and possible use of its serum level as a disease severity biomarker.

Within the psoriasis patient group, endocan serum levels exhibited a significant negative correlation with eGFR, and psoriasis cases having decreased eGFR presented significantly higher endocan serum levels. Furthermore, our multivariate regression analysis for independent risk factors of renal impairment among psoriasis cases revealed that endocan is an independent risk factor for renal impairment.

Supporting our findings, Su et al. demonstrated high endocan levels in CKD patients that was inversely correlated with eGFR.[28] Furthermore, it was revealed that serum endocan level had a significant positive correlation with inflammatory markers such as high sensitive CRP and pentraxin 3 and was associated with endothelial dysfunction indicators including flow-mediated vasodilatation and carotid intima-media thickness in CKD cases.[29]

How endocan contributed to impaired renal function is not completely well-known, and the exact mechanism of renal impairment in psoriasis is not explained yet. It has been suggested that endocan has an active role in: up-regulation of cell adhesion molecules such as E-selectin, ICAM-1, VCAM-1 and LFA-1; endothelial activation through resistin induction; and endothelial cytoskeleton rearrangement that leads to cellular contraction, all of which are well-known in psoriasis pathogenesis[24] and CKD.[15] Thus, it is possible that similar pathogenesis occurs in psoriasis and its associated renal impairment in which endocan is an active player.

Unlike eGFR, endocan level is a reliable biomarker as eGFR depends on creatinine level in serum and urine which can get affected by many factors including ethnicity, age, sex, muscle mass, body hydration status and meat consumption.[30]

Relatively, a small sample size was the main limitation of this study. Accordingly, we recommend further large-scale studies to validate our findings as this is the first study that evaluates the relationship between endocan and eGFR in psoriasis patients.

In conclusion, endocan is associated with psoriasis disease severity and can be used reliably to predict renal damage in psoriasis patients. At an endocan serum level of 507.23, our study showed its sensitivity=87.5%, specificity=82.3%, and accuracy=82.9% for early detection of kidney impairment in psoriasis patients. We recommend a large scale study to examine predictive power at different stages of renal involvement in psoriasis patients from the molecular to apparent morphological and functional changes in kidneys.

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