

# Diabetes and Inflammation; Association Between C-Reactive Protein and Diabetic Nephropathy in Rawalpindi

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## Author's Contribution

<sup>1,4</sup>Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work, <sup>2,5,6</sup>Drafting the work or revising it critically for important intellectual content, <sup>3</sup>manuscript writing, data analysis, <sup>4</sup>Final approval of the version to be published

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## ABSTRACT

**Objective:** To determine the frequency of elevated C-reactive protein in type 2 diabetics and to compare the levels of C-reactive protein between people with diabetes and non-diabetics nephropathy among the population of Rawalpindi, Pakistan.

**Methodology:** This cross-sectional study Diabetic and Medical OPD of Fauji Foundation Hospital, Rawalpindi from January 2019 to July 2019. A total of 150 patients who had type 2 diabetes, aged between 35 to 60 years, irrespective of gender, were included. Blood samples were collected for blood sugar random, fasting, renal function test, WBC count, and C-reactive protein. Urine samples were collected for the measurement of 24-hour urinary proteins. The presence or absence of proteinuria was used to categorize patients into two groups. Group A consisted of 58 patients with type 2 diabetes who did not have nephropathy, and Group B consisted of 92 patients with type 2 diabetes who had nephropathy (proteinuria greater than 30 mg/dl in 24 hours).

**Results:** The mean age in our study was 49.41±7.66. Ninety-two patients (61.3%) presented with diabetic nephropathy. CRP levels (> 8200 ng/ml) were raised in 50 (54.3%) patients of group B and 19 (32.8%) patients of group A. The difference was statistically significant (p-value 0.010).

**Conclusion:** This study showed a higher prevalence of raised CRP in type 2 diabetics with nephropathy. This reinforces the idea that low-grade inflammation has an essential role in the inception and evolution of diabetic renal disease.

**Keywords:** C-Reactive Protein, Diabetes mellitus, Nephropathy, Proteinuria

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## Introduction

Diabetes Mellitus is defined as a heterogeneous group of disorders characterized by Diabetes Mellitus is defined as a heterogeneous group of disorders characterized by hyperglycemia and glucose Intolerance.<sup>1</sup> Globally, the number of people suffering from diabetes mellitus has quadrupled in the last three decades and it is the ninth major cause of death.<sup>2</sup> Diabetes-related kidney damage causes damage to the glomerulus, arterioles, tubules, and

interstitium of the kidneys. In the United States and many other industrialized countries, diabetic nephropathy is the primary cause of kidney failure. Patients with Type 2 diabetes mellitus often suffer from this chronic consequence, which reduces their quality of life.<sup>3</sup>

Diabetes mellitus is one of the significant health problems in Pakistan, with a high prevalence rate of 26.3% of the local population above 19 years of age according to 2<sup>nd</sup> (latest) NDSP (National Diabetes Survey

of Pakistan (2016-2017)<sup>4</sup> and it is expected to rise. It is estimated to increase the economic burden by 61% by 2030.<sup>5</sup> The leading risk factors for diabetes include unhealthy dietary habits, smoking, obesity, sedentary lifestyle, lack of proper health policy. The country lacks consensus guidelines for diabetes management.<sup>4</sup>

The actual burden of diabetes mellitus is attributable to its complications, including diabetic nephropathy, diabetic retinopathy, diabetic neuropathy, stroke, and myocardial infarction. Diabetic Nephropathy is one of its significant complications; it's a renovascular complication; it involves all cell elements of the kidney, including glomeruli.<sup>6</sup> Damage to glomeruli results in increased permeability to proteins such as albumin and transferring and increased extracellular matrix protein synthesis.<sup>7</sup> These proteins invariably pass through the basement membrane and urine.<sup>8</sup> Chronic damage results in a progressive deterioration of renal function. This progressive disease always leads to end-stage renal disease and thus contributes to increased morbidity and mortality.<sup>6-8</sup>

Insulin resistance is the underlying cause of type 2 diabetes mellitus. Constant inflammation is triggered by insulin resistance. Diabetes mellitus has been linked to chronic inflammation in a number of studies.<sup>9-10</sup> Therefore, it is reasonable to conclude that chronic inflammation plays a significant role in the development of diabetes mellitus problems.<sup>11</sup> One study shows that C-reactive protein (CRP) has a strong association with type 2 diabetes mellitus. The frequency of occurrence of raised CRP in Type 2 diabetes mellitus is 65%.<sup>12</sup> As far as diabetic nephropathy is concerned, the relationship between low-grade inflammation and diabetic Nephropathy is still not established.<sup>6</sup> In a study, the frequency of occurrence of raised C-reactive protein in type 2 diabetics with diabetic nephropathy was 96% compared to without nephropathy, which is 7% of patients.<sup>13</sup>

The main sites for CRP production are the liver and adipocytes.<sup>13</sup> Various components of the inflammatory cascade, e.g. interleukin 6, interleukin one, and tumor necrosis factor, act as stimuli for CRP formation.<sup>13</sup> It is a highly sensitive inflammatory marker and is considered one of the best vascular inflammatory markers.<sup>14</sup>

The present study is designed to describe whether inflammation underlies the development of diabetic nephropathy by comparing the levels of C-reactive proteins among the diabetic and non-diabetic population

of Rawalpindi, Pakistan. This can help detect early nephropathy, halt the progression of nephropathy, and new therapeutic strategies based on inflammatory progression.

## Methodology

This cross-sectional study has been done in the diabetic and medical OPD of Fauji Foundation Hospital, Rawalpindi, from January 2019 to July 2019. Following approval from the ethical review committee, FFH Rawalpindi. The WHO calculator was used to estimate the sample size of 150 cases, with a confidence level of 5%, and anticipated the prevalence of diabetic nephropathy in 65% of the population<sup>9</sup>, and absolute precision of test 8%. Non-probability, consecutive sampling technique was used.

We included type 2 diabetic patients whose ages were between 35 to 60 years, irrespective of gender. Patients with acute illness within the past one week, including infection, acute myocardial infarction, malignancy, renal derangements (serum creatinine > 1.5 mg/dl), severe uncontrolled hypertension (B.P.> 160/100mmHg) were excluded from our study.

After taking informed consent, a detailed history was taken, including baseline demographic characteristics such as age, gender. The patient's symptoms, including fever, sore throat, chest pain, shortness of breath, were asked to rule out infection and myocardial infection. The blood pressure of the patients was measured; the oral cavity was examined to see for hyperemia suggestive of infection. ECG was done to rule out myocardial infarction.

Blood samples were taken and sent to a pathological laboratory for random blood sugar, fasting, renal function test, WBC count, and C-reactive protein levels (Quantitative by enzyme-linked immunosorbent assay). A chemical Pathologist with 20 years of experience. Subjects were asked to collect a urine sample for 24 hours after omitting the morning sample and were sent for protein analysis by using the immunoturbidimetric test. Subjects were categorized into two groups depending upon the presence or absence of proteinuria. Group A comprised subjects with type 2 diabetes mellitus without proteinuria, and Group B included type 2 diabetes mellitus with proteinuria.

Type 2 Diabetes Mellitus was defined as fasting blood glucose levels greater than seven mmol/l and random

levels more than 11 mmol/l. C - Reactive Protein was considered positive/raised at a group of more than 8200 ng/ml by using the immunoturbidimetric test. Any patient with proteinuria more than 30 mg/dl in 24 hours was considered a case of diabetic nephropathy, defined as kidney injuries associated with diabetes mellitus and affecting kidney glomerulus; arterioles; Kidney tubules; and the interstitium.<sup>15</sup> After checking the blood sugar level, CRP levels, and 24-hour urinary proteins, we got 58 patients in group A having diabetes without Nephropathy and 92 patients in group B having diabetes with Nephropathy (proteinuria > 30 mg/dl in 24 hrs.).

Data was collected on a structured Performa and was analyzed using the SPSS software version 17. Age, C-reactive protein, proteinuria was expressed as Mean ± SD. Frequencies and percentages were calculated for the categorical variables like gender, diabetic nephropathy, and CRP categories. The frequency of positive CRP was compared between groups A and B using the chi-square test. The significance level was defined as a p-value less than 0.05.

## Results

The mean age (yrs.) of our study population was 49.41±7.66, ranging from 35 to 60 years. Table I summarizes age and diabetes duration in the study population.

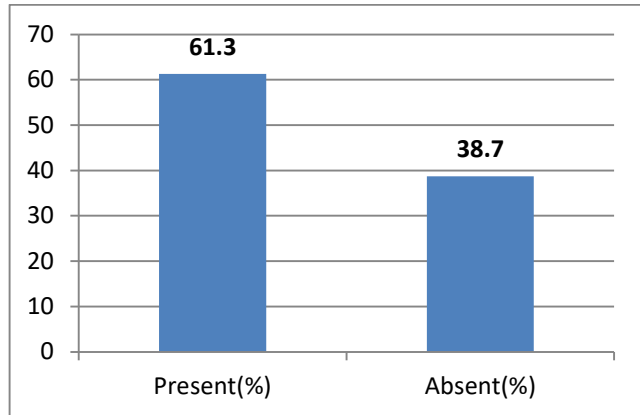
Diabetic Nephropathy was present in 92 (61.3%) patients, which means that these patients have proteinuria of more than 30 mg/dl in 24 hrs. This is depicted in figure 1.

The majority of the patients were females. CRP was positive in 69 (46.0) patients with a level of more than 8200 ng/ml, as shown in figure 2.

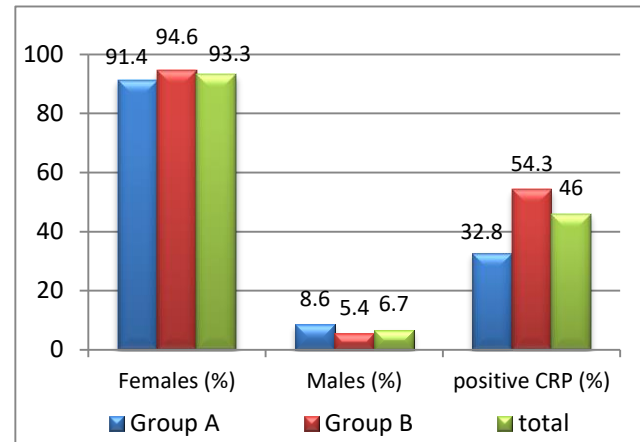
CRP levels were compared between the two groups. In our study, 50 patients (54.3%) in group B had raised CRP values (> 8200 ng/ml). This disparity was statistically significant, having a p-value of 0.010, as shown in Table II.

**Table I: Distribution of demographic characters among the study population.**

Characteristic	Total	Group A	Group B
Age in years (Mean ± SD)	49.41±7.662	49.43 ± 7.286	49.39 ± 7.930
Duration of D.M. in years (mean ± SD)	8.17±5.48	7.67 ± 5.62	8.67 ± 5.32



**Figure 1. Distribution of diabetic Nephropathy in the study population.**



**Figure 2. Distribution of gender and CRP positivity in study subjects.**

**Table II: Comparison of CRP levels between the two groups.**

CRP levels	Group A n (%)	Group B n (%)	p- value
Positive	19 (32.8)	50 (54.3)	0.010
Negative	39 (67.2)	42 (45.7)	

## Discussion

Diabetes mellitus is the second most common endocrine abnormality, according to study a conducted by Candido Muñoz and colleagues in 2019<sup>16</sup>, which has an overall effect on body metabolism and is a significant contributor to both morbidities and mortality. Its prevalence is increasing the world over. The mechanism underlying type 2 Diabetes mellitus is insulin resistance.<sup>17</sup> According to Tsalamandris S and colleagues, several studies now demonstrate that there is some apparent association between Type 2 Diabetes Mellitus and inflammation.<sup>18</sup> A study by K Luc, published in 2020, showed that inflammation can result in impaired secretion of insulin

and insulin resistance.<sup>19</sup> Recent epidemiological data shows that people with this infection are increasingly likely to develop end-stage renal failure. Several acute-phase indicators have been found at significantly high levels in animal and human models of diabetic nephropathy.<sup>18-19</sup> These include C-reactive protein (CRP), various cytokines including IL-6, and many other proteins belonging to the class of acute phase reactants inclusive of fibrinogen and amyloid A.<sup>19-20</sup> A study conducted by Lamiya Pojskić, in Cantonal Hospital Zenica, describes that positive CRP is a marker of albuminuria in patients that have type 2 diabetes.<sup>21</sup>

CRP in plasma originates from various body tissues, mainly from the liver and adipocytes.<sup>22</sup> According to a study by Nicola R and colleagues, it is considered a marker of inflammation as its levels increase when there is systemic inflammation. Central stimuli for its generation consist of various cytokines, including tumor necrosis factor (TNF)-alpha, IL-1, and IL-6 during different inflammatory situations like acute injury, infections, and malignancies.<sup>23</sup> Metin Çağdaş and colleagues have stated that various studies show raised CRP levels in patients with coronary artery disease (CAD).<sup>24</sup> These findings have prompted further exploration of whether it can be used as a predictor of CAD.<sup>25</sup> Its role is also being evaluated as a predictive factor of exacerbations in autoimmune diseases like Systemic lupus erythematosus and rheumatoid arthritis.<sup>26</sup> Ying Tang and colleagues reported that CRP is an important risk factor in a number of age-related disorders including diabetes mellitus and kidney diseases.<sup>27</sup>

In our study, the mean age was 49.41 years  $\pm$  7.66, with the majority of patients being females. Baloch et al also reported similar results with 47.8  $\pm$  10.22 years. Their control group comprised 20 (37%) males, while females constituted 34(62.9%), whereas the nephropathy group contained 18 (33.3%) male and 36 (66.6%) female patients.<sup>13</sup> The effect of gender on the prevalence and severity of diabetic nephropathy has also been investigated in other studies. A study by Clotet et al. stated that male diabetics are more prone to developing nephropathy than females.<sup>15</sup> In our study, the majority of patients were females in total study subjects and nephropathy group, as our hospital serves the families of ex-army servicemen, which consists mainly of females, and it is the main limitation of our study.

In our study, the prevalence of raised CRP in diabetic nephropathy patients was 54.3%, which is slightly lower

than that reported by Algebra et al.<sup>12</sup> Another study conducted in university of Montreal Canada said CRP was positive in 96.2% of people with diabetes and nephropathy.<sup>28</sup> A study published by Habib et al. showed that CRP levels were higher in diabetic patients with nephropathy than those without.<sup>29</sup> Similarly, Sinha et al. also described that raised CRP was associated with the development of diabetic nephropathy.<sup>30</sup>

## Conclusion

This study showed the higher prevalence of raised CRP in type 2 diabetics with nephropathy, suggesting that low-grade inflammation is the cause of the development and progression of renal disease in type 2 diabetic patients.

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