

## High Sensitive C-Reactive Protein Level as a Predictor of the Development of Microalbuminuria in Children with IDDM

Essmat A. Elsharkawy, Gihan L. Abd-elhakim\*, Gihan Mohammed M. Babrs\*  
and Amany William Ebaid\*

*Department of Clinical Pathology, Minia University Hospital; Department of Pediatrics\*, Suzar  
Muharak Minia University Hospital, Egypt.*

### ABSTRACT

**Background:** In IDDM, diabetic nephropathy is the major life threatening complication, including microalbuminuria and steady decline in glomerular filtration rate (GFR), which ultimately leads to ESRD.

**Objectives:** Our study aimed to evaluate the relation between high-sensitivity C-reactive protein (hsCRP) and microalbuminuria in insulin dependent DM in children for early detection of diabetic nephropathy in these patients.

**Methods:** Fifty diabetic patients with normoalbuminuria and 50 with microalbuminuria were included in the study. Patients with primary renal disease, cardiovascular disease, infections and those receiving NSAID or gentamycin were excluded from the study. Patients were subjected to complete urine analysis, albumin/creatinine ratio, complete blood picture, renal function tests (blood urea nitrogen and serum creatinine), HbA1c, lipid profile (serum cholesterol, HDL, LDL and serum triglycerides), high sensitivity CRP using assay.

**Results:** A significantly higher hsCRP was found in the microalbuminuric group than the normoalbuminuric group with significant positive correlations between microalbuminuria and hsCRP, HbA1c, and duration of diabetes.

**Conclusions:** high level of hsCRP in microalbuminuric patients is an early indicator of glomerular damage. Children and adolescents with IDDM should undergo annual monitoring for microalbuminuria and hsCRP, markers for identifying an individual at risk of diabetic nephropathy.

### INTRODUCTION

In IDDM, there is a subclinical chronic inflammation, C-reactive protein (CRP) is known to be a marker of inflammation and increased level has been described in IDDM and type 2 DM, and this subclinical inflammation is strongly correlated to the severity and duration of hyperglycemia<sup>1t</sup>.

Although the mechanisms that trigger the activation of subclinical inflammation in

IDDM are not fully understood, it's likely that chronic exposure to glucose and, possibly, high levels of advanced glycosylation end products, which are associated with the development of diabetic complications, activate the macrophage-monocyte system and, consequently, stimulate the production and secretion of cytokines and acute phase proteins<sup>t2-31</sup>.

A high-sensitivity CRP test measures

low levels of CRP<sup>(1)</sup>. In IDDM, diabetic nephropathy is the major life threatening complication, including microalbuminuria and steady decline in glomerular filtration rate (GFR), which ultimately leads to ESRD. In IDDM patients, microalbuminuria often appears then regresses back to normoalbuminuria, especially within the first 5-10 years after diagnosis of diabetes.

Studies conducted in both adult and adolescent patients with IDDM indicate that persistent MA significantly predicting the development of diabetic nephropathy as high as 80% over a 10 year period<sup>(1)</sup>.

### AIM OF THE WORK

Our study aimed to evaluate the relation between high-sensitivity C-reactive protein (hsCRP) and microalbuminuria in insulin dependent DM in children for early detection of diabetic nephropathy in these patients.

### PATIENTS AND METHODS

This study was carried out on 100 patients with IDDM attending Minia University hospital and Suzan Mubarak Children and Obstetric University hospital at the diabetes clinic, who accepted to participate in the study.

The study was done over the period from June to September 2009. Informed consent verbally was obtained from all patients. Studied patients were 50 males and 50 females with their age ranging from 5-18 years. All patients were using insulin since the diagnosis of diabetes.

#### Exclusion criteria for the patients were:

- 1- Presence of an infection as excluded by complete blood count and urine analysis.

- 2- Presence of primary renal disease as nephritis or nephrotic syndrome as excluded by lipid profile, urine analysis renal function tests and liver function tests.
- 3- Use of drugs which can affect albuminuria as NSAID and gentamicin.
- 4- Evidence of clinical cardiovascular disease.

Patients were classified into 2 main groups:

**Group 1:** includes 50 diabetic patients with urine free albumin or albumin less than standard level for microalbuminuria.

**Group 2:** includes 50 diabetic patients with microalbuminuria (A/C > 0.2).

All patients were subjected to thorough history taking, complete clinical examination including anthropometric measures (Wt, recorded to the nearest 0.5 kg., Ht, determined to the nearest 0.5 cm with a rigid measure against a vertical wall and body mass index), vital signs stressing mainly on blood pressure, using suitable mercury sphygmomanometer after 10 minutes rest with the patient in sitting position, blood pressure was measured two times at 5 minutes interval, presence or absence of edema and systemic examination (chest, heart and abdominal examination).

Laboratory investigations: complete urine analysis, albumin/creatinine ratio (albumin measured in urine samples by the Mandray Bs 300 and the creatinine measured also in urine samples). Urine samples were stored up to the time of measurement of urine creatinine by the spectrophotometer then A/C ratio is calculated from the results, microalbuminuria is defined as 30-299 mg/g creatinine, and

overt nephropathy or clinical albuminuria is > 300 mg/g creatinine)«, complete blood picture, renal function tests (blood urea nitrogen and serum creatininc), I IbA 1 C, lipid profile (serum cholesterol, 1-IDL, LDL and serum triglycerides), high sensitivity CRP using immunoenzymometric assay (Cat#: 3125-300)<sup>(7)</sup>.

**Statistical analysis**

Data entry and analysis were all done with an IBM compatible computer using software called Statistical Package for Social Science (SPSS) for window version 13. Graphics were done using Excel 2003. Quantitative data were presented by mean and standard deviation compared by (Student t test) between the two groups. Correlations used to compare two quantitative variables. Qualitative data was presented by frequency distribution (number and percentage) and compared between

groups by (chi square test). The probability of less than 0.05 wag used as a cut off point for all significant tests.

**RESULTS**

Group II with microalbuminuria showed a higher age and a higher blood pressure (systolic and diastolic) than group I. We found no statistically significant difference between the two groups as regards anthropometric indices. Table 3 shows comparisons between the two groups as regards some laboratory data and revealed significantly higher levels of HBA 1 c (%), hsCRP, blood Urea, serum creatininc and A/C ratio in microalbuminuric group II. A significant positive correlation was found between microalbuminuria and hsCRP, HbA1c, and duration of diabetes.

**Table 1: Comparison between group I and group II as regards clinical characteristics.**

Clinical Characteristics		Group I (No. = 50)	Group II (No. = 50)	p Value
Age (years) Mean ± SD		10.4 ± 3.4	15.2 ± 2.8	0.0001**
Sex	Males No (%)	20 (40%)	31 (62%)	0.04*
	Females No (%)	30 (60%)	19 (38%)	
Blood Pressure	Systole Mean ± SD	100.6 ± 12.2	113.4 ± 6.8	0.0001**
	Diastole Mean ± SD	67.6 ± 9.5	74.4 ± 5.4	0.005**

\* = significant

\*\* = highly significant

**Table 2: Comparison between group I and group II as regards anthropometric measures.**

Anthropometric Measures	Group I (No. = 50)	Group II (No. = 50)	p Value
	Mean ± SD	Mean ± SD	
Weight (kg)	29.02 ± 9.4	30.1 ± 7.3	0.5
Height (cm)	131.5 ± 15.1	135.1 ± 9.9	0.2
BMI	16.2 ± 1.9	16.9 ± 1.6	0.06

**Table 3: Comparison between group I and group II as regards some laboratory data.**

Laboratory findings	Group I (No. = 50)	Group II (No. = 50)	p Value
	Mean ± SD	Mean ± SD	
HBA1c (%)	9.6 ± 2.5	13.2 ± 3.1	0.0001**
Hs CRP (mg/dl)	1.6 ± 0.9	5.2 ± 1.6	0.0001**
Blood Urea (mg/dl)	44.5 ± 9.5	55.1 ± 8.1	0.0001**
Serum Creatinine (mg/dl)	0.77 ± 0.16	1.3 ± 0.33	0.0001**
Serum Cholesterol (mg/dl)	144.8 ± 18.8	149.7 ± 17.5	0.1
HDL (mg/dl)	49.08 ± 8.4	48.08 ± 8.2	0.1
LDL (mg/dl)	93.7 ± 15.8	93.6 ± 14.9	0.5
Triglycerides (mg/dl)	91.5 ± 20.6	90.5 ± 19.8	0.8
A/C ratio	0.001 ± 0.04	0.51 ± 0.19	0.0001**

**Table 4: Correlation between CRP and Duration of diabetes, HbA1c in patients with microalbuminuria.**

Laboratory Findings	Patients with Microalbuminuria (No. = 50)	
	CRP	
	r	p
Duration of Diabetes (years)	0.51	0.0001
HbA1c %	0.50	0.0001

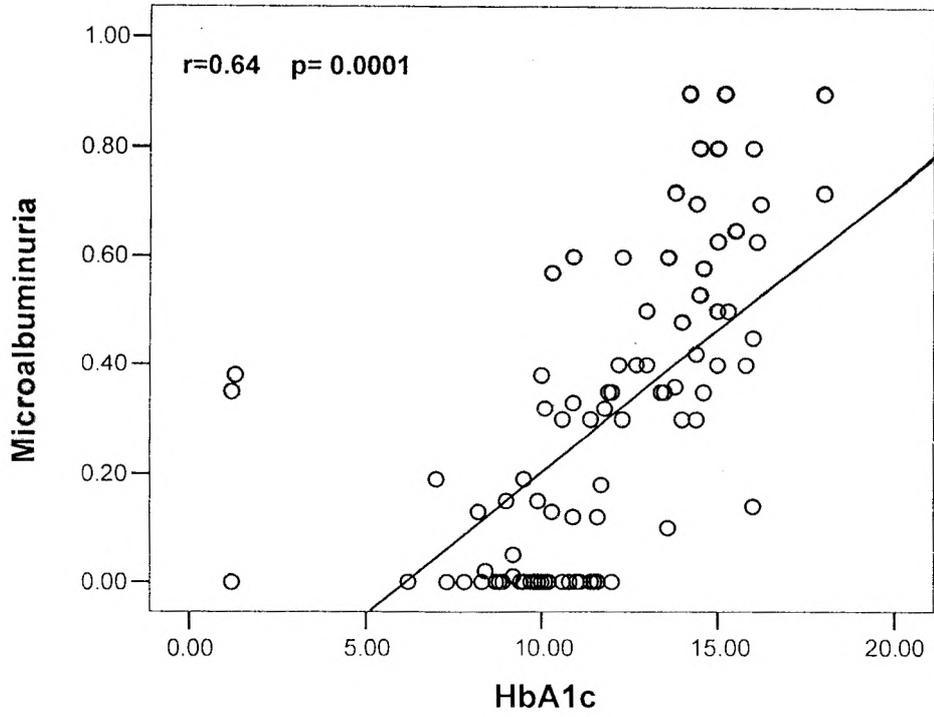
**Table 5: Correlation between microalbuminuria and laboratory parameters in the studied diabetic patients.**

Laboratory Findings	Microalbuminuria	
	Diabetic Patients (No. = 50)	
	r	p
Duration of Diabetes (years)	0.71	0.0001**
HbA1c	0.64	0.0001**
CRP	0.92	0.0001**
Blood Urea (mg/dl)	0.63	0.0001**
Serum Creatinine (mg/dl)	0.90	0.0001**

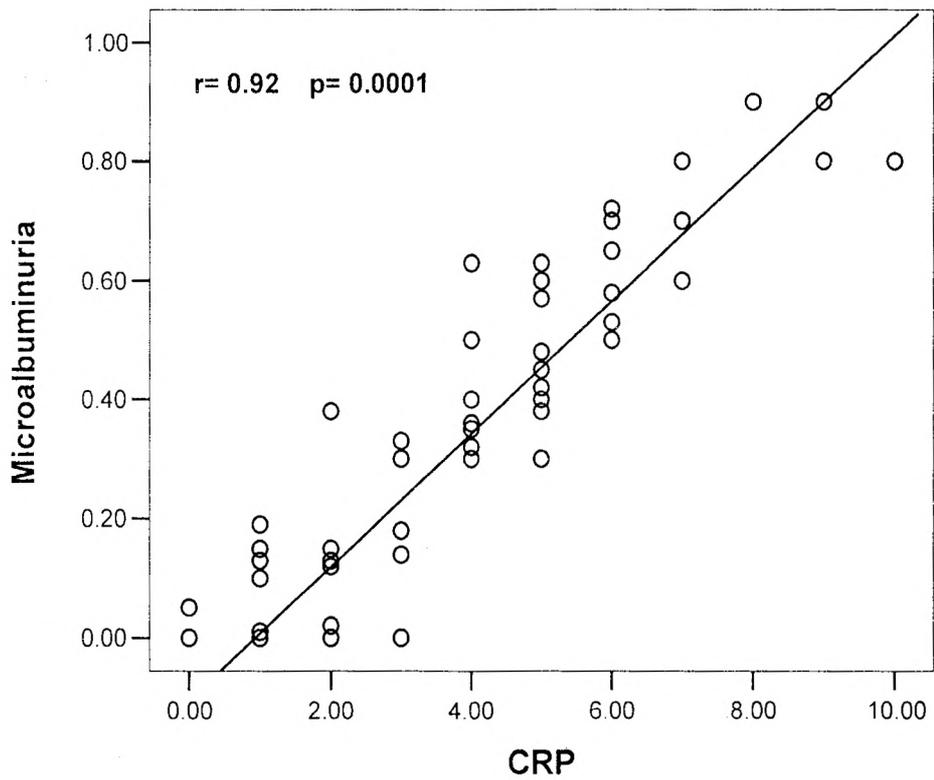
N.B. Grades of r: 0.00 to 0.24 (weak or no association),  
0.50 to 0.74 (moderate association),

0.25 to 0.49 (fair association),  
0.75+ (strong association).

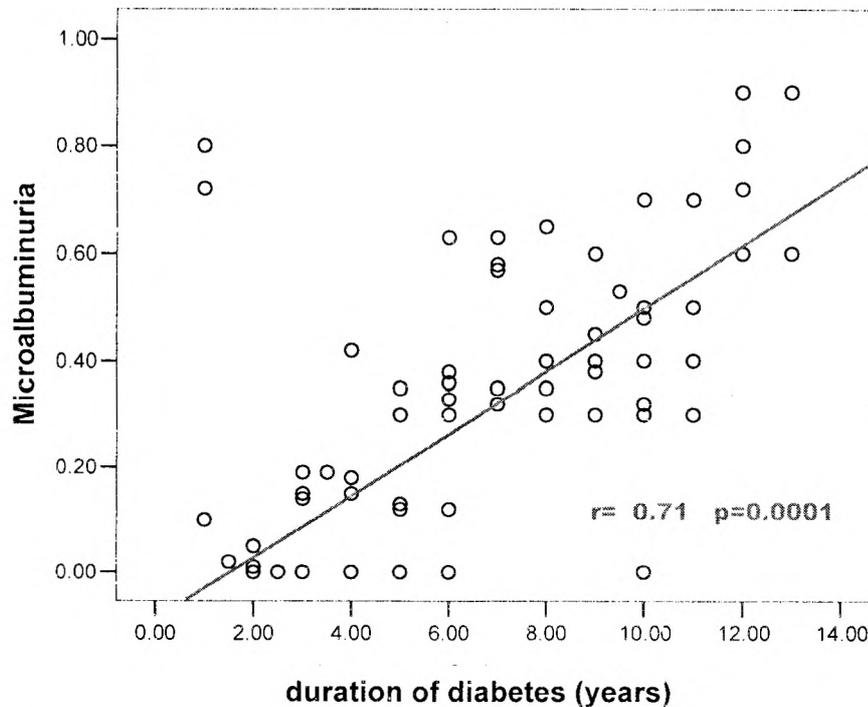
\*\* = highly significant



**Fig. 1: Correlation between microalbuminuria and HbA1C.**



**Fig. 2: Correlation between microalbuminuria and hsCRP.**



**Fig. 3: Correlation between microalbuminuria and duration of diabetes.**

## DISCUSSION

Diabetes mellitus is a metabolic disease resulting from deficiency of insulin secretion mostly due to an autoimmune destruction of insulin producing beta cells of islets of Langerhans in the pancreas. It is characterized by hyperglycemia, polyuria, polydipsia and polyphagia<sup>(4)</sup>. Microalbuminuria is defined as 30-299 mg/g creatinine, and overt nephropathy or clinical albuminuria is > 300 mg/g creatinine<sup>(5)</sup>.

Persistent microalbuminuria is an important predictor of the development of diabetic nephropathy and is also a predictor of cardiovascular complications<sup>(7)</sup>.

One of the most important predictive factors of the development of microalbuminuria is poor glycemic Control<sup>19</sup>.

The aim of the study was to evaluate

the role of hsCRP in early detection of microalbuminuria. We found that in the microalbuminuric group, the BP values (systolic and diastolic) were at higher normal levels as regarding age, sex percentile charts for Bp (p — 0.0001 for systolic and 0.005 for diastolic Bp).

This agrees with M. Saraheimo et al., 2003<sup>(10)</sup> and Jose et al., 2004<sup>(11)</sup> who studied microalbuminuria development in short term IDDM and postulated that patients who developed microalbuminuria had higher prevalence of high normal arterial blood pressure than normoalbuminuric patients.

In this study, we found that the level of HbA1C was significantly higher in microalbuminuric patients than in normoalbuminuric patients (indicating poor glycemic

control) and there was a strong positive correlation between HbA 1 C and microalbuminuria ( $p = 0.0001$ ).

This is in agreement with Skrivahaug et al., 2006<sup>(12)</sup>, Janet et al., 2007<sup>(13)</sup> and Julie et al., 2008<sup>(14)</sup> who postulated that poor glycemic control is a well-defined contributor to the development and progression of microalbuminuria among type 1 diabetic patients and mentioned that intensive glycemic control was protective against progressive microalbuminuria.

This was against what was proved by Goldschmidt et al., 1995<sup>(15)</sup>, who studied microalbuminuria among type 1 diabetic patients and found that there was no significant difference in glycemic control in patients with normal compared with those with elevated albumin excretion rate in type 1 DM.

Also, Ali et al., 2007<sup>(16)</sup>, found that there was no reasonable relationship between microalbuminuria and lack of glycemic control and that the level of blood sugar didn't have significant difference in the microalbuminuric and non-microalbuminuric children.

In our study hsCRP had higher levels in the microalbuminuric group compared to the normoalbuminuric group, and this could be explained by the development of a state of subclinical inflammation and endothelial dysfunction in the microalbuminuric group, (Table 3). We had also detected a strong positive correlation between hsCRP and microalbuminuria in microalbuminuric patients ( $p = 0.0001$ ).

This result was in agreement with Schram et al., 2005<sup>(17)</sup> who studied the association between markers of inflammation

and micro vascular complications and mentioned that inflammation may contribute to increased urinary albumin excretion and decreased GFR by increasing glomerular permeability.

This is what was proven by Jenkins A J et al., 2008 who studied the cross-sectional association of C-reactive protein with vascular risk factors and vascular complications and mentioned that CRP was found to be elevated with increased urinary albumin loss.

The previous studies are against what was mentioned by Julie Lin et al., 2008<sup>(18)</sup>. They studied inflammation and progressive nephropathy in type 1 DM and mentioned that no consistent direct relationship was seen between higher hsCRP and change in AER and there was no significant effect of hsCRP on change of AER over time.

Blood urea nitrogen and serum creatinine showed higher levels in microalbuminuric patients ( $p = 0.0001$ ). This is in agreement with the study done by Janet et al. 2007<sup>(13)</sup> who demonstrated in her study that systolic BP and serum creatinine predicted increased albumin excretion rate.

Another positive and very highly significant correlation was detected between HbA 1 C and hsCRP and this could be explained as hsCRP is a marker of inflammation, and since chronic exposure to glucose and high levels of advanced glycosylation end products stimulate the production and secretion of acute phase proteins including hsCRP ( $p = 0.0001$ ).

This is in agreement with Julie et al., 2008<sup>(14)</sup> who studied inflammation and progressive nephropathy in type I DM, and mentioned that poor glycemic control is

associated with increased hsCRP and other markers of endothelial activation in type 1 DM, explained by the fact that hyperglycemia impairs vascular endothelial cell function, probably in part through oxidation of LDL and increased formation of free radicals.

In the present study there was a significant relationship of hsCRP with diabetes duration, which might indicate an effect of the chronic metabolic derangement of diabetes on hsCRP production ( $p = 0.0001$ ).

This is supported by the opinion of Debra et al., 2005<sup>(19)</sup> who studied the effect of intensive glycemic control on levels of

markers of inflammation in type 1 DM, and measured the level of hsCRP by follow up after 3 years and found that there was a significant rise in the level of hsCRP over years.

#### *Conclusion and recommendation*

High levels of hsCRP in microalbuminuric patients is an early indicator of glomerular damage and early therapeutic intervention may delay progression to diabetic nephropathy. Thus children and adolescents with IDDM should undergo annual monitoring for microalbuminuria and hsCRP for identifying an individual at risk of diabetic nephropathy.

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