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Inflammatory Biomarkers (Il-18, Hs-Crp) and Serum Lipids: A Novel Approach to Screen Early Diabetic Nephropathy

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Abstract: ***Background and Objectives-Dyslipidemia and inflammation may promote renal disease via mechanisms of vascular endothelial cell dysfunction in type 2 diabetes mellitus (DM). The present study was undertaken to find out the association of inflammatory biomarkers (IL-18, hs-CRP) and lipid profile in type 2 diabetes mellitus with or without diabetic nephropathy. Methodology-The present one year cross sectional study was conducted in the SSIMS & Research center. Davangere. A total of 100 patients with type diabetes mellitus were selected for the study. Based on the simple random sampling where every third patient who fulfilled the selection criteria was included in the study. Results-In the present study, males outnumbered (64%) females (36%) with male to female ratio of 1.77:1. All the subjects had an abnormal hs-CRP (100%) with a mean of 19.96 ± 9.59 mg/L and IL-18 was elevated in 71%. The mean IL-18 level was 260.89 ± 69.79 pg/mL. 60% of the patients had urinary excretion of albumin ranging from traces to >5 mg/dL. It was observed that 44% of the study population belonged to stage 1. The mean eGFR level was 89.31 ± 40.56 mL/min. The lipid abnormalities and inflammatory biomarkers (IL-18, hs-CRP) were found to be significantly high in patients with diabetic nephropathy. Conclusion and interpretation-Findings of this study indicate an association of diabetic dyslipidemia and chronic inflammation with the pathogenesis of diabetic nephropathy.***

Keywords: Diabetes mellitus; Diabetic nephropathy; High sensitivity C reactive protein; inflammatory bio-markers; Interleukin-18

1. Introduction

Diabetes Mellitus is a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both.[1]

Diabetes mellitus (DM) is a chronic and potentially disabling disease which is reaching an epidemic proportion in many parts of the world. It is a major and growing threat to global public health. The biggest impact of the disease is on adults of working age; particularly in developing countries. The vast majority of cases of the diabetes fall into two broad categories: those having little or no endogenous insulin secretory capacity (IDDM or type 1 DM) and those who retain endogenous insulin secretory capacity but have a combination of resistance to insulin action and an inadequate compensatory insulin secretory response (NIDDM, or Type 2 DM).[1,2]

DM is associated with several complications. The complications of diabetes mellitus include retinopathy, nephropathy, and neuropathy (both peripheral and autonomic). The risk for atherosclerotic vascular disease is also increased in persons with DM. The risk for microvascular and neuropathic complications is related to both duration of diabetes and the severity of hyperglycemia; the increased risk for vascular disease actually antedates the onset of hyperglycemia to the degree associated with diabetes mellitus.[1]

Type 2 DM is now recognized as an inflammatory condition associated with insulin resistance and abnormal endothelial vascular reactivity. Several studies[3-5] have documented a positive association between dyslipidemia and inflammation and end-stage renal disease (ESRD) or advanced chronic kidney failure. Dyslipidemia and inflammation may promote renal disease via mechanisms of vascular endothelial cell dysfunction in type 2 diabetes mellitus (DM). Lin J, Hu FB, Rimm EB and Rifai have highlighted the fact that Several potentially modifiable lipid and inflammatory biomarkers are elevated in the setting of moderately decreased GFR in men with type 2 DM and may be the link between renal insufficiency and increased risk for cardiovascular events in this population.[6]

However, the relation between these biomarkers and mild or moderate renal dysfunction has not been well characterized, especially in type 2 diabetes mellitus (DM). Sparse data, however, are available on the relation of lipids and inflammatory biomarkers and glomerular filtration rate (GFR) in type 2 DM. Even in the face of compelling evidence in favor of this theory, there are very few studies done in this area especially in India. Hence the present study was undertaken to find out the association of inflammatory biomarkers (IL-18, hs-CRP) and lipid profile in type 2 diabetes mellitus with or without diabetic nephropathy which may reveal new approaches to the prevention of progressive renal insufficiency.

2. Methodology

The ethical clearance was obtained from the Ethical and Research Commite. A total of 100 patients with type 2

diabetes mellitus were selected for the study. Patients with type 1 diabetes mellitus, on dialysis or had a kidney transplant, taking statins and ACE inhibitors, acute febrile illness, urinary tract infection, congestive heart failure, hypertension, ischemic heart disease and acute coronary syndromes were excluded from the study. All the patients fulfilling selection criteria were explained about the nature of the study and a written informed consent was obtained.

Demographic data such as age, sex, occupation, history regarding hypertension, diabetes mellitus and complications, cerebrovascular events viz, angina pain, myocardial infarction, ischemic disease were recorded. A thorough physical examination such as anthropometry, vitals and systemic examination was conducted. These findings were recorded on a predesigned and pretested proforma. A thorough clinical examination was conducted and the findings were also recorded. Body mass index was calculated and body mass index in the range of less than 18.5 kg/m^2 were considered as underweight, 18.5 to 24.9 kg/m^2 were considered as normal, 25.0 to 29.9 kg/m^2 were considered as overweight and more than 30 kg/m^2 were considered as obese. The waist circumference was measured using a standard measuring tape in cms. Waist circumference of ≥ 90 cms in males and ≥ 80 cms in females was considered as abnormal.

Investigations such as fasting blood sample for estimation of IL-18, hs-CRP, blood glucose, HbA1C, lipid profile (total cholesterol, triglycerides, HDL, LDL) and were done. Others tests like electrocardiogram were done wherever indicated. Urine Micro-Albumin Excretion (UAE) Test (Microalbumin to creatinine Ratio) was done by immunoturbidometry and urine creatinine was done by Jaeffe's method and interpreted as traces (0.00 to 0.30), 1+ (0.30 to 1.00), 2+ (1.00 to 5.00) and 3+ (>5.00). Serum Creatinine was by Jaeffe's method. Based on the MDRD formula eGFR was calculated and based on eGFR patients were staged as Stage I (90+, Normal or minimal kidney damage with normal GFR), II (60 to 89, Mild decrease in GFR), III (30 to 59, Moderate decrease in GFR), IV (15 to 29, Severe decrease in GFR) and V (<15, Kidney failure). According to Trøseid M et al Estimation of IL-18 was done using standard recombinant IL-18 enzyme linked immuno sorbent assay (ELISA) kit. Interleukin-18 levels above 216 pg/mL were considered as abnormal.[7]

Statistical analysis

The categorical data was expressed as rates, ratios and proportions and comparison was done using chi-square test. The continuous data was expressed as mean ± standard deviation (SD) and the comparison was done using unpaired 't' test. A probability value ('p' value) of less than or equal to 0.05 was considered as statistically significant.

3. Results

In the present study, males accounted for 64%, whereas females accounted for 36%. Majority of the subjects were between 61 and 70 years accounting for 38%, with 15 and 37 subjects between 41-50 and 51-60 respectively. Only a small number were below 40 or above 70 years (n=1, n=1 respectively). The mean age for the study population was 60.3 ± 9.43 years. Majority (73%) of the patients had long standing diabetes (more than five years). The mean duration was 10.22 ± 7.00 years. Most of the subjects had long standing diabetes of more than 5 years (n=73). 80 % of these patients were on oral hypoglycemic drugs and remaining patients were on insulin.

The study population was screened for the presence of hypertension, cerebrovascular accidents, coronary artery disease, diabetic retinopathy and peripheral neuropathy. 77% were hypertensive. 43% patients reported a history of cerebrovascular accident. 64 patients had a significant past history suggestive of coronary artery disease. 46 patients had diabetic retinopathy and 14 were found to have diabetic peripheral neuropathy.

The body mass index among the study population revealed 53 subjects in the pre-obese group with a BMI between 25 to 29.99 kg/m^2 and 46 patients were obese with a BMI of > 30 kg/m^2. Only one patient had a normal BMI between 18.5-24.99 kg/m^2. The mean BMI of the study population was 29.69 ± 2.45 Kg/m^2. In accordance with the IDF criteria for South Asians, waist circumference of ≥ 90 cms in males and > 80 cms in females is regarded as abnormal. All the subjects in the study had an abnormal waist circumference. The mean waist circumference for the study population was found to be 102.06 ± 5.75 cms. The mean blood pressure in this study was 141.76 ± 16.03 mm Hg systolic and 90.06 ± 9.60 mm Hg diastolic.

Of the 100 patients studied, 36 subjects had high serum cholesterol levels (more than 200mg/dl). The mean cholesterol level was 182.62 ± 38.21 mg/dL. 90% of the study population had high low density lipoprotein levels (more than 100 mg/dL.). The mean LDL was 75.92 ± 20.66 mg/dL. 74 subjects (74%) were found to have an abnormal TG, while the remaining 26 subjects had a Triglyceride level of < 150 mg/dL. The mean triglyceride level was 166.16 ± 40.91 mg/dL. 39 subjects were found to have abnormal HDL levels whereas 61 subjects were found to be normal. The mean HDL level of this study was 41.49 ± 9.74 mg/dL. HOMA-IR was considered to be abnormal at levels in excess of 3.80. In the present study, all the patients had an elevated HOMA-IR indicating insulin resistance. The mean HOMA-IR level in this study was 15.53 ± 7.94. In the present study, all the subjects had an abnormal hs-CRP with a mean of 19.96 ± 9.59 mg/L.

Using the standard MBL recombinant human IL-18 ELISA kit, values of ≥ 216 pg/mL was considered abnormal. In the present study, 70 patients (71%) were found to have an elevated IL-18 level, whereas 30 subjects had an IL 18 ≤ 215 pg/mL. The mean IL-18 level in this study was 260.89 ± 69.79 pg/mL. About 63% of the subjects had poor glycemic control as demonstrated by the HbA1c levels of more than 8%. The mean HbA1c in the study population was 8.84 ± 1.98 percent. 60% of the study population had urinary excretion of albumin ranging from traces to < 0.3 mg/dl, suggestive of microalbuminuria (Graph 1). It was observed that 44% of the study population belonged to stage 1 and 37 % belonged to stage

2. The mean eGFR level was 89.31 ± 40.56 mL/min (Graph 2).

The cholesterol values were found to be elevated in 36 patients (p=0.819). And the values increased as the diabetic nephropathy progressed with stages and this was statistically significant (p=0.001). The LDL values were found to be high in 90% of the study population (p=0.021). The HDL values were found to be low in 39 patients and normal in 61 patients, which was statistically not significant (p=0.057). Amongst the 39 patients, HDL was low in all stages of diabetic nephropathy (p<0.001). The triglycerides were found to be abnormally high in 75 patients (p=0.90). Amongst the various stages of diabetic nephropathy, triglycerides were found to be high in each stage (p<0.001) (Table 1). The inflammatory biomarkers were found to be elevated in majority of the patients. hsCRP was found to be high in all 100 patients. On further analysis according to stages of diabetic nephropathy, no stage wise association or any pattern was found (p=0.497). IL-18 values were found to be high in 70 subjects (p=0.492). When analyzed according to stages of diabetic nephropathy it was found to be raised significantly, in all stages (p<0.001) (Table 2). Table 3 shows stages of diabetic nephropathy and mean serum cholesterol, low density lipoprotein, high density lipoprotein and triglycerides levels. Table 4 shows stages of diabetic nephropathy and mean hs-CRP and IL-18 levels. In all stages of diabetic nephropathy, mean hs-CRP and IL-18 levels were high.

4. Discussion

In the present study, males outnumbered (64%) females (36%) with male to female ratio of 1.77:1. In a study by araki et al, males constituted 60% patients of the total 250 diabetic patients in whom progression of diabetic nephropathy was studied. Majority of the subjects were between 61 and 70 years accounting for 38%, with 15 and 37 subjects between 41-50 and 51-60 respectively. Only a small number (1 each) were below 40 or above 70 years. The mean age for the study population was 60.3 ± 9.43 years. In a study[8] the mean age of the study population was 61±9 years. In another study[10] the mean age of study population was 65.5±7.9 years.

In the present study majority 73% of the patients had long standing diabetes (more than five years). Overall, the mean duration was 10.22±7.00 years. A study[8] observed that duration of diabetes in their study population was 13±8 years. In the present study, more than half (53%) were overweight (BMI 25 to 29.99 kg/m^2) and 46% were obese (BMI > 30 kg/m^2). Overall, the mean BMI of the study population was 29.69 ± 2.45 Kg/m^2. This was high when compared with a study[8] in Japanese population, in who mean BMI was 23±3years.

All the subjects in the study had an abnormal waist circumference based on the IDF criteria. The mean waist circumference for the study population was found to be 102.06 ± 5.75 cms. This was significantly high when compared to study[8] population of, in who mean waist circumference was 88±9 cms. The mean blood pressure in this study was 141.76±16.03 mm Hg systolic and 90.06±9.60 mm Hg diastolic. This was comparable to the average blood pressure in study[8] where it was 134±15 mm Hg systolic and 138±16 mm hg Diastolic.

In our study, we observed 36% patients had high serum cholesterol levels (more than 200 mg/dl); The mean cholesterol level was 182.62 ± 38.21 mg/dL. This was comparable to Saudi Arabian population study[6] where the mean cholesterol level was 200 mg/dl. Multiple studies[8,9] on Japanese population also observed high serum cholesterol levels 100.6±14.2 mmol/l and 99.3±15 mmol/l respectively. Another study[10] observed the mean cholesterol 190.5±15.6 mg/dl. This value was raised and was statistically significantly associated with diabetic nephropathy. Previous studies[8-10] carried out has proved that increased serum cholesterol levels are associated with progression of diabetic nephropathy. In our study, the cholesterol values were found to be elevated in 36 patients (p=0.819) and the values increased as the diabetic nephropathy progressed with stages and was statistically significant (p=0.001).

It was observed that LDL values were found to be high in 90% of the study population (p=0.021) and the mean LDL was 75.92±20.66 mg/dL. This was in contrast to Saudi Arabian population study[6] where the mean LDL level was 123 mg/dl. The two Japanese studies[8,9] also observed high LDL levels 72.36±14.22 mmol/l and 59.58±15.22 mmol/l respectively. Another study[10] observed that mean LDL value was 146.88±11.88 which was raised and statistically significantly associated with diabetic nephropathy. Previously published studies[6,8-10] on the association between LDL and presence of kidney disease have yielded ambiguous results, with a couple of investigations reporting a positive association, and others reporting no association

In the present study, HDL values were found to be low in 39 patients and normal in 61 patients, which was statistically not significant (p=0.057) and mean HDL level was 41.49 ± 9.74 mg/dL. In all the stages of diabetic nephropathy in these patients it was noted that HDL was low (p<0.001). This was similar to Saudi Arabian population study[6] where the mean HDL level was 39mg/dl and they noted that lower HDL levels were more common in those with moderate renal insufficiency, defined as GFR < 60ml/min/1.73 m2. The study[8,9] on Japanese population also observed low HDL levels 26.46±64.8 mmol/l and 28.98±7.92 mmol/l respectively. Another study[10] observed that mean HDL values were 41.87±2.87 mg/dl and this value was raised and was statistically significantly associated with diabetic nephropathy. This observation is consistent with previous investigations demonstrating that those with kidney dysfunction have 11% to 32% lower HDL levels.

Diabetic dyslipidemia is associated characteristically with increased Triglyceride levels. In our study, the triglycerides were found to be abnormally High in 75 patients (p=0.90). Amongst each stage of diabetic nephropathy Triglycerides were found to be high in each stage (p<0.001). The mean Triglyceride level was 166.16 ± 40.91 mg/dL. This was similar to Saudi Arabian

Population study by Lin et al, where the mean TG level was 157 mg/dl and they Noted that higher TG levels were more common in those with moderate renal Insufficiency, defined as GFR < 60 ml/min/1.73 m^2. A study[8] also observed High TG levels 1.06±0.41 mmol/l. Another study[10] observed that Mean TG value was 177.88±88.67 which was raised and statistically significantly associated with diabetic nephropathy.

The pathogenesis of diabetic nephropathy is related to chronic hyperglycemia. The mechanisms by which chronic hyperglycemia leads to diabetic nephropathy, involve the effects of soluble factors (growth factors, angiotensin II, endothelin, AGEs), hemodynamic alterations in the renal microcirculation (glomerular hyperfiltration or hyperperfusion, increased glomerular capillary pressure), and structural changes in the glomerulus (increased extracellular matrix, basement membrane thickening, mesangial expansion, fibrosis). Glycated hemoglobin is proven measure of glycemic control in diabetic patients. In the present study majority, about 63% of the patients had poor glycemic control as demonstrated by the HbA1c levels of more than 8%. The mean HbA1c in the study population was 8.84±1.98 percent. In their study nakamura et al observed the mean HbA1c was 7.3±1.1 and in a study[8] it was 7.5±0.9.

Diabetic nephropathy is stratified into five stages based on estimated GFR Calculated using MDRD formula. It was observed that 44% of the study Population belonged to stage 1 and 37 % belonged to stage 2. The mean eGFR Level was 89.31 ± 40.56 mL/min. This was similar to the study[8] where the mean eGFR (min $ml^{-}1/1.73$ m2) was 104±21 min $ml^{-}1/1.73$ m^2. Highly sensitive C-reactive protein is proven as a marker of inflammation by various previous studies. In the present study, all the subjects had an abnormal hs-CRP with a mean of 19.96 ± 9.59 mg/L. Similarly it was reported to be high in another study[9] 1.05±1.43 mg/l without statistical significance. Also another study[8] noted similar results i.e. raised hsCRP levels but without statistical significance. In our study, it was observed that this biomarker of inflammation was raised in all stages of diabetic nephropathy. On further analysis of this marker, no stage wise increase in the mean values was observed in our study.

Interleukin-18, a recently described member of the IL-1 cytokine super family, is now recognized as an important regulator of innate and acquired immune responses. IL-18 is expressed at sites of chronic inflammation, in autoimmune diseases, in a variety of cancers, and in the context of numerous infectious diseases and in 71% of the patients IL-18 level was elevated. Overall, the mean IL-18 level in this study was 260.89±69.79 pg/mL. In a study[8] it was observed that IL-18 was raised i.e. 154 ng/l in majority of the patients and was statistically significant. Similarly another study[9] also it was observed that mean IL-18 levels in their study was 179 ±63 and this value was statistically significant. Similarly other study[10] observed that, mean IL-18 value was 115.96±89.8 pg/ml and this value was raised and was statistically significantly associated with diabetic nephropathy.

In our study the cholesterol and LDL values were found to be significantly elevated in patients with diabetic nephropathy and the values increased as the diabetic nephropathy progressed ($p<0.05$). Whereas, the HDL was found to be low in 39 patients and normal in 61 patients with no statistically significant difference being observed ($p=0.057$). However, amongst the stages of diabetic nephropathy, HDL was low in all stages ($p<0.001$). The triglycerides were found to be abnormally high in 75 patients ($p=0.90$). Amongst the stages of diabetic nephropathy, Triglycerides were found to be high in each stage ($p<0.001$). The inflammatory biomarkers were found to be elevated in majority of the patients. hsCRP was found to be high in all 100 patients. On further analysis according to stages of diabetic nephropathy no stage wise association or any pattern was found ($p=0.497$). IL-18 values were found to be high in 70 subjects ($p=0.492$). It was found to be statistically significantly raised in all stages of diabetic nephropathy ($p<0.001$).

5. Conclusion

Findings of this study indicate an association of diabetic dyslipidemia and chronic inflammation with the pathogenesis of diabetic nephropathy. Hence inflammatory biomarkers (IL-18, hsCRP) can be used as an early screening test for diabetic nephropathy. The possibility of IL-18 as a therapeutic target needs to be explored in further studies.

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Table 1: Correlation of lipid profile with stages of kidney disease

Parameters		Stages									
		I (n=44)		II (n=37)		III (n=13)		IV (n=5)		V (n=1)	
		No	%	No	%	No	%	No	%	No	%
CHL	Normal	29	65.91	22	59.46	9	69.23	3	60	1	100
	abnormal	15	34.09	15	40.54	4	30.77	2	40	0	0.00
	Total	**44**	**100**	**37**	**100**	**13**	**100.00**	**5**	**100**	**1**	**100**
		Two way ANOVA between grade $F_{3,92}$=0.309; p=0.819									
		Two way ANOVA between Cholesterol $F_{1,92}$=45.459; p<0.001									
		Interaction $F_{3,93}$=0.373; p=0.772									
LDL	Normal	4	9.09	4	10.81	2	15.38	0	0	0	0.00
	abnormal	40	90.91	33	89.19	11	84.62	5	100	1	100
	Total	**44**	**100**	**37**	**100**	**13**	**100.00**	**5**	**100**	**1**	**100**
		Two way ANOVA between grade $F_{3,92}$=0.921; p=0.434									
		Two way ANOVA between LDL$F_{1,93}$=48.812; p<0.001									
		Interaction $F_{3,93}$=0.947; p=0.396									
HDL	Normal	26	59.09	20	54.05	10	76.92	5	100	0	0.00
	abnormal	18	40.91	17	45.95	3	23.08	0	0	1	100
	Total	**44**	**100**	**37**	**100**	**13**	**100.00**	**5**	**100**	**1**	**100**
		Two way ANOVA between grade $F_{3,92}$=2.595; p=0.057									
		Two way ANOVA between HDL $F_{1,92}$=59.638; p<0.001									
		Interaction $F_{3,92}$=1.358; p=0.261									
TGA	Normal	15	34.09	6	16.22	2	15.38	2	40	1	100
	abnormal	29	65.91	31	83.78	11	84.62	3	60	0	0.00
	Total	**44**	**100**	**37**	**100**	**13**	**100.00**	**5**	**100**	**1**	**100**
		Two way ANOVA between grade $F_{3,92}$=0.193; p=0.901									
		Two way ANOVA between TGA $F_{1,92}$=42.600; p<0.001									
		Interaction $F_{3,92}$=1.780; p=0.157									

Table 2: Correlation of biomarkers with stages of kidney disease

Parameters		Stages									
		I (n=44)		II (n=37)		III (n=13)		IV (n=5)		V (n=1)	
		No	%	No	%	No	%	No	%	No	%
IL-18	Normal	13	29.55	11	29.73	4	30.77	2	40.00	0	0.00
	abnormal	31	70.45	26	70.27	9	69.23	3	60.00	1	100
	Total	**44**	**100**	**37**	**100**	**13**	**100**	**5**	**100**	**1**	**100**
		Two way ANOVA between grade $F_{3,92}$=0.810; p=0.492									
		Two way ANOVA between IL-18 $F_{1,92}$=42.600; p<0.001									
		Interaction $F_{3,92}$=0.248; p=0.863									
Hs-CRP	Normal	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	abnormal	44	100	37	100	13	100	5	100	1	100
	Total	**44**	**100**	**37**	**100**	**13**	**100**	**5**	**100**	**1**	**100**
		Two way ANOVA between grade $F_{3,92}$=0.799; p=0.497									

Table 3: Stages of diabetic nephropathy and mean lipid parameters

Parameters		Stages									
		I (n=44)		II (n=37)		III (n=13)		IV (n=5)		V (n=1)	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
CHL	Nor	159.3	28.9	164.6	30.3	168.3	28.8	154.0	9.0	190.0	0.0
	Abnormal	216.3	25.2	221.4	28.2	207.5	9.0	228.0	39.6	0.0	0.0
	Overall	178.75	38.7	187.6	40.6	180.4	30.5	184.0	45.2	190.0	0.0
LDL	Nor	110.3	6.9	121.8	18.4	105.0	1.4	0.0	0.0	0.0	0.0
	Abnormal	71.8	15.3	70.0	17.8	71.9	15.8	79.0	24.4	88.0	0.0
	Overall	75.3	18.4	75.6	24.0	77.0	19.0	79.0	24.4	88.0	0.0
HDL	Nor	122.4	27.7	113.2	33.6	94.5	72.8	143.0	4.2	146.0	0.0
	Abnormal	180.7	26.9	182.5	28.5	190.1	41.3	164.3	11.5	0.0	0.0
	Overall	160.8	38.8	171.2	38.8	175.4	56.1	155.8	14.4	146.0	0.0
TGA	Nor	34.8	6.1	35.9	5.0	38.1	6.5	31.4	7.7	0.0	0.0
	Abnormal	52.3	5.8	49.2	5.6	56.7	4.2	0.0	0.0	42.0	0.0
	Overall	41.9	10.5	42.0	8.5	42.4	10.1	31.4	7.7	42.0	0.0

Table 4: Stage of kidney disease and mean biomarkers

Parameters		Stages									
		I (n=44)		II (n=37)		III (n=13)		IV (n=5)		V (n=1)	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Hs-CRP	Nor	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Abnormal	18.3	8.4	21.6	10.0	20.4	11.4	18.0	9.7	38.0	0.0
	Overall	18.3	8.4	21.6	10.0	20.4	11.4	18.0	9.7	38.0	0.0
IL-18	Nor	180.5	10.3	189.0	16.6	186.0	19.7	195.5	7.8	0.0	0.0
	Abnormal	277.7	44.8	306.1	66.8	300.1	62.4	305.0	83.1	346.0	0.0
	Overall	249.0	58.7	271.3	78.2	265.0	75.5	261.2	84.1	346.0	0.0