

Original Research Article

Relationship of cutaneous manifestations with inflammatory markers in diabetic nephropathic patients on haemodialysis

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ABSTRACT

Background: Diabetic nephropathy is a serious life threatening complication of type-2 diabetes mellitus. Apart from severe kidney dysfunction these patients are prone to various cutaneous complications including psoriasis and eczema due to accumulated nitrogenous waste products. Inflammation is the basic cause of cutaneous complications and many inflammatory markers have been shown elevated in chronic kidney dysfunction. Hence a study has been planned to assess the levels of inflammatory markers such as C-reactive protein (CRP) and interleukin-6 (IL-6) as well as to correlate these markers with creatinine levels along with existing cutaneous complications.

Methods: The study included 50 diabetic nephropathic patients undergoing regular haemodialysis. A heparinised blood sample was collected and plasma was employed for estimation of glucose, creatinine, CRP and IL-6. A detailed dermatological examination was done to record the cutaneous complications like pruritis, xerosis, hyper pigmentation and half & half nails.

Results: The results show a significant raise in CRP and IL-6 levels in proportion to the severity of kidney dysfunction as reflected by creatinine levels. Also a positive relationship was observed between the inflammatory markers and multiplicity of cutaneous complications.

Conclusions: It can be concluded from the present study that evaluation of inflammatory markers, CRP and IL-6 along with creatinine is beneficial in controlling cutaneous complications in DN patients undergoing regular haemodialysis.

Keywords: Diabetic nephropathy, Creatinine, C-reactive protein, Interleukin-6

INTRODUCTION

Diabetic nephropathy is a severe life threatening diabetic complication where in large amount of metabolic nitrogenous waste products do accumulate due to chronic kidney dysfunction and do induce a metabolic stress which may trigger up systemic inflammation.

It is known that several dermatological complications including psoriasis, eczema and sebaceous gland diseases have an inflammatory background due to underlying, chronic kidney disease and the diabetic nephropathy patients (DN) are vulnerable for inflammation induced skin complications.¹⁻³ Few earlier reports show that inflammatory markers are elevated in DN patients but the relationship of these inflammatory markers with

commonly observed dermatological complications and their severity have not been accounted.⁴⁻⁶

Hence a study was undertaken to correlate levels of inflammatory markers, C-reactive protein (CRP) and Interlukin-6 (IL-6) with cutaneous complications in DN patients undergoing regular heamodialysis.

METHODS

The DN patient in the age group of 30-60 years, undergoing regular heamodialysis in dialysis unit at Subbaiah Medical College Hospital and its affiliated hospitals were recruited in to the present study (Group DN). This study was carried out during the period March 2019 to June 2019. These patients were clinically examined for dermatological symptoms and complications like pruritis, xerosis, hyperpigmentation and half & half nails.

Type-2 diabetic subjects in the age group of 30-60 years, attending medical OPD of these hospitals were randomly selected and considered as control group (Group DM). Normal subjects in the age group of 30-60 years were taken from the employees of Subbaiah Medical College Hospital and its affiliated hospitals (Group N). A fasting heparinized blood sample (5 ml) was collected from the normal subjects, (Group N), control diabetic patients (Group DM) and diabetic nephropathic patients undergoing heamodialysis (Group DN) after obtaining an informed consent from each one of them. These blood samples were centrifuged at 3000 rpm for 8 min and the separated plasma was employed for the estimation of glucose, creatinine, CRP and IL-6.⁷⁻¹⁰ These DN patients were further sub-grouped as per their plasma creatinine levels which are taken as an indicator of kidney dysfunction as well as sub-grouped as per the existence of one or more cutaneous complications such as pruritis, xerosis, hyperpigmentation and half and half nails.

Statistical analysis

The results obtained were expressed as their Mean±SD and were statistically evaluated using Graph Pad Instat version-3.10. P<0.05 was considered as significant.

RESULTS

The results of the present study are given in Table 1-5. Group CR1 patients had plasma creatinine level between 5 mg/dl to 7 mg/dl, Group CR2 patients had creatinine levels 7.1 mg/dl to 10 mg/dl and Group CR3 patients had creatinine levels above 10 mg/dl (Group CC1 patients had one of the four mentioned cutaneous complications, Group CC2 had any two such complications and Group CC3 had three or four such complications. The details are given in Table 1 and 2.

Table 3 narrates the plasma levels of glucose, creatinine, CRP and IL-6 in normal subjects (Group N). Type-2

diabetic subjects (Group DM) as well as in diabetic nephropathic patients undergoing heamodialysis (Group DN). It is evident from the table that the levels of glucose, creatinine, CRP and IL-6 are significantly elevated (p<0.001) in group DM and group DN as compared to group N. Further these levels are significantly (p<0.001) raised in group DN as compared to group DM suggesting that the degree of kidney dysfunction is directly related to elevation of inflammatory markers.

Table 1: Grouping of DN patients as per their creatinine levels.

Groups	Creatinine (mg/dl)	Number of patients
Group CR1	5-7 mg/dl	7
Group CR2	2.1-10 mg/dl	21
Group CR3	> 10 mg/dl	22

Table 2: Grouping of DN patients as per existence of one or more cutaneous complications.

Groups	Number of patients
Group CC1	Any one complication 7
Group CC2	Any two complication 20
Group CC3	Three / four complication 23

Table 3: Plasma levels of glucose, creatinine, CRP and IL-6 in all the groups.

Groups	Glucose (mg/dl)	Creatinine (mg/dl)	CRP (mg/l)	IL-6 (pg/ml)
Group N (40)	88.27 ±13.30	0.85 ±0.10	2.90 ±1.10	5.40 ±1.50
Group DM (40)	152.31 ±21.80***	3.00 ±0.50***	4.20 ±1.10***	8.8 ±3.50***
Group DN (50)	216.0 ±27.0***	11.40 ±4.50***	8.70 ±2.10***	24.50 ±8.80***

The values expressed as their Mean±SD. The number in parentheses indicates the number of subjects. Probability *p>0.05, **p>0.01 and ***p>0.001.

Table 4: Plasma levels of CRP, IL-6 in Group CR1, Group CR2 as well as in Group CR3.

Groups	CRP mg/l	IL-6 pg/ml
Group CR1 (7)	4.39±1.05	12.39±3.60
Group CR2 (21)	9.66±1.80***	23.02±4.40***
Group CR3 (22)	9.32±1.50	34.80±3.80***

The values expressed as their Mean±SD. The number in parentheses indicates the number of subjects. Probability *p>0.05, **p>0.01 and ***p>0.001.

Table 4 gives plasma levels of CRP and IL-6 in Group CR1, Group CR2 as well as in Group CR3. It is evident from the table that IL-6 levels are significantly raised ($p < 0.001$) in Group CR2 and in Group CR3 as compared to Group CR1 whereas CRP levels are significantly elevated ($p < 0.001$) in Group CR2 as compared to Group CR1 suggesting that the rise in IL-6 levels are proportionate to the elevations in plasma creatinine levels in DN patients there by confirming that kidney dysfunction is related to inflammation in DN patients undergoing hemodialysis.

Table 5: Plasma levels of CRP and IL-6 in Group CC1, Group CC2 as well as in Group CC3.

	CRP mg/L	IL-6 pg/ml
Group CC1 (7)	4.20±1.80	12.50±4.10
Group CC2 (20)	10.40±1.60***	22.80±8.80***
Group CC3 (23)	10.20±0.80	33.60±4.20***

The values expressed as their Mean±SD. The number in parentheses indicates the number of subjects. Probability * $p > 0.05$, ** $p > 0.01$ and *** $p > 0.001$.

Table 5 illustrate the plasma levels of CRP and IL-6 in DN patients (Group CC1, Group CC2 and Group CC3) undergoing hemodialysis. It is clear from the data given in table that IL-6 levels in Group CC2 and Group CC3 are significantly raised ($p < 0.001$) as compared to Group CC1 whereas the elevation in CRP is seen only in Group CC2 as compared to CC1 suggesting that there is a positive correlation between cutaneous manifestations and systemic inflammation.



Figure 1: Photographs of half nails, Hyperpigmentation and xerosis. (A) Half and half nails, (B) hyperpigmentation, (C) xerosis.

Figure 1 shows the photographs of cutaneous complications observed in DN patients.

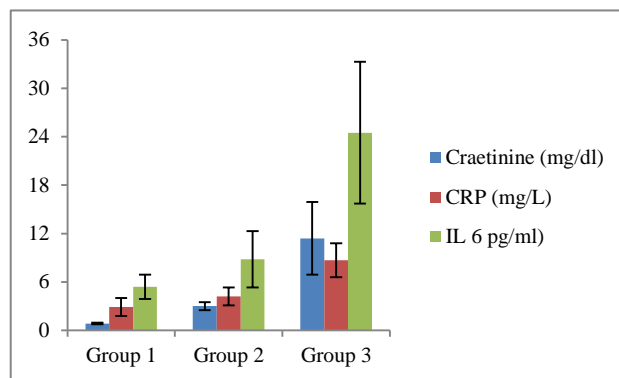


Figure 2: Comparison of creatinine, CRP and IL-6 in group N, group DM and in group DN.

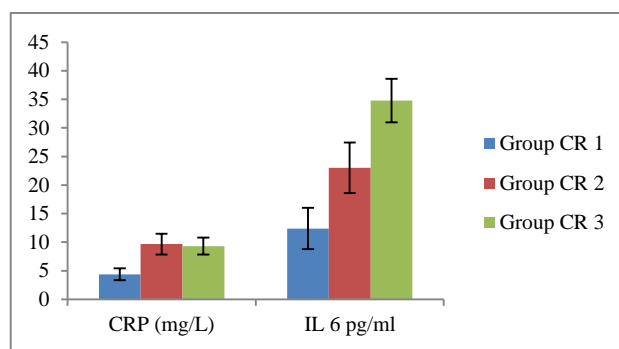


Figure 3: Comparison of CRP and IL-6 levels in group CR-1, group CR-2 and in group CR-3 patients.

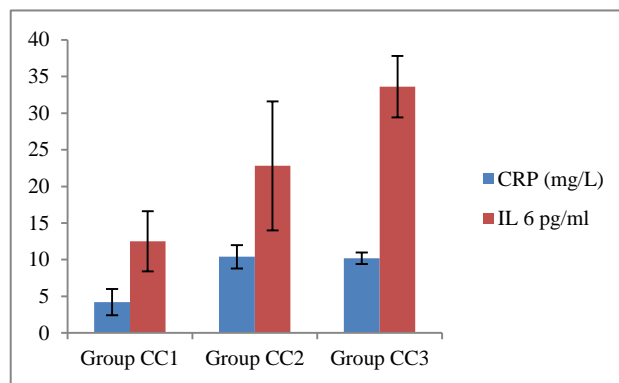


Figure 4: Comparison of CRP and IL-6 levels in group CC-1, group CC-2 and in group CC-3.

Figure 2 gives the comparison of creatinine, CRP and IL-6 in group N, group DN as well as in group DM. It is clear from the bar graphs shown that a significant elevation in these parameters is seen in DN patients as compared to both group N subjects and group DM subjects.

Figure 3 shows the comparison of inflammatory markers CRP and IL-6 in groups CR1, CR2 as well as in CR3.

It is evident from the graphs that both the inflammatory markers (CRP, IL-6) are elevated in group CR2 and CR3 as compare to group CR1. Further the raise observed in IL-6 is significant in both groups CR2 and CR3 as compare to group CR1 suggesting that an inflammatory load is seen in group CR3 patients.

Figure 4 gives the comparative bar graphs of CRP and IL-6 in group CC1, group CC2 as well as in group CC3. It is clear from this graphs that a significant elevation of IL-6 is observed in group CC3 as compare to both group CC1 and group CC2 suggesting a parallel relationship of rise in IL 6 with severity of kidney dysfunction as measured by plasma creatinine levels.

DISCUSSION

Inflammation is a chronic condition which has been agreed as a significant etiological factor in the pathogenesis of many common diseases including type-2 diabetes mellitus, coronary artery diseases, obesity and metabolic syndrome.¹¹⁻¹⁴ Apart from these many cutaneous complications including psoriasis and eczema have been claimed to have inflammation background.¹⁵ Inflammation can be assessed by an elevation in inflammatory markers specifically CRP and IL-6.^{16,17} Inflammation been defined as a complex physiological response to harmful stimulation of the body followed by clinical symptoms like redness, swelling, heat and pain. It is also characterized by elevated levels of inflammatory markers of which CRP and IL-6 are significant and most commonly employed in clinical assessment of inflammation. CRP is an acute phase protein synthesized mainly in liver and its production as well as functions is regulated by cytokines.¹⁸⁻²⁰

It is further observed in the present study that the DN patients are afflicted by one or more cutaneous complications like pruritis, xerosis, hyperpigmentation and half & half nails (Figure 1). It also observed in the present study that about 14% of DN patients exhibited one or the other afore mentioned cutaneous complications like pruritis, xerosis, hyperpigmentation or half & half nails where as 40% exhibited combination of any two such complications and about 46% patients exhibited three or four complications together (Table 4).

It is clear by the result given in Table 3 and in Figure 2 that the DN patients have elevated levels of CRP and IL-6 which are the markers of inflammation. The significant elevation in CRP and IL-6 observed in both group DM and group DN indicates a close relationship between inflammatory markers and kidney dysfunction. Further the elevations in CRP and IL-6 in cutaneous complications dependent sub-groups of DN patients (Table 5 and Figure 4) clearly indicates the cutaneous complications are related to inflammatory markers in DN patients. This is in agreement with earlier reports.^{1,3,15-20} It is clear from the results that elevated CRP and IL-6 are seen in DN patients having multiple cutaneous

complications proving that a rise in inflammatory marker levels is directly related to cutaneous complications (Table 5).

It is evident from the present study that a close relationship does exist between the level of kidney dysfunction and inflammatory markers (CRP, IL-6) as well as between inflammatory markers and multiplicity of cutaneous complications in DN patients (Table 4 and Figure 3).

CONCLUSION

It can be concluded from the present study that evaluation of inflammatory markers, CRP and IL-6 along with creatinine is beneficial in controlling cutaneous complications in DN patients undergoing regular hemodialysis.

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