A STUDY ON 'hs C REACTIVE PROTEIN' AS PREDICTIVE MARKER OF CARDIOVASCULAR EVENTS IN DIABETIC RENAL DISEASE PATIENTS

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CERTIFICATE

This is to certify that this dissertation work entitled **"A STUDY ON 'hs C REACTIVE PROTEIN' AS PREDICTIVE MARKER OF CARDIOVASCULAR EVENTS IN DIABETIC RENAL DISEASE PATIENTS"** is a bonafide record of work done by **Dr.D.SUGANYA**, in the **DEPARTMENT OF MEDICINE**, P.S.G. Institute of Medical Sciences & Research, Coimbatore-641 004, under my supervision and guidance.

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CONTENTS

INTRODUCTION

A decade ago, the treatment of hypercholesterolemia and Hypertension was expected to eliminate CAD by the end of the 20th century. Lately, however, that optimistic prediction has needed revision. Cardiovascular diseases are expected to be the main cause of death globally Within the next 15 years owing to a rapidly increasing prevalence in Developing countries and Eastern Europe and the rising incidence of obesity, Diabetes and Diabetes related complication like chronic kidney disease (CKD) in both the developing world and the Western world (1).

Cardiovascular diseases cause 38 percent of all deaths in North America and are the most common cause of death in European men under 65 Years of age and the second most common cause in women. These facts force us to revisit cardiovascular disease and consider new strategies for prediction, prevention, and treatment.

REVIEW OF LITERATURE

Throughout the world Cardiovascular disease, End-stage renal disease and Diabetes mellitus are emerging as epidemics. Moreover, Contribution of one towards existence of others is alarming. Cardiovascular disease (CVD) is the leading cause of death in both patients with End- stage renal disease (ESRD) as well as in Diabetes mellitus (DM). With the shift in global effort from 'Treating the disease' to 'Preventive medicine' it is time to identify. The predisposing factors, modifiable and non modifiable factors that decide the occurrence of the killer disease – CVD, in its fertile soil – ESRD and DM.

DIABETES AND CARDIOVASCULAR DISEASE

A large body of epidemiological and pathological data documents that Diabetes is an independent risk factor for CVD in both men and Women. (3, 4, 5). Diabetes is now perceived as ischemic heart disease equivalent .Women with diabetes seem to lose most of their inherent protection against developing CVD.(3, 6). CVDs are listed as the cause of Death in ≈65% of persons with Diabetes (7). Diabetes acts as an independent risk factor for several forms of CVD. To make matters worse, when patients with Diabetes

develop clinical CVD, they sustain a worse prognosis for survival than do CVD patients without Diabetes.(8, 9, 10).

DIABETES AND RENAL DISEASE

Renal disease is a common and often severe complication of Diabetes (12). Approximately 35% of patients with type 1 diabetes of 18 Years' duration will have signs of Diabetic renal involvement (13). Up to 35% of new patients beginning dialysis therapy have type 2 diabetes (14).

Diabetes contributes signicantly to ESRD and it is almost the number one cause for renal failure in West. This same scenario is slowly appearing in our Indian subcontinent also; the budding Global capital of Diabetes. One in every three renal failure patients is a Diabetic. For patients with diabetes who are on renal dialysis, mortality rates probably exceed 20% per year (14). When diabetes is present, CVD is the leading cause of death among patients with ESRD(20, 21, 22).

Detection of Clinical and Sub clinical CVD

Prospective studies (23) document an increased likelihood of sudden cardiac death and unrecognized myocardial infarctions in patients with Diabetes. Moreover, acute ischemic syndromes, peripheral arterial disease, and advanced CVD complications occur more commonly in patients with

Diabetes than in those without (23). Because the typical cardiac symptoms often are masked in patients with diabetes, the diagnosis of Myocardial Infarction commonly is missed or delayed. Effective strategies for earlier detection of clinical CVD could reduce morbidity and mortality in patients with diabetes.

In addition, detection of subclinical atherosclerosis and early clinical manifestation of CVD could lead to more effective primary prevention in some patients with diabetes(23). Noninvasive evaluation of cardiac function in hyperglycemic patients suspected of having myocardial dysfunction may be a useful guide to cardiovascular management in some of these patients. Many patients with diabetes suffer from an autonomic dysfunction that impairs quality of life and predisposes to life-threatening cardiovascular complications(23). Finally, the finding of subclinical CVD signals the need for institution of more aggressive preventive measures.

Like Diabetes Mellitus, Chronic kidney disease itself is an independent risk factor for cardiovascular disease (26).

CVD in CKD

It is now becoming apparent that there is a high prevalence of CVD even in the earlier stages of CKD, and that CKD is a risk factor for CVD

[25]. Arterial vascular disease and cardiomyopathy are the primary types of CVD [25]. In CKD, it is useful to consider two subtypes of arterial vascular disease, namely atherosclerosis and arteriosclerosis or large vessel remodeling. Atherosclerosis is an intimal disease characterized by the presence of plaques and occlusive lesions. There is a high prevalence of atherosclerosis in CKD. Atherosclerotic lesions in CKD are frequently alcified, as opposed to fibroatheromatous, and have increased medial thickness in comparison with lesions in the general population (25).

Patients with CKD also have a high prevalence of arteriosclerosis and remodeling of large arteries. Remodeling may be due either to pressure overload, which is distinguished by wall hypertrophy and an increased wall to lumen ratio, or flow overload, which is characterized by a proportional increase in arterial diameter and wall thickness(25).

Patients with CKD also have a high prevalence of cardiomyopathy (25). Analogous to remodeling of largevessels, pressure overload leads to increased ratio of LV mass to diameter(concentric LVH), while volume overload leads to a proportional increase in LV mass and LV diameter (LV dilatation with LVH).

CLINICAL PRESENTATIONS OF CVD

Atherosclerosis, Inducible ischemia, carotid IMT, EBCT (may be less useful than in the GP for atherosclerosis because of medial rather than intimal calcification), ischemiaIHD (myocardial infarction, angina, Sudden cardiac death), Cerebrovascular disease, PVD, HF, Arterial Vascular Disease(24, 25).

CVD Risk Factors in CKD

Traditional risk factors defined as those in the Framingham Heart Study that have been used to estimate the risk of developing symptomatic ischemic heart disease(29). Most of the traditional CVD risk factors, such as older age, diabetes mellitus, systolic hypertension, LVH, and low HDL cholesterol are highly prevalent in CKD(30). The cardiovascular risk conferred by many traditional risk factors, such as diabetes, older age, and LVH, largely parallels the relationships described in the general population(28). However, some important differences have been noted with regard to other risk factors. For example, “U” shaped relationships exist between all- cause mortality and both blood pressure and total cholesterol levels in dialysis patients(30, 31). Several studies have suggested that the Framingham risk equation is insufficient to capture the extent of CVD risk

in subjects with CKD [29- 32]. One explanation for these findings is that traditional risk factors may have qualitatively and/ or quantitatively different risk relationships with CVD in CKD, as compared to the general population. For example, individuals with CKD may have had a longer and more severe exposure to hypertension than subjects without CKD. In addition, subjects with CKD may have been treated for hypertension.

The existing risk scores for cardiovascular diseases like the Framingham risk equation does not include the duration of exposure to risk factors nor treatment. Another explanation is that other factors (“ non-traditional” risk factors), which are not included in Framingham risk equations, may play an impor tant role in promoting ischemic heart disease in subjects with Diabetes and CKD(31). The non-traditional risk factors being elevated C- reactive protein(CRP), Von -willibrand factor, PAI-1, Interleukin-6.Of note, many of the hypothesized non-traditional risk factors are related to CKD(32).

CRP IN ATHEROSCLEROSIS

Highly sensitive C-Reactive protein (hs-CRP)

hs C-reactive protein is an acute-phase reactant, synthesised primarily in the liver, that provides a measurement of low-grade systemic inflammation.

In an attempt to improve global cardiovascular risk prediction, considerable interest has focused on hsCRP-, a marker of inflammation that has been shown in multiple prospective epidemiological studies to predict incident myocardial infarction, stroke, peripheral arterial disease, and sudden cardiac death. CRP levels have also been shown to predict risk of both recurrent ischemia and death among those with stable and unstable angina, those undergoing percutaneous angioplasty, and those presenting to emergency rooms with acute coronary syndromes. These highly consistent clinical data are supported by abundant laboratory and experimental evidence that demonstrate that atherothrombosis, in addition to being a disease of lipid accumulation, also represents a chronic inflammatory process. In terms of clinical application, hsCRP seems to be a stronger predictor of cardiovascular events than LDL cholesterol, and it adds prognostic information at all levels of calculated Framingham Risk and at all levels of the metabolic syndrome.

Using widely available high-sensitivity assays, hsCRP levels of <1, 1 to 3, and >3 mg/L correspond to low-, moderate-, and high-risk groups for future cardiovascular events. Individuals with LDL cholesterol below 130 mg/dL who have CRP levels >3 mg/L represent a high-risk group often missed in clinical practice. The addition of hsCRP to standard cholesterol

evaluation may thus provide a simple and inexpensive method to improve global risk prediction and compliance with preventive approaches.

In the last few years hs C-reactive protein (CRP) has gained a lot of attention in the general population, especially with regard to its link with atherosclerosis. There are several studies to suggest that hsCRP may be useful as a parameter in predicting future cardiovascular events in both the general population and in patients with end-stage renal disease. A statistical association between hsCRP and cardiovascular disease was observed in various studies, the predictive power of this association is significant when adjusted for other risk factors(24).

All stages of atherosclerotic disease may be considered an inflammatory response to injury that is promoted by the classic cardiovascular risk factors: atherogenic lipid profile, hyperglycaemia hypertension and smoking(24).

With ongoing inflammation, macrophages are increased in umber and, after ingestion of oxidised lipids, become foam cells(27). Activated foam cells release hydrolytic enzymes, cytokines, growth factors and procoagulant substances. This results in the proliferation and migration of vascular smooth muscle causing further damage to the vascular system(27). Lesions are

enlarged and eventually form a fibromuscular cap, which reduces vascular compliance and results in hypertension; they may also rupture, resulting in myocardial infarction or stroke(3).

The relative contributions of hsCRP as a marker, as a causative agent, and as a consequence of atherosclerotic vascular disease are clear now, both in the general population and in the diabetic and kidney disease patients(2).

Comparison of hsCRP to Other Novel Risk Factors

hsCRP is not the only inflammatory biomarker that has been shown to predict myocardial infarction and stroke. More sophisticated measures of cytokine activity, cellular adhesion, and immunologic function (such as interleukin-6, intercellular adhesion molecule-1, macrophage inhibitory cytokine-1, and soluble CD40 ligand) have all been shown to be elevated among those at increased vascular risk.(37) These approaches, however, are unlikely to have clinical utility because the assays required for their assessment are either inappropriate for routine clinical use or the protein of interest has too short a half-life for clinical evaluation. Measures for fibrinogen, a biomarker involved in both inflammation and thrombosis, remain poorly standardized, and methodological issues limit use of this parameter despite consistent population-based data. Other broad measures of

systemic inflammation, such as the white blood cell count or the erythrocyte sedimentation rate, have proven unreliable in clinical settings. By contrast, high-sensitivity assays for CRP have been standardized across many commercial platforms. Moreover, hsCRP is highly stable, allowing measures to be made accurately in both fresh and frozen plasma without requirements for special collection procedures. This is due in part to the stable pentraxin structure of hsCRP and its long plasma half-life of 18 to 20 hours.

In selected patients, such as those with markedly premature and unexplained atherosclerosis, evaluation of other markers, such as lipoprotein(a) and homocysteine, may have clinical utility. In available population-based studies, however, the relative magnitude of these biomarkers has been small in direct comparison to hsCRP. Recent data also indicate that hsCRP is a stronger predictor of risk than nuclear magnetic resonance-based evaluation of LDL particle size and concentration.(38).

Clinical Trials Data

- hsCRP is the strongest marker of risk for future vascular events compared with 12 reported risk factors, including cholesterol [NEJM 342:836-43]

- hsCRP distinguishes between low and high-risk patients, even in those with LDL-C below 130mg/dL (– a safe level according to current guidelines). [Intern Med 252:283-94]
- hsC-reactive protein is a relatively moderate predictor of coronary heart disease, adding to the predictive value of established risk factors such as total serum cholesterol. [NEJM 350: 1387-1397]
- Elevated serum levels of hsCRP predict risk for plaque rupture. [NEJM340:115-26]
- High hsCRP has been associated with restenosis after percutaneous coronary intervention. [J Am Coll Cardiol 38:2006-12]
- hsCRP is easily and inexpensively measured with standardised high-sensitivity assays, with a range for risk detection that is comparable with total cholesterol. hsCRP rapidly increases in response to injury and inflammation by as much as 1000 times, declining to baseline levels within 7–10 days.

Risk Categories based on hsCRP level

(Results are always expressed in mg/L)

Relative Risk Category	Average hs-CRP level
Low	< 1 mg/L
Average	3.0 to 5.0 mg/L
High	> 5.0 mg/L

There are currently number of prospective studies to demonstrate the benefits of screening for hsCRP. However, intermediate risk patients (10-20% risk over 10 years) and those with the metabolic syndrome, diabetes, CKD may be more appropriate targets(4).Furthermore, there is a larger absolute risk reduction in treating people with elevated hsCRP, which demonstrates the potential utility of hsCRP in primary prevention and as a marker [NEJM 344:1959-65].

Interpreting hsCRP Assays, and Cost-Effectiveness

In most clinical settings, a single hsCRP assessment is likely to be adequate as long as levels less than 10 mg/L are observed. Because major infections, trauma, or acute hospitalizations can elevate hsCRP levels (usually 100-fold or more), levels greater than 10 mg/L should initially be

ignored and the test repeated at a future date when the patient is clinically stable.

Many investigators have recommended 2 measures of hsCRP, with the lower value or the average being used to determine vascular risk, a practice consistent with recommendations for cholesterol evaluation.

In rare instances where levels of hsCRP are markedly elevated, alternative sources of systemic inflammation such as lupus, inflammatory bowel disease, or endocarditis should be considered. In such cases, there is usually an accompanying elevation in the erythrocyte sedimentation rate. Accumulated experience in outpatient settings has shown such values to be infrequent. Because hsCRP levels are stable over long periods of time, are not affected by food intake, and demonstrate almost no circadian variation, there is no need to obtain fasting blood samples for hsCRP assessment. Despite being an acute phase reactant, the variability in hsCRP levels in given individuals is quite similar to that associated with cholesterol screening, as long as the hsCRP levels are within the clinical range defined above.(39) Traditional assays for hsCRP do not have adequate sensitivity to detect levels required for vascular disease prediction.

To alleviate this problem, high-sensitivity CRP assays have been developed and are now widely available.(40) The cost of hsCRP screening is comparable to that of standard cholesterol evaluation and far less than almost all other alternative approaches to cardiovascular screening under consideration.

Both in terms of years of life saved and cost-to-benefit ratios, hsCRP screening seems to be highly effective.(41) In many settings, the approach of adding hsCRP to LDL screening may yield immediate cost-savings in terms of negative predictive value and the subsequent avoidance of unnecessary clinical testing, particularly when compared with far more expensive screening approaches such as electron beam calcium tomography
or MRI. CRP levels within the range detected with high-sensitivity assays have demonstrated specificity for vascular events.(42) Although it has not been determined whether serial hsCRP assessment provides incremental clinical value, some physicians have elected to use hsCRP as part of their annual physical examination.

Clinical Recommendations

As documented above, for primary prevention,

1. hsCRP is an independent predictor of future cardiovascular events that

2. Adds prognostic information to lipid screening, t
3. To the metabolic syndrome,
4. And to the Framingham Risk Score.

In outpatient settings, the primary use of CRP should be at the time of cholesterol screening, when knowledge of CRP can be used as an adjunct for global risk assessment.(43)

Goals of Screening and Therapeutic Options

The primary goal of cardiovascular screening programs should be the identification of high-risk individuals who can be targeted for smoking cessation, diet, exercise, and blood pressure control. It is well established that compliance with lifestyle recommendations is directly related to the absolute risk perceived by individual patients. Thus, because the addition of CRP to lipid evaluation provides an improved prediction tool, consideration of CRP may have usefulness for this reason alone. There is currently no definitive evidence that lowering CRP will necessarily reduce cardiovascular event rates; studies addressing this issue are only now being designed. However, many interventions known to reduce cardiovascular risk have been linked to lower CRP levels. In particular, weight loss, diet, exercise, and smoking cessation all lead to both reduced CRP levels and reduced vascular risk.

Several pharmacological agents proven to reduce vascular risk influence CRP levels. Of these, the statin drugs are the most important, and studies with pravastatin, lovastatin, cerivastatin, simvastatin, and atorvastatin have all shown that, on average, median CRP levels decline 15% to 25% as early as 6 weeks after initiation of therapy. As shown in the large-scale Cholesterol And Recurrent Events (CARE)(46) and PRavastatin INflammation/CRP Evaluation (PRINCE)(45) trials and subsequently confirmed in other settings, there is little evidence that the magnitude of LDL reduction predicts the magnitude of CRP reduction. On the other hand, aggressive LDL reduction remains a critical therapeutic goal, and thus serial LDL evaluation should remain the primary method to monitor statin compliance. However, whereas all subjects taking statins achieve a beneficial reduction in LDL levels, there seems to be responders and non-responders for statins in terms of CRP reduction. Whether this latter observation is important in terms of clinical event reduction is currently unknown. Analyses of 2 randomized trials suggest that the magnitude. Newer scopes for CRP as Therapeutic Target

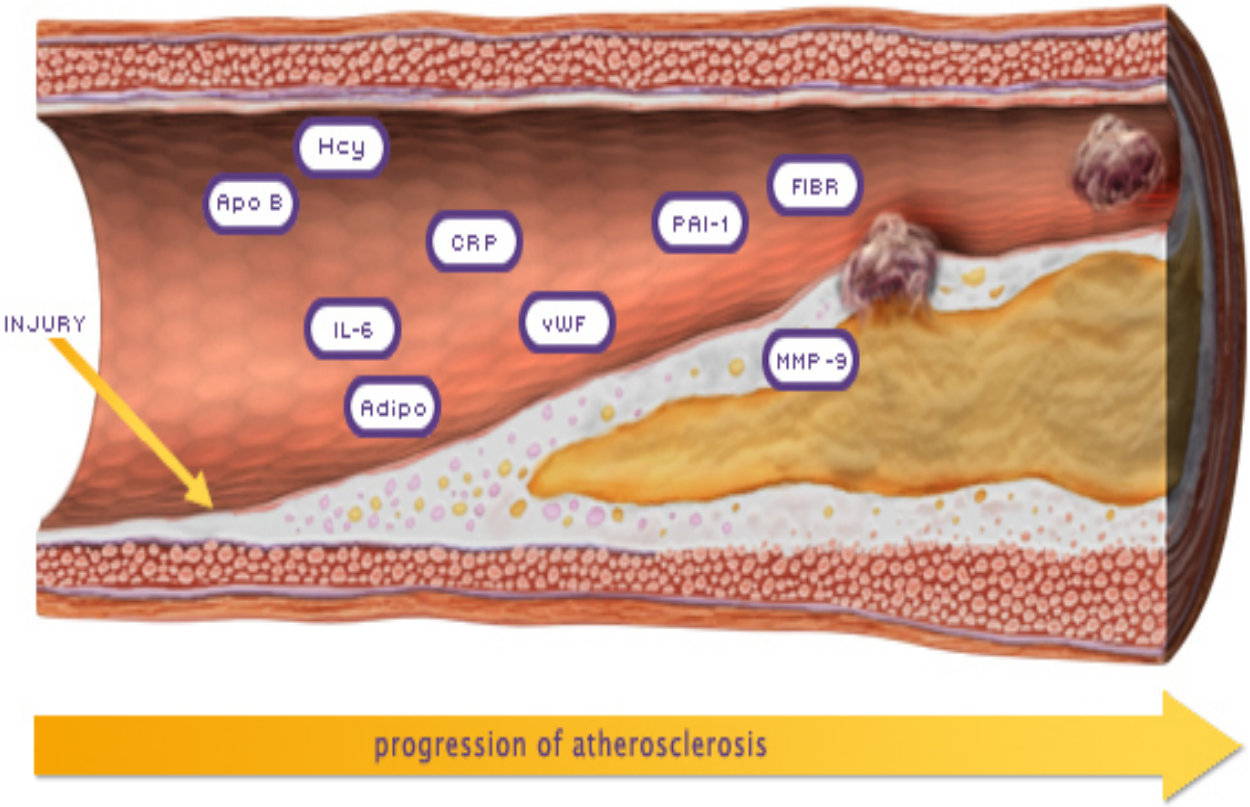
Prospective treatments

CRP concentrations can be lowered by weight loss, exercise and treatment with statins or PPAR a/Y agonists [Circulation 105:564-9, Circulation 106:403-6, Circulation 103: 1933-5, Circulation 106: 679-84].

Rosiglitazone therapy may improve CRP and other markers of CVD. A large-scale randomised clinical trial – Justification for the Use of Statins

Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) will test whether rosuvastatin will reduce cardiovascular disease in patients with elevated hs-CRP, who do not currently meet criteria for statin therapy.

MEDIATORS OF INFLAMMATION



AIM

We set out to investigate the hypothesis that elevated C-reactive protein (CRP) levels a marker of an (altered immune response) inflammation, would correlate with coronary artery disease in patients with diabetic chronic renal disease.

MATERIAL AND METHODS

This study is of Observational Study Design. Inclusive of a total 50 patients. Between 2004 – 2006 at **P.S.G.Institute of Medical Sciences and Research.**

AIM OF STUDY

We set out to investigate the hypothesis that elevated C-reactive protein (CRP) levels a marker of an (altered immune response) inflammation, would correlate with coronary artery disease in patients with diabetic chronic renal disease.

INCLUSION CRITERIA

Patients with Stage 1 to stage 3 chronic kidney disease (according to NKF- DOQI Guidelines)of Diabetic etiology

Diabetes mellitus both type 1 and type 2

EXCLUSION CRITERIA

- Advanced stages of renal disease
- Congestive cardiac failure
- Hypoproteinemia
- Inter current infection in the past 3 weeks
- Connective tissue disorder.

PROFOMA

Name : Age: Sex:

OP NO : IP NO:

Address :

Ht : Wt : BMI:

DOA : DOD :

Presenting complaint:

Past H/O: DM yrs

HTN yrs

Personal H/O: Smoking Y/N

If Y yrs

Quantity

Alcohol Y/N

If Y yrs

Quantity

Treatment H/O: DM

SHT

OTHERS

Family H/O: DM / SHT / CAD /

Others

Examination:

GC:

Markers of CAD:

PR: BP:

CVS:

RS:

GIT:

CNS:

ECG changes: Y/N

If Y

AWMI Y/N

IWMI Y/N

RVMI Y/N

LWMI Y/N

PWMI Y/N

Others

TMT +/- L/M/H

ECHO EF:

RWMA LAD

LSC

RCA

Multiple

LV clot

MR

Angio: LMCA N/Ab N

LAD N/Ab N

Diagnols N/Ab N

Septals N/Ab N

LCX N/Ab N

RCA N/Ab N

Others

Blood Investigations:

FLP :

hs CRP :

Sr.Creat :

HbA1C :

FBS :

PPBS :

UA :

CONSENT

I, ---------- exercise my free power of choice, hereby give my consent to be included in the study. I have been informed to my satisfaction by my attending doctor, the purpose of this study and the laboratory investigation that will be done with the sample obtained from me. I have been given the opportunity by the attending doctor to question on all aspects of the study and have understood the information given as a result. I hereby give permission for the doctor's incharge of this study to release the results of study for academic purposes.

Signature of the patient Date:

Signature of independent Date:

Witness

I confirm that I have explained the nature and purpose of this study to my patients.

Signature of Doctor

RESULTS

CHARACTERISTICS OF THE CASES AND THEIR RELATIONSHIP WITH CARDIOVASCULAR EVENTS

There is no statistically significant between the mean age of patients with cardiovascular events and normal cases.

TABLE 1

AGE AND CARDIOVASCULAR EVENTS

Age Group	Cardiovascular Events			
	Yes		No	
	No.	%	No.	%
< 40	5	25	3	10
41-50	4	20	7	23.3
51-60	9	45	14	46.7
>60	2	10	6	20
Range	38-68		37-67	
Median	52		53	
Mean	50.4		53.3	
S.D.	9		8.1	
‘p’	0.2755			

TABLE 2

SEX AND CARDIOVASCULAR EVENTS

Sex	Cardiovascular Events			
	Yes		No	
	No.	%	No.	%
Male	15	75	25	83.3
Female	5	25	5	16.7
'p'	0.355			

The sex composition of the two groups does not have a statistically significant difference.

TABLE 3

HBA 1C AND CARDIOVASCULAR EVENTS

HBA 1C	Cardiovascular Events			
	Yes		No	
	No.	%	No.	%
Normal	7	35	27	90
Abnormal	13	65	3	10
'p'	0.0002			

The percentage of persons with abnormal HBA1C values is significantly higher in patients with cardiovascular events.

TABLE 4

SMOKING AND CARDIOVASCULAR EVENTS

Smoking habit	**Cardiovascular Events**			
	Yes		**No**	
	No.	**%**	**No.**	**%**
Yes	5	25	6	20
No	15	75	24	80
‘p’	0.467			

Smoking habit and cardiovascular events do not have significant relationship.

TABLE 5

HYPERTENSION AND CARDIOVASCULAR EVENTS

Hypertension	Cardiovascular Events			
	Yes		No	
	No.	%	No.	%
Yes	16	80	22	73.3
No	4	20	8	26.7
‘p’	0.4247			

Hypertension and cardiovascular events do not have a statistically significant relationship.

TABLE 6

LDL CHOLESTEROL AND CARDIOVASCULAR EVENTS

LDL Choles	Cardiovascular Events			
	Yes		No	
	No.	%	No.	%
Normal	5	25	12	40
Abnormal	15	75	18	60
Range	38.7-190		70-170	
Median	120		116	
Mean	127.9		112.2	
S.D.	39.2		25.6	
P	0.1043 (Not Significant)			

Mean LDL Cholesterol values in abnormal patients and in normal cases do not differ significantly.

Table 7

CRP and Cardiovascular events

CRP	Cardiovascular Events			
	Yes		No	
	No.	%	No.	%
Normal	-	-	6	20
Abnormal	20	100	24	80
Range	3.43-15.7		2.8-10.3	
Median	9.84		4.31	
Mean	9.48		5.15	
S.D.	4.06		2.52	
P	0.0001			

CRP Values are significantly higher in patients with cardiovascular events then in normal patients. This difference is statistically significant.

TABLE 8

ECHO AND CARDIOVASCULAR EVENTS

ECHO	Cardiovascular Events			
	Yes		No	
	No.	%	No.	%
Normal	5	25	22	73.3
Abnormal	15	75	8	26.7
'p'	0.0021			

Statistical Tools

Data collected in the questionnaire were tabulated in a master chart. Analysis of the data was done by using the software “Epidemiological Information Package Version 3.3.2, 2005” developed for World Health Organisation”. Frequencies, Percentages, Range, Median, Mean, Standard Deviation and ‘p’ values were calculated using this package.

DISSCUSSION

1) Our data suggest that the elevated C-reactive prote**in** level is a predictor of cardiovascular events in Diabetic Renal Disease population. Unlike other markers of inflammation (ICAM, IL-6etc), C-reactive protein levels are stable over long periods, have no diurnal variation, can be measured inexpensively with available high-sensitivity assays, and have shown specificity in terms of predicting the risk of cardiovascular disease.24, 28, 29, 30

2) C-reactive protein is a stronger predicter of cardiovascular events than the LDL cholesterol level. The same was suggested by Paul M Ridker and Co-workers and several other workers also and our study demonstrates the same observation(33).THE addition of crp to standard cholesterol evaluation may thus provide a effective and inexpensive and non invasive method to improve clobal risk prediction and compliance with approaches.

3) Tighter glycemic controls are associated with better cardiovascular outcomes.

CONCLUSION

CRP level is independently associated with Coronary artery disease in our study group of Diabetic CKD patients and is useful predictive marker for Cardiovascular events(IHD)in the study population.

ABBREVIATIONS

CVD	-	Cardio Vascular Disease
CAD	-	Coronary Artery Disease
DM	-	Diabetes Mellitus
ESRD	-	End Stage Renal Disease
hs CRP	-	Highly sensitive C- Reactive protein
CIMT	-	Carotid Intimal Medial Thickening
CKD	-	Chronic Kidney Disease
LVH	-	Left Ventricular Hypertrophy
IHD	-	Ischemic Heart Disease
PVD	-	Peripheral Vascular Disease
HF	-	Heart Failure
LDL	-	Low Density Lipoprotein
HTN	-	Hypertension
AWMI	-	Anterior Wall Myocardial Infarction
IW	-	Inferior Wall
RV	-	Right Ventricle
RWMA	-	Regional Wall Motion Abnormality
TMT	-	Tread Mill Test
LV	-	Left Ventricle

MR	Mitral Regurgitation
LMCA	Left Main Circumflex Artery
LAD	Left Anterior Descending
LCX	Left Circumflex
RCA	Right Circumflex Artery
FLP	Fasting Lipid Profile

BIBLIOGRAPHY

1. Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. Lancet 1997;349:1436-1442.

2. The Predictive Value of C-Reactive Protein in End-Stage Renal Disease: Is It Clinically Significant? Blood Purification 2006;24:335-341

3. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation. 1998;97:1837–1847.

4. Wilson PW. Diabetes mellitus and coronary heart disease. Am J Kidney Dis. 1998;32:S89–S100.

5. McGill HC Jr, McMahan CA. Determinants of atherosclerosis in the young: Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. Am J Cardiol. 1998; 82:30 T–36T.

6. Brezinka V, Padmos I. Coronary heart disease risk factors in women. Eur Heart J. 1994;15:1571–1584.

7. Geiss LS, Herman WH, Smith PJ, National Diabetes Data Group. Diabetes in America. Bethesda, Md: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 1995:233–257.

8. Stone PH, Muller JE, Hartwell T, York BJ, Rutherford JD, Parker CB, Turi ZG, Strauss HW, Willerson JT, Robertson T, et al, the MILIS Study Group. The effect of diabetes mellitus on prognosis and serial left ventricular function after acute myocardial infarction: contribution of both coronary disease and diastolic left ventricular dysfunction to the adverse prognosis. J Am Coll Cardiol.1989;14:49–57.

9. Singer DE, Moulton AW, Nathan DM. Diabetic myocardial infarction: interaction of diabetes with other preinfarction risk factors. Diabetes. 1989; 38:350–357.

10. Smith JW, Marcus FI, Serokman R. Prognosis of patients with diabetes mellitus after acute myocardial infarction. Am J Cardiol. 1984;54:718–721.

11. Wingard DL, Barrett-Connor EL, Scheidt-NaveC, McPhillips JB. Prevalence of cardiovascular and renal complications in older adults

with normal or impaired glucose tolerance or NIDDM: a population-based study. Diabetes Care. 1993;16:1022–1025.

12. Nelson RG, Knowler WC, Pettitt JD, Bennett PH, National Diabetes Data Group. Kidney diseases in diabetes. In: Diabetes in America. Bethesda, Md: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 1995:349–400.

13. Mogensen CE, Christensen CK, Vittinghus E. The stages of diabetic renal disease: with emphasis on the stage of incipient diabetic nephropathy. Diabetes. 1983;32:64–78.

14. US Renal Data System. USRDS 1994 Annual Data Report. Bethesda, Md: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 1994.

15. Cowie CC, Port FK, Wolfe RA, Savage PJ, Moll PP, Hawthorne VM. Disparities in incidence of diabetic end-stage renal disease according to race and types of diabetes. N Engl J Med. 1989;321:1074–1079.

16. Rostand SG, Kirk KA, Rutsky EA, Pate BA. Racial differences in the incidence of treatment for end-stage renal disease. N Engl J Med. 1982; 306:1276–1279.

17. Stephens GW, Gillaspy JA, Clyne D, Mejia A, Pollak VE. Racial differences in the incidence of end-stage renal disease in types I and II diabetes mellitus. Am J Kidney Dis. 1990;15:562–567.

18. Lopes AA, Port FK, James SA, Agodoa L. The excess risk of treated end-stage renal disease in blacks in the United States. J Am Soc Nephrol. 1993;3:1961–1971.

19. Nelson RG, Pettitt DJ, Carraher MJ, Baird HR, Knowler WC. Effect of proteinuria on mortality in NIDDM. Diabetes. 1988;37:1499–1504.

20. McMillan MA, Briggs JD, Junor BJ. Outcome of renal replacement treatment in patients with diabetes mellitus. BMJ. 1990;301:540–544.

21. Hirschl MM, Heinz G, Sunder-Plassmann G, Derfler K. Renal replacement therapy in type 2 diabetic patients: 10 years' experience. Am J Kidney Dis. 1992;20:564–568.

22. Rischen-Vos J, van der Woude FJ, Tegzess AM, Zwinderman AH, Gooszen HC, van den Akker PJ, van Es LA. Increased morbidity and mortality in patients with diabetes mellitus after kidney transplantation as compared with non-diabetic patients. Nephrol Dial Transplant. 1992;7:433–437.

23. Principles Of Internal Medicine – Harrison's 16th Edition.

24. C-reactive protein NEJM 342:836-43

25. Circulation 107:391-7.

26. de Jager, J., Dekker, J. M., Kooy, A., Kostense, P. J., Nijpels, G., Heine, R. J., Bouter, L. M., Stehouwer, C. D.A. (2006). Endothelial Dysfunction and Low-Grade Inflammation Explain Much of the Excess Cardiovascular Mortality in Individuals With Type 2 Diabetes: The Hoorn Study. ArteriosclerosisAnd Thromb Vasc Biol 26: 1086-1093.

27. Braunwald text book of cardiology

28. Sarnak MJ, Levey AS. Cardiovascular disease and chronic renal disease: A new paradigm. Am J Kid Dis 35: Suppl 1, S117- S131, 2002.

29. Cheung A, Sarnak M, Yan G, et al.Atherosclerotic cardiovascular risks in chronic Hemodialysis patients. Kidney Int 58: 352- 362, 2000

30. Sarnak M, Coronado B, Greene T, et al. Cardiovascular disease risk factors in chronic renal insufficiency. Clinical Nephrol 57: 327- 335, 2000.

31. Kasiske B, Chakkera H, Roel, J. Explained and unexplained ischemic heart disease risk after renaltransplantation. J Am Soc Nephrol 11: 1735-1743, 2000.

32. Longenecker J, Coresh J, Powe N et al. Traditional cardiovascular disease risk factors in dialysis patients compared with the general population: The CHOICE Study. J Am Soc Nephrol 13: 1918- 1927, 2002.

33. Comparison of C-Reactive Protein and Low-Density Lipoprotein Cholesterol Levels in the Prediction of First Cardiovascular events November 14, 2002 NEJM.

34. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. N Engl J Med 2000;342:381-389.

35. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329: 977-986.

36. Diabetes Control and Complications Trial Research Group. The effect of intensive diabetes therapy on measures of autonomic nervous system function in the Diabetes Control and Complications Trial (DCCT). Diabetologia 1998;41:416-423

37. Blake GJ, Ridker PM. Novel clinical markers of vascular wall inflammation. *Circ Res*. 2001;89:763–771.

38. Blake GJ, Otvos JD, Rifai N, et al. Low-density lipoprotein particle concentration and size as determined by nuclear magnetic resonance spectroscopy as predictors of cardiovascular disease in women. *Circulation* 2002;106:1930–1937.

39. Ockene IS, Matthews CD, Rifai N, et al. Variability and classification accuracy of serial high-sensitivity C-reactive protein measurements in healthy adults. *Clin Chem*. 2001;47:444–450.

40. Roberts WL, Moulton L, Law TC, et al. Evaluation of nine automated high sensitivity C-reactive protein methods: implications for clinical and epidemiological applications. *Clin Chem*. 2001;47:418–423.

41. Blake GJ, Ridker PM, Kuntz KM. Projected life-expectancy gains with statin therapy for individuals with elevated C-reactive protein levels. *J Am Coll Cardiol*. 2002;40:49–55.

42. Rifai N, Buring JE, Lee I-M, et al. Is C-reactive protein specific for vascular disease in women? *Ann Intern Med*. 2002;136:529–533.

43. Ridker PM. High-sensitivity C-reactive protein: potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. *Circulation*. 2001;103:1813–1818.

44. Blake GJ, Ridker PM. Novel clinical markers of vascular wall inflammation.*Circ Res*. 2001;89:763–771.

45. Albert MA, Danielson E, Rifai N, et al. Effect of statin therapy on C-reactive protein levels: the Pravastatin Inflammation/CRP Evaluation (PRINCE): a randomized trial and cohort study. *JAMA*. 2001;286;64–70.

46. Ridker PM, Rifai N, Pfeffer M, et al. Long-term effects of pravastatin on plasma concentration of C-reactive protein. *Circulation*. 1999;100:230–235.