hs-C-REACTIVE PROTEIN IN

CHRONIC RENAL FAILURE WITH AND WITHOUT

CARDIOVASCULAR COMPLICATIONS

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CERTIFICATE

This is to certify that this dissertation titled "**hs-C-REACTIVE PROTEIN IN CHRONIC RENAL FAILURE WITH AND WITHOUT CARDIOVASCULAR COMPLICATIONS**" submitted by **Dr.S.Jawahar** to the Tamil Nadu Dr.M.G.R. Medical University, Chennai is in partial fulfilment of the requirement for the award of M.D. Degree Branch I (General Medicine) and is a bonafide research work carried out by him under direct supervision and guidance.

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DECLARATION

I **Dr. S. Jawahar** hereby declare that I carried out this work on "**hs-C-REACTIVE PROTEIN IN CHRONIC RENAL FAILURE WITH AND WITHOUT CARDIOVASCULAR COMPLICATIONS**" at Department of General Medicine, Government Rajaji Hospital, Madurai Medical College, Madurai. I also declare that this bonafide work or a part of this work was not submitted by me or any others for any award, degree, diploma to any university or board either in India or abroad.

This is submitted to the Tamilnadu Dr.M.G.R. Medical University, Chennai in partial fulfillment of the rules and regulation for the M.D. Degree examination in General Medicine.

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CONTENTS

ABBREVIATIONS

AGEs	-	Advanced Glycation End products
CRD/CRF	-	Chronic Renal Disorders/Failure
C-RP	-	C-Reactive Protein
CVD	-	Cardiovascular Disease
ECG	-	Electrocardiogram
ECHO	-	Echocardiogram
EPO	-	Erythropoietin
ESR	-	Erythrocyte Sedimentation Rate
ESRD	-	End Stage Renal Disease
GFR	-	Glomerular Filtration Rate
Hb	-	Haemoglobin
HD	-	Haemodialysis
hs CRP	-	highly sensitivity (assay of) C-Reactive Protein
IHD	-	Ischaemic Heart Disease
IL	-	Interleukin
LDL	-	Low Density Lipoprotein
Lp	-	Lipoprotein
LVH	-	Left Ventricular Hypertrophy
PD	-	Peritoneal Dialysis

INTRODUCTION

Cardiovascular disease is the leading cause of morbidity and mortality in patients with CRF (Chronic renal failure) at all stages. Estimates of the increase in CVD (Cardiovascular disease) risk attributable to CRF range from 10 to 200 fold depending on the stage of CRF, other risk factors and comorbid conditions. Between 30 to 45% of patients reaching ESRD (end stage renal disease), already have advanced cardiovascular complications. Thus the management of patients with CRF should emphasize prevention of cardiovascular complications as well as measures aimed at alleviating the progression and complications of CRF itself[1].

It is obvious that 'traditional risk factors, such as hypertension, chronic heart failure, dyslipidemia, tobacco smoking and diabetes mellitus may account for a large part of the increased cardiovascular mortality rate observed in these patients. However, based on recent research, it is evident that also other 'non traditional', risk factors such as, chronic inflammation, oxidative stress and malnutrition, may contribute to an increased cardiovascular mortality among dialysis patients[5].

Traditional risk factors are inadequate as predictors of cardiovascular mortality in CRF patients. Even though diabetes mellitus and smoking were

strongly associated with CVD, neither serum total cholesterol nor systolic blood pressure was associated with coronary heart disease in these patients[7]. Hence it is prudent to look for other factors contributing to the morbidity and mortality in CRF patients. Recently CRP (C-reactive protein) has emerged as a more sensitive and specific indicator of an “acute phase” inflammatory metabolic response[1]. Our study tries to assess the correlation of hs CRP levels in CRF patients, particularly the CRF patients with cardiovascular complications.

Assumption

The available western reports concluded an association between elevated CRP levels and cardiovascular morbidity and mortality among CRF cases. It is likely that hsCRP may be altered among the CRF patients of this area. However authenticated reports about this is lacking in this part of the country our presents study attempts to find out the same and its usefulness in clinical practice.

AIMS AND OBJECTIVES

i. To estimate the hsCRP levels in newly detected chronic renal failure patients.

ii. To identified variations in the hsCRP level among CRF patients with and without cardiovascular complications.

iii. To find out the correlation between hsCRP levels and albuminuria, haemoglobin levels, retinopathy as well as cardiovascular complications among CRF patients.

REVIEW OF LITERATURE

CRF

CRF is a progressive and significant reduction in glomerular filtration rate (GFR). This occurs gradually and the time period of its occurrence may vary from months to several years. The progression of renal failure ultimately leads to uremic syndrome which is defined as symptoms and signs associated with end-products of nitrogen metabolism. When GFR becomes less than 5ml/min, CRF is very severe and will prove fatal unless renal replacement therapy is undertaken.[10]

Aetiology

The aetiological spectrum of CRF differs somewhat in different parts of the world. Primary glomerulonephritis is the commonest cause of CRF in developing countries of the world whereas diabetic glomerulosclerosis is emerging as the most common cause of CRF in developed countries where life-expectancy of diabetics has increased considerably as a result of better diabetic care.[16]

Important causes of CRF[16]

A. Primary glomerulonephritis

i. Proliferative

ii. Focal glomerulosclerosis

iii. Membranous

iv. Membranoproliferative

v. Cresentic

B. Secondary glomerulopathy (systemic diseases)

i. Diabetes mellitus

ii. SLE

iii. Amyloidosis

iv. Vasculitis

C. Interstitial renal diseases

i. Chronic interstitial nephritis

ii. Chronic pyelonephritis

iii. Reflux nephropathy

D. Hypertensive renal disease

i. Nephrosclerosis

ii. Renal artery stenosis

E. Obstructive nephropathy

i. Urinary calculus

ii. Prostatic enlargement

iii. Tumours – kidney/bladder

F. Heredo familial renal disease

i. Autosomal dominant polycystic kidney disease

ii. Medullary cystic disease

iii. Alport's syndrome

Stages of CRF[10]

Stage	Description	GFR ml/mt per $1.73m^2$
1	Kidney damage with normal or increased GFR	90
2	Kidney damage with mildly decreased GFR	60-89
3	Moderately decreased GFR	30-59
4	Severely decreased GFR	15-29
5	Renal failure	<15(or dialysis)

Pathophysiology of uremia

The pathophysiology of uremic syndrome can be divided into two sets of abnormalities:

i. Those consequent to the accumulation of products of protein metabolism.

ii. Those consequent to the loss of renal functions, such as fluid and electrolyte homeostasis and hormonal abnormalities.

Uremia may contribute to some of the clinical features like anorexia, malaise, vomiting and headache. In addition to urea, excretion of additional categories of nitrogenous excretory products which are affected are quanido compounds, urates and hippurates, end products of nucleic acid metabolism, polyamines, myoinositol, phenols, benzoates and indoles.

Nitrogenous compounds with a molecular mass of 500 to 12,000 Da (so called “middle” molecules) are also retained in CRF, contributing to morbidity and mortality.

A host of metabolic and endocrine functions normally subserved by the kidney are also impaired, resulting in (a) anaemia, (b) malnutrition (c) impaired metabolism of carbohydrates fats and proteins; (d) metabolic bone disease.

Cardiovascular and pulmonary disturbances in CRF

1. Arterial hypertension
2. CCF or pulmonary oedema
3. Accelerated atherosclerosis

4. Pericarditis
5. Cardiomyopathy
6. Uremic lung
7. Arrhythmias
8. Vascular calcification
9. Anaemia (indirectly worsens CVD)

Symptoms and signs with CRF[16]

A. General

i. Oedema

ii. Pallor

iii. Malnutrition

B. Gastrointestinal

i. Anorexia

ii. Nausea / Vomiting

iii. Stomatitis

iv. Gastritis

v. GI bleeding

C. Cardiovascular

i. Hypertension

ii. Pericarditis

iii. Cardiomyopathy

iv. Congestive heart failure

D. Neurological

i. Peripheral neuropathy

ii. Lack of mental alertness

iii. Encephalopathy

iv. Asterixis

v. Convulsions

E. Musculoskeletal

i. Renal osteodystrophy (Bone pains)

ii. Myopathy (Muscular weakness)

F. Haemopoietic

i. Anaemia

ii. Bleeding and coagulation defects

G. Pulmonary complications

Pulmonary infections; TB

H. Skin (Pruritus)

Cardiovascular Abnormalities in CRF[10]

Hypertension is a particularly common cause and consequence of CRD (chronic renal disease), CRF especially in the elderly. It should be noted that

cardiovascular morbidity and mortality precludes most patients with CRF from reaching the stage of ESRD (End stage renal disease). Identification of CRF as a major risk factor for cardiovascular morbidity and mortality and the expectation of effective interventions to diminish premature cardiovascular mortality and increasing longevity overall, will increase the cohort of patients reaching ESRD.

A. Ischaemic cardiovascular disease

CRF at all stages constitutes a major risk factor for ischaemic cardiovascular disease, including occlusive coronary heart disease, cerebrovascular disease and peripheral vascular diseases. Increased prevalence of coronary heart disease in CRF derives from both traditional ("classic") and CRF related ("non traditional") risk factors.

The CRF related risk factors include:

i. Anaemia

ii. Hyperphosphatemia

iii. Hyperparathyroidism

iv. Microinflammation (which is found in all stages of CRF but is undoubtedly aggravated by dialysis).

The inflammatory state elicits a rise in acute phase reactants such as IL-6 and C-RP, which contribute to the coronary occlusive process and are

predictors of CVD (cardio vascular disease) risk. Other abnormalities augment myocardial ischaemia. These include reduced myocardial tolerance to ischaemia due to LVH (left ventricular hypertrophy) and microvascular disease. Also coronary reserve (defined as the increase in coronary blood flow in response to greater demand) is attenuated. Nitric oxide, an important mediator of vasodilatation is reduced in CRF even at early stages of CRF, and also because nitric oxide is scavenged by reactive oxygen species. In addition, coronary arteriolar hypertrophy / hyperplasia limits vascular capacity.

B. Congestive heart failure

Congestive heart failure and / or pulmonary oedema in uremia can be due to

(i) Abnormal cardiac function secondary to myocardial ischaemia.

(ii) LVH

(iii) Salt and water retention

(iv) Uremic lung

A unique form of pulmonary congestion and oedema may occur even in the absence of volume overload and is associated with normal or mildly elevated intracardiac and pulmonary capillary wedge pressure. This entity is characterized radiologically by peripheral vascular congestion giving rise to a

“butterfly wing” distribution, is due to increased permeability of alveolar capillary membranes. This “low pressure” pulmonary oedema as well as cardiopulmonary abnormalities associated with circulatory overload, usually respond promptly to vigorous dialysis.

C. Hypertension and left ventricular hypertrophy (LVH)

Hypertension is the most common complication of CRF and ESRD. It may develop early during the course of CRF and is associated with adverse outcomes – in particular, more rapid loss of renal function and development of CVD. Numerous epidemiological studies and clinical trials have shown a relationship between the level of blood pressure and the rate of progression diabetic and non diabetic kidney disease.

Administration of EPO (Erythropoietin) may raise blood pressure and increase the requirement for antihypertensive drugs in CRF patients. Left ventricular hypertrophy and dilated cardiomyopathy are among the most ominous risk factors for excess cardiovascular morbidity and mortality in patients with CRF and ESRD and are thought to be related primarily to prolonged hypertension and extracellular fluid volume overload. In addition anaemia and the surgical placement of an AV fistula for future / ongoing dialysis access may generate a high cardiac output state and pulmonary hypertension which also intensify the burden placed on left ventricle.

Since volume overload is the major cause of hypertension in uremia the normotensive state can be restored by appropriate use of salt restriction or natriuretic drugs are ultrafiltration in the dialysis setting. Neverthless, because of hyperreninemia and other disturbances in renal vasoconstrictors and vasodilators some patients remain hypertensive despite rigorous salt and water restriction and ultrafiltration.

D. Pericarditis and Pericardial Effusion

Pericardial pain with respiratory accentuation by a friction rub, are the hallmarks of uremic pericarditis. The finding of the multi component friction rub strongly supports the diagnosis.

Pericarditis may be accompanied by the accumulation of pericardial fluid that is readily detected by echocardiography, that sometimes leads to cardiac tamponade. Pericardial fluid in uremic pericarditis is more often heamorrhagic than in viral pericarditis.

E. Anaemia[16]

Anaemia in CRF is due to several factors such as:

i. Chronic blood loss

ii. Haemolysis

iii. Bone marrow suppression by retained uremic factors

iv. Reduced renal production of EPO

v. Secondary hyperparathyroidism

The degree of anaemia in CRF parallels roughly the degree of renal failure[3]. Decreased EPO production by the diseased kidneys seems to be the main mechanism of renal anaemia but other factors such as inhibitors of EPO and deficiency of haemopoietic nutrients like folic acid and iron may contribute to anaemia in CRF.

Untreated anaemia leads to left ventricular hypertrophy which increases the risk of sudden death[16].

Conditions associated with major elevations of CRP[20]

Tissue damaging processes, infections, inflammatory diseases of unknown etiology and malignant neoplasms are associated with major acute phase response of CRP. CRP levels reflect quite precisely the extent and activity of the disease.

Conditions with elevated CRP

A. Infections

i. Most systemic microbial infections

ii. Systemic fungal infections

iii. Chronic bacterial infections

iv. Malaria, especially falciparum malaria (high CRP)

v. Pneumocystis, toxoplasma infection

B. Chronic inflammatory diseases

i. Rheumatoid arthritis

ii. Ankylosing spondylitis

iii. Proriactic arthritis

iv. Systemic vascultis

v. Reiter's disease

vi. Crohn's disease

In diseases with pathology relatively inaccessible to direct examination, eg: systemic vasculitis, Crohn's disease etc., CRP estimation provides best available objective index of disease activity.

C. Tissue necrosis

i. Myocardial infarctin

ii. Tumor embolisation

iii. Acute pancreatitis

[Stable angina and coronary arteriography do not stimulate CRP production].

D. Trauma

i. Surgery

ii. Burns

iii. Fractures

E. Malignancy

i. Lymphoma

ii. Hodgkin's disease

iii. Carcinoma

iv. Sarcoma

C - Reactive Protein (CRP)[20]

CRP is an acute phase reactant synthesized in liver. If belongs to a family of soluble proteins called pentraxins (radial pentameric structure). Their production is induced by inflammatory cytokines like IL1 & IL 6 (interleukins), and they are able to activate the classical pathway of complement by directly binding to complement C1q.

CRP was named for its calcium dependent interaction with somatic C-polysaccharide of pneumococci.

Liver makes huge quantities of CRP and serum amyloid associated protein which are not found at all in normal serum[2]. In 24 hours, the liver can synthesize about 15 grams of CRP. The response persists in individuals with chronic infections, chronic inflammation or invasive / metastatic neoplasms and

is sustained. CRP through its capacity to activate complement, can exacerbate ischaemic and possibly also other forms of tissue damage.

CRP molecule consists of five identical nonglycosylated, polypeptiole subunits each of mass 23027 Daltons and containing 206 aminoacid residues arranged in annular configuration with cyclic pentameric symmetry[2].

Functions of CRP[20]

i. It recognizes and 'scavenges' cellular debris and promotes its clearance.

ii. Protects against infection with pneumococci and H. Influenza.

iii. Complement activation by CRP exacerbates ischaemic injury.

iv. It is proatherogenic – by binding to phospholipids and lipoproteins.

v. It is prothrombotic – CRP stimulates tissue factor production by macrophages.

vi. CRP suppresses polymorph migration (which is anti-inflammatory).

Serum concentration

CRP is a trace protein in normal healthy individual.

Median value is 0.08mg/dL (0.8mg/L).

Normal range is 0.03 mg/dL to 0.17 mg/dL[20] .

The half life of CRP in circulation is 19 hours and is constant in all conditions regardless of the presence of acute phase response or its cause. The speed of change and incremental range of CRP concentration are exceptional among all acute phase reactants. The single major determinant of the circulating concentration of CRP is its rate of synthesis; hence serum CRP level usually closely reflects the extent and activity of disease. Drug or other treatments do not affect CRP production unless they affect the disease process. The only physical condition which interferes with the capacity to interpret CRP levels is serious hepato-cellular impairment.

CRP as cardiovascular risk predictor[3]

The American Heart Association and the centre for Disease Control and prevention has recently issued guidelines for the use of hs CRP in clinical practice.

h.s. CRP level	Cardiovascular risk
<0.10mg/dL (<1mg/L)	Low risk
0.10 mg/dL to 0.3mg/dL (1 to 3 mg/L)	Moderate risk
>0.3mg/dL (>3mg/L)	High risk

In primary prevention, a large series of prospective of epidemiological studies has convincingly demonstrated that CRP, when measured with high

sensitivity assays (hs-crp), strongly and independently predicts risk of myocardial infarction, stroke, peripheral arterial diseases and sudden cardiac death even a among apparently healthy individuals. These data apply to women as well as to men across all age levels.

CRP is not only a marker of inflammation, but also may influence vascular vulnerability through several mechanisms like:

i. Enhanced expression of local adhesion molecules
ii. Increased expression of endothelial plasminogen activator inhibitor
iii. Reduced nitric oxide bioavailability
iv. Altered LDL uptake by macrophages, and
v. Colocalization with complement within atherosclerotic lesions

Consistently high values of CRP represent very high risk of future cardiovascular disease because risk appears linear across the full range of CRP.

Advantages in hs-CRP screening[20]

i. CRP levels are stable over long period of time
ii. Have no circadian variation
iii. Not affected by food intake, and
iv. Screening can be done on an outpatient basis

Strong evidence shows that hs-CRP adds prognostic information at all levels of LDL cholesterol, at all levels of the Framingham risk score, and at all levels of the metabolic syndrome.

Of the commercially available predictors for cardiovascular risk hs-CRP has the greatest magnitude of prediction value. Further hs CRP adds important prognostic information to global risk prediction.

CRP evaluation will likely become a routine part of coronary risk prediction.

Reliability of CRP and ESR[20]?

The only other comparable non-specific index of the presence of disease which is routinely measured is the ESR. The ESR reflects, in part, the intensity of the acute phase response, especially that of fibrinogen and the α-globulins, but is also largely determined by the concentration of immunoglobulins, which are not acute phase reactants. These proteins have half-lives of days to weeks. The rate of change of ESR is thus very much slower than that of the CRP level, and it rarely reflects precisely the clinical status of the patient at the actual time of testing. ESR is also dependant on the number and morphology of the red cells, which bear no relation to the acute phase response. Finally there is significant diurnal variation in ESR, depending on food intake, which is not seen in CRP.

The ESR is therefore of limited use as an objective index. The dynamic range of the ESR is also much less than that of CRP and the precision and reproducibility of ESR measurement is poor compared to robust immunoassays for CRP. Thus in all clinical situations, frequent prospective measurement of CRP reflect disease activity very much more closely than ESR. Finally ESR does not provide the information given by the high sensitivity measurement of CRP. ESR remains a useful screening test for the detection of paraproteinemias, especially multiple myeloma, which do not necessarily provoke an active phase response.

Association of CRP in CRF patients in recent studies

Stevinkel[28] et al 2000; In their review article, conclude that chronic inflammation, as evidenced by increased levels of various acute phase reactants such as CRP, fibrinogen, serum amyloid A (SAA), transferring, albumin and prealbumin is a common feature in dialysis (CRF) patients.

The inflammation may rather be a marker of an atherogenic milieu and inflammation has been proved to be associated with endothelial dysfunction, insulin resistance and oxidative stress, all of which may accelerate atherosclerosis.

A number of ‘non traditional’ risk factors for CVD such as hyperhomocysteinemia, oxidative stress, vascular calcification, malnutrition and inflammation are commonly found in CRF patients. They provide a rationale for the remarkable prevalence of atherosclerotic CVD in these patients.

Further the author says that in their prospective study, they have found that various markers of malnutrition and inflammation are strong independent predictors of mortality in dialysis patients.

Mechanisms by which various acute phase reactants may cause atherosclerotic CVD.

a. Possible “direct” mechanisms

i. CRP deposition in the arterial wall
ii. CRP causes direct tissue damage
iii. SAA affects lipoprotein structure
iv. Lp-a, promotes athero – and thrombogenesis
v. Fibrinogen promotes athero and thrombogenesis and increases plasma viscosity.

b. Possible “indirect’ mechanisms

i. Endothelial dysfunction eg: reduced nitric oxide
ii. Insulin resistance

iii. Increased oxidative stress

iv. Stimulation of AGEs (advanced glycation end products)

v. Persistent atherogenic infections eg. C. Pneumoniae, H.pylori

Stenvinkel[28], et al 2000; In their study propose two types of malnutrition in CRF patients, type 1: associated with uremic syndrome per se and type 2: cytokine – driven type of malnutrition. The proposed features are:

	Type 1	**Type 2**
i. Serum albumin	Normal /low	Low
ii. Co-morbidity	Uncommon	Common
iii. Presence of inflammation	No	Yes
iv. Food intake	Low	Low/normal
v. Resting energy expenditure	Normal	Elevated
vi. Oxidative stress	Increased	Markedly increased
vii. Protein catabolism	Decreased	Increased
viii. Reversal by dialysis and nutritional support	Yes	No

Their study recognized that about 30-50% of predialysis, HD and PD patients had serologic evidence of an activated inflammatory response as evidence by elevated CRP levels[29,33,31].

The proposed potential causes of inflammation in patients with CRF are:

i. Reduced renal clearance of cytokines

ii. Reduced renal clearance of AGEs

iii. Chronic heart failure

iv. The atherosclerotic process per se

v. Various inflammatory diseases

vi. Unrecognized persistent infections eg. C.pneumoniae, H.pylori

In a study Kimmel[11] et al, 1998; reported the generation of pro-inflammatory cytokines (IL-1, IL-6 and TNFα) which have been markedly elevated in CRF patients and predicts the mortality. Serum levels of CRP appears to reflect the generation of such cytokines.

In a study Heinrich[8] et al, 1995; suggested that, by virtue of its acute phase behaviour the CRP may be a marker for severity and progression of atherosclerotic processes in the vessels[12].

They also showed that elevated CRP can predict cardiovascular mortality.

MATERIALS AND METHODS

Setting	:	This work was done at Government Rajaji Hospital, affiliated to the Madurai Medical College, Madurai.
Collaborating Department:		Department of Medicine in collaboration with departments of Nephrology and Cardiology.
Design of study	:	Cross sectional and analytical study.
Period of study	:	January 2005 to February 2006.
Ethical approval	**:**	Approval for the study was obtained from the ethical committee of Government Rajaji Hospital, Madurai.
Consent	**:**	Prior informed consent was obtained from all the cases and controls included in the study.
Sample size	:	42 newly detected CRF patients. 10 controls (normal individuals)

Selection of study subjects: (Cases and Controls)

Cases : Newly detected CRF patients admitted to Govt. Rajaji Hospital, who satisfied the inclusion criteria were selected for the study.

Controls : Age and sex matched healthy volunteers were selected after getting consent.

Inclusion criteria

i. Elevated blood urea levels

ii. Elevated serum Creatinine levels

iii. Ultrasound abdomen – medical renal disease

Exclusion criteria

i. Diabetes mellitus

ii. Previous history of IHD

iii. Acute / chronic liver diseases

iv. Rheumatoid arthritis

v. Documented connective tissue disorders

vi. Previously diagnosed renal failure patients

vii. Surgical causes of CRF (obstructive uropathies) / trauma

viii. Smokers

ix. Fever within 1 week prior to admission

x. Skin infections / any other overt infections

xi. Malignancy

xii. Children

xiii. Pregnant women

xiv. Immunosuppressive drug therapy

Socio demographic data

- ❖ Age
- ❖ Sex
- ❖ Socio demographic and clinical data were collected. The study subjects were subjected to relevant investigations.

Clinical details

- Anaemia was identified.
- Systolic and diastolic blood pressures were measured.
- General and Systemic examination was done.
- Cardiovascular risk factors were assessed.
- Fundus examination was done.

Laboratory data

- Total and differential count of WBCs was done.
- Hb in gm% was estimated by Sahli's method.

- Urine albumin was estimated using standard dipsticks.(semi quantitative method)
- Blood urea estimation was done manually by using diacetyl monoxime (DAM) method.
- Serum creatinine estimation was done by using COBAS auto analyser
- Serum hs CRP estimation was done by Nephalometry method
- ECG 12 lead Electro Cardio Gram was done.(Philips)
- ECHO – Echo Cardio Graphic evaluation was done
- Ultra sono gram abdomen.

Definitions used for this study

1. Anaemia – Hb level below 10gm/dL (marked anaemia) [Sood S.K, U.Rusia, Ann of Nat. Acad. of Med. Sci, India, 1986; 22(4): 235.

2. CRF – is a pathophysiologic process resulting in the attrition of nephron number and function and frequently leading to end-stage-renal disease (ESRD) [Loss of cortico medullary distinction by ultra sono gram]
3. LVH – ECG findings – based on Sokolon-Lyon criteria [Sokolon, Lyon 1949, Casale et al 1987].

4. Hypertensive Retinopathy (Grading) – based on Keith-Wagener-Baker classification of funduscopic changes.
5. Cardio vascular complications – left ventricular hypertrophy ishchaemic changes LV dysfunction, Pericardial effusion

Procedure for data collection

There were about 272 CRF patients diagnosed during the study period, of whom more than 65% were found to be diabetics. 13% were IHD patients. After applying strict selection criteria and getting consent only 42 patients (28males and 14females) were selected for this study. The patients initially underwent clinical evaluation and routine laboratory tests and were subjected to ultrasound examination of abdomen.

After diagnosis of CRF, the patients were subjected to ophthalmologic evaluation to study hypertensive retinopathy. ECG was taken for all the patients and then echocardiographic evaluation was done for them.

Blood samples were collected from the patients after over night fasting and one time estimation of hs – CRP was done by nephalometry method.

Limitations of this study

1. CRF patients with comorbid conditions, though common were not included for this study.

2. The lower limit of the hs CRP estimation by (Nephalometry method) laboratory was 0.10mg/dL. [below which it may not be accurate].
3. Hypertension could be the cause or the consequence of CRF.
4. Serial estimation of hs CRP was not done in this study.

Financial support : Nil

Conflicting interest: Nil

Statistical analysis :

Data was method in Microsoft excel spirit sheet. Analysis of data was done utilizing the software - Epidemiological Information Package 2002 (Epi info 2002) developed by the Centers for Disease Control and Prevention-Atlanta, USA for World Health Organization. Mean standard deviation and 'p' values were calculated using this package. Chi Square test was done were ever necessary to find out significance of relationship between both groups. Since the variances were not homogenous, KRUSKUL-WALLY'S TEST (X^2 test) was used to find out the significance of difference.

RESULTS

In the present study 42 cases of CRF satisfied rigid selection criteria. Their age ranged from 23 years to 67 years and the mean ± S.D. was 48.6 ± 10.3 years. The distribution of cases in relation to age group is provided in table no.1 given below.

Table 1: Distribution of study subjects with relation to AGE

Age Group (years)	**Study Cases**		**Control Cases**	
	No	**%**	**No**	**%**
≤ 30	2	4.8	2	20
31-40	7	16.7	2	20
41-50	14	33.3	2	20
51-60	15	35.7	2	20
> 60	4	9.5	2	20
Total	42	100	10	100
Mean	48.6		44.9	
S.D.	10.3		15.9	

'p' = 0.4857 (Not significant)

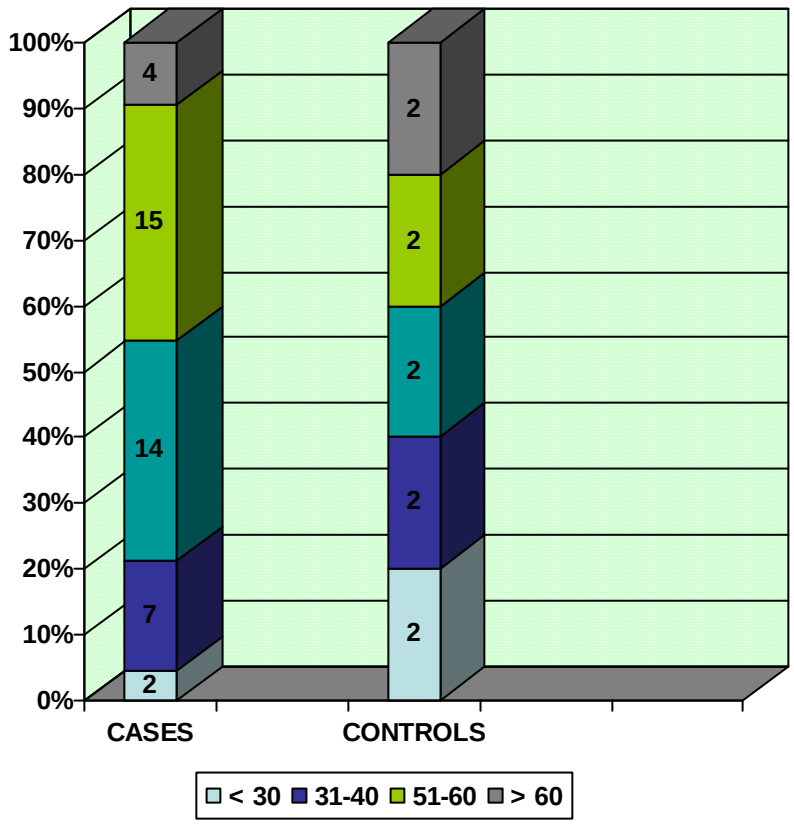
The mean age for the study population was 48.6 with S.D of ± 10.3 years

The mean age for the control group was 44.9 with S.D of ±15.9 years

Among the CRF patients in this study 29 patients (69%) were found to be in the age group between 40 to 60 years.

***The patients did not differ statistically from the control with reference to age.**

Figure : 1



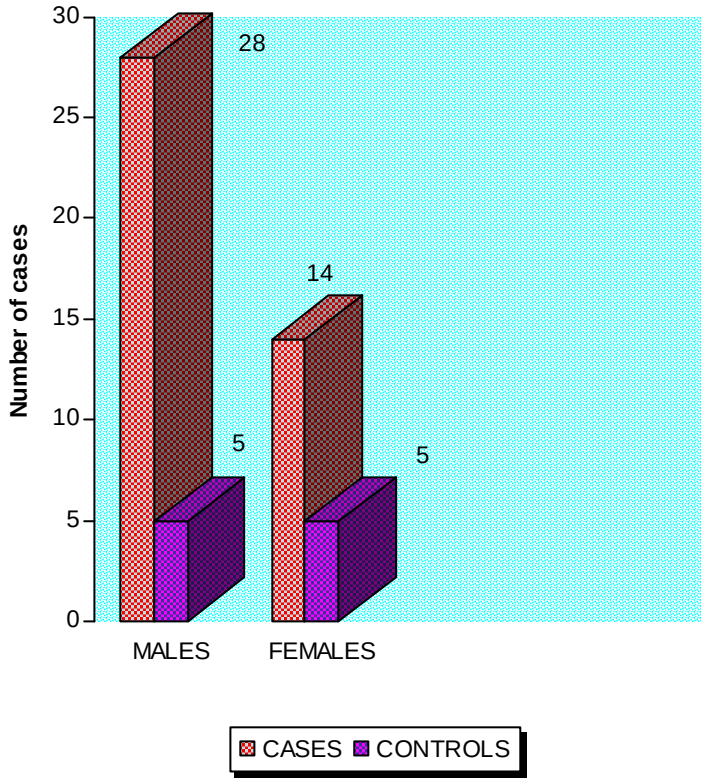
In our study there were 28 male CRF patients and 14 Females CRF patients; the control group consisted of 5 males and 5 females. Details are provided in table .2 and figure 2.

Table 2: Distribution of study subjects with reference to gender:

Gender	Study Cases		Control Cases		Total	
	No	%	No	%	No	%
Males	28	66.7	5	50	33	78.6
Females	14	33.3	5	50	19	21.4

'p' = 0.2647 (Not significant)

There was no statistical difference as for as the gender status of the study and control group.



Details of selected characteristics of the study group is given below:

Table 3 : PARAMETERS

Parameters	Study			Controls	
	Range	Mean	S.D	Range	Mean	S.D
Blood sugar mg%	68-126	101.5	15.8	96-120	109.4	806
Urea mg%	68-252	143.8	46.1	30-38	35.3	2.8
Sr.Creatinine mg%	2.2-13.8	6.5	2.83	0.8-1.1	0.93	0.12
Hb. Gm%	5.2-10.9	8.75	1.31	13.0-14.2	13.6	0.4
C.R.P mg%	0.10-3.02	1.22	0.99	0.07-1.1	0.08	0.01
Sys. B.P mmHg	1.10-2.40	16507	23.8	100-130	119	9.9
Dias. B.P. mmHg	70-140	104	13.3	70-86	77.2	5.5

The hs CRP levels in the study group were significantly elevated when compared to the control group. (continued)

Study group – Mean – 1.22 md/dl (12.2 mg/l) with S.D. of ± 0.99

The control group - Mean – 0.08 mg/dl (0.8 mg/l)with a S.D. of ± 0.01

The mean Hb% in this study group was 8.75 gm% with S.D. of ± 1.31 gm% which was significantly lower than the control group – (13.6 gm% S.D. of ± 0.4).

During our study there was no mortality.

Table 4: MEAN CRP LEVELS IN CASES AND CONTROLS

The CRP level varied from 0.10 – 3.02mg% in the study group whereas in the control group it varied from 0.07 – 1.1mg%.

The Mean and SD among the study group is given below

	CRP Levels (mg /dl)				
	Range	**Mean**	**S.D.**	**'p' value**	**Significance**
Cases	0.10 – 3.02	1.22	0.99	0.0001	Significant
Controls	0.07 – 1.1	0.08	0.01		

The mean CRP level in the study group was 1.22mg% with SD of ± 0.99.

The mean CRP level in the control group was 0.08 (<0.10) with SD of ± 0.01.

This was statistically significant. It was also found the CRP level was independent of serum creatinine.

Table 5 : RETINOPATHY

Retinopathy	Study		Without CVD		With CVD	
	No	%	NO	%	No	%
Normal	1	2.4	1	6.7	0	-
Grade I	3	7.1	2	13.3	1	3.7
Grade II	24	57.1	10	66.7	14	51.9
Grade III	14	33.3	2	13.3	12	44.4

In our study about 24 patients (57.1%) were suffering from Grade – II retinopathy and 14 patients (33.3%) were suffering Grade – III retinopathy at the time of admission.

This was statistically significant.

Table 6: RETINOPATHY AND MEAN CRP LEVELS IN CASES

Retinopathy	CRP Levels			
	Mean	**S.D.**	**'p' value**	**Significance**
Normal	0.14	-	0.0001	Significant
Grade I	0.65	0.8		
Grade II	1.14	0.98		
Grade III	1.56	1.01		

The CRP levels correlated positively with the severity of retinopathy in CRF patients and it was statistically significant.

Table 7: Anaemia (Moderate to severe - <10gms%)

Hb %	Study		Controls		'p' value	Significance
	No	%	No	%		
14.3	10		100		0.0001	Significant

dL with SD of ± 0.45. The statistical analysis was very much significant (p - 0.0001).

DISCUSSION

Despite the recent considerable improvements in Renal replacement therapy, cardiovascular disease still remains the main cause of morbidity and mortality in CRF patients[10]. It is evident from recent studies [(Lidner[15], et al (1974); Stenvinkel[29], et al (1999); and Cheung[5], et al (2000)]; that the atherosclerotic process is accelerated in CRF patients. A number of 'non traditional' risk factors for CVD, such as homocysteinemia, oxidative stress,

vascular calcification, malnutrition and inflammation are commonly found in CRF patients[2].

Evidence from experimental and clinical studies has shown that inflammation in general, and CRP specifically, may contribute directly to pathogenesis of atherosclerosis and its complications both in general community and in patients with CRF[20].

Recent studies [Zimmermann[33], et al, Yeun[31], et al, Owen[18], et al and Yeun, Kaysen] recognized that about 30-50% of predialysis, HD and PD (CRF) patients suffered from CVD and they had elevated CRP levels.

In the present study that the mean hsCRP level was 1.22 mg/dL in CRF patients which was significantly higher than the mean CRP level of the control group 0.08 mg/dL (<0.10mg%). The mean CRP level of 1.22mg/dL in our CRF patients was definitely higher than the reference value of 0.3mg/dL for high cardiovascular risk (American Heart Association guidelines)[19].

Elevated CRP as an independent risk factor for cardiovascular disorders was confirmed by various authors [Ridker[22], et al (2002); Pradhan[21], et al (2002); and Albert[1], et al (2002)]. It was applicable to both men and women and across all age levels as well as to diverse populations. Elevated CRP levels in the present study was independent of age and gender. Thus the present

observation of elevated hsCRP levels in CRF patients concurred with early published report.

The most significant process that correlates with inflammation is atherosclerotic CVD as evidenced by elevated CRP. Recent studies have established that the levels of proinflammatory cytokines such as IL-6 or acute phaseproteins like CRP predict CVD (Ridker[23], et al, 1997).

Heinrich[8], et al (1995) concluded in their study that, CRP may be a marker for severity and progression of atherosclerotic processes in the vessels. In the present study out of the 42 CRF cases 24 (57.1% were suffering from grade II retinopathy and 14 patients (33.3%) were suffering from Grade III retinopathy. This was statistically very much significant compared to the control group. Also, the CRP levels in CRF patients correlated positively with the severity (Grade) of retinopathy. The mean CRP level for patients with Grade II retinopathy was 1.14mg/dL and for Grade III 1.56mg/dL. In view of significantly elevated CRP levels in patients with CRF, and its correlation with increasing severity in retinopathy it is likely that it is a marker for ongoing vessel changes.

Echocardiographic findings in the CRF patients of our study

In the present study the echocardiographic evaluation revealed that out of the 42 CRF patients only 15 had normal cardiac function and 27 patients

(64.3%) had cardiovascular abnormalities in the form of left ventricular hypertrophy, ischaemic changes (hypokinesia of wall/septum) LV dysfunction and pericardial effusion. The mean CRP level in CRF patients without CVD was 0.18 mg/dL whereas for CRF patients with CVD was 1.96 mg/dL which was significantly higher. An association between elevated CRP and CVD were shown by earlier workers from different parts of the world (Stenvinkel[29], et al 1999). In a recent updated metaanaylsis including 2,557 cases, Danesh[6], et al 2000, reported that the combined risk ratio for coronary heart disease was 1.9 times higher in the patients who had the highest CRP. Elevated CRP has been shown to predict cardiovascular mortality by (Yeun[32], et al 2000; Zimmermann[33], et al 1999). The same conclusion was given by Bergstorn[2], et al 1995 and Iseki[9], et al 1999.

Anaemia is commonly seen in CRF and its severity parallels roughly with the degree of renal failure[16]. Similar observations were made among CRF patient of the present study. It was found that 36 of the 42 CRF (85.7%) patients suffered from anaemia, which was statistically significant. The mean hsCRP levels of this anaemic CRF patients was 1.39mg/dL which was very high (8 times higher) than the mean hsCRP level of 0.18mg/dL in CRF patients without anaemia. The severity of anaemia indirectly correlated with the severity

of CRF. Interestingly it is to be noted here that anaemia per se does not influence CRP levels[3].

An attempt was made to find out whether any association exists between severity of albuminuria and serum levels of hs-CRP. In the present study severity of albuminuria (semiquantitative method) showed direct relation to severity of CRF. Of the 42 patients 20 had albuminuria of 1+, 17 had 2+ and 3 had 3+. The prevalence of albuminuria was (95.2%) in the CRP patients. And the mean CRP levels showed a linear relation with the degree of proteinuria, indirectly implicating the severity of CRF.

The present study brought out significantly elevated hsCRP levels in cases of CRF and association between hsCRP and albuminuria, anaemia, retinopathy and cardiovascular complications, which were supported by an array of published literature from different parts of the world. Time has come to consider whether any infective etiology could contribute for the onset and worsening of chronic kidney disease.

The areas for future research are suggested below;

1. Usefulness of antimicrobial therapy to arrest or delay the progression of CRF.
2. To identify how frequently to estimate hsCRP levels in CRF patients.

3. The identification of newer pathogenic organisms as contributory factors for the development of cryptogenic CRF.

CONCLUSIONS

- The hsCRP levels among CRF patients was independent of age, gender or serum creatomy levels.
- The hsCRP levels was significantly elevated in CRF patients (Range 0.10 – 3.02mg%, mean 1.22mg% with SD ± 0.99mg%) when

compared to healthy controls (Range 0.07 – 1.1mg% mean 0.08 with SD ± 0.01).

- The hsCRP levels were elevated significantly in those CRF patients with cardiovascular complications (Range 0.13 – 3.02mg% mean 1.96 with SD of ± 0.45mg%) when compared with those without cardiovascular complications (Range 0.10 – 0.3mg% mean 0.18 with SD of ± 0.06mg%) there by indicating that elevated hsCRP is a marker of development of cardiovascular morbidity.
- The present study has brought out an association between elevated hsCRP and degree of albuminuria, haemoglobin levels, severity of retinopathy as well as cardiovascular morbidity.
- Areas for futures research and recommendations were identified.

RECOMMENDATIONS / SUGGESTIONS

Chronic renal failure is characterized by exceptionally high mortality rate, much of which is the result of cardiovascular disease. Recent studies demonstrate that chronic inflammation, as evidence by increased levels of pro-inflammatory cytokines and CRP is a common feature in CRF patients.

At the time of diagnosing CRF in a patient, the clinician is at dark about the duration of the renal failure in the patient and his current morbidity status. When the clinician is at dilemma about which patient to choose for intensive therapy, the hs-CRP estimation gives the vital clue. It is the best single available parameter because of its stability and reproducibility over time and above all its ability to predict the prognosis.

1. It is hereby suggested that hs-CRP estimation should be included in the routine evaluation of all CRF patients.

2. CRF patients with elevated hsCRP should be adequately counseled regarding their proneness to develop cardiovascular complications.

3. In this era of consumer litigations, hs-CRP estimation in CRF patients helps the clinician to boldly submit a patient with high CRP levels for extensive cardiac evaluation and to start necessary preventive measures /treatment.

4. CRF patients with elevated hsCRP require detailed cardiological workup and addition of therapeutic agents to prevent cardiovascular mortality and morbidity.

SUMMARY

In the present study a group of 42 newly detected CRF patients (28 males and 14 females) were selected and 10 normal individuals (5 males and 5

females) were selected as control group after careful application of inclusion and exclusion criteria. They were subjected to detailed sociodemographic clinical and systemic examination and routine laboratory tests. The study subjects underwent ultrasonographic evaluation. A single time fasting blood sample was obtained and hs-CRP assay was done. Then they underwent funduscopic and echocardiographic evaluation. The results obtained were statistically analysed using Epi info-2002.

CRF patients are susceptible to cardiovascular morbidity and mortality. Various risk factors have been identified in them. One another risk factors was elevated hsCRP the present study has made an attempt to find out hsCRP levels in the selected CRF patients and correlate the levels with albuminuria, haemoglobin levels, severity of retinopathy and cardiovascular complications.

The hsCRP levels were significantly elevated in the CRF patients (Mean 1.22mg% SD ± 0.99mg%) than the control (Mean 0.08mg% SD ± 0.01mg%) and it was independent of age, gender and serum creatinine levels. However elevated hsCRP correlated with albuminuria, haemoglobin levels, severity of retinopathy and cardiovascular morbidity.

The hsCRP measurement may well prove an exception in view of its robustness, its relative stability in individuals over time, and most importantly its ability to add to the cardiovascular risk information.

Areas for future research and recommendation were identified.

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MASTER CHART

Sl. No.	Case Control	Age	Sex	Blood Sugar	Urea	Hb%	Sr.Cr	Retinopathy Gr	CRP	ECH	Echo	BP.(on Adm)	Urine Alb
1	CN	22	M	108	36	14	0.9	-	0.09	N	N	110/70	-
2	CN	24	F	112	38	13.6	0.8	-	0.09	N	N	100/70	-
3	CN	45	M	98	30	13.4	0.8	-	0.08	N	N	120/80	-
4	CN	42	F	120	32	13	1	-	0.07	N	N	120//80	-
5	CN	35	M	96	36	14.2	0.9	-	0.09	N	N	110/70	-
6	CN	38	F	102	35	13.2	1	-	0.08	N	N	120/76	-
7	CN	56	M	114	39	14	1.1	-	0.09	N	N	130/80	-
8	CN	53	F	108	34	13.6	0.9	-	0.07	N	N	120/80	-
9	CN	66	F	120	35	13.2	0.8	-	0.09	N	N	130/80	-
10	CN	68	M	116	38	13.8	1.1	-	0.08	N	N	130/86	-
11	CS	50	M	126	218	10.4	10.1	III	0.17	LVH	N	150/90	1+
12	CS	23	M	68	72	8.8	3.8	-	0.14	N	N	110/70	-
13	CS	50	M	80	125	9.6	5.2	II	1.69	LVH	HID	160/90	1+
14	CS	52	F	110	130	8.8	3.8	III	0.09	LVH	HD	160/90	2+
15	CS	60	M	68	118	5.2	3.8	II	0.83	N	HID	240/140	2+
16	CS	60	M	100	252	9.8	12.3	III	2.37	LVH	HD	190/110	2+
17	CS	53	M	117	68	9.2	3	III	2.06	LVH	HID	230/140	1+
18	CS	41	F	75	170	9.6	9.4	II	0.09	LVH	N	170/100	1+

Sl. No.	Case Control	Age	Sex	Blood Sugar	Urea	Hb%	Sr.Cr	Retinopathy Gr	CRP	ECH	Echo	BP.(on Adm)	Urine Alb
19	CS	37	M	78	163	10.2	11	III	0.21	LVH	N	200/120	2+
20	CS	65	F	102	75	8.4	2.8	III	0.13	LVH	H	200/100	2+
21	CS	65	M	88	60	10.6	2.2	II	0.26	N	N	140/90	-
22	CS	42	M	82	161	7.4	3.2	II	2.13	N	HID	190/120	2+
23	CS	65	F	73	122	8.8	4	III	2.56	N	HID	200/130	3+
24	CS	33	F	112	98	10.9	3.2	I	0.12	N	N	160/100	1+
25	CS	55	M	114	104	8.2	4.4	II	1.91	LVH	HD	160/90	1+
26	CS	55	M	112	142	9	5.6	III	3.01	LVH	HID	170/110	2+
27	CS	67	M	108	178	6.8	8.8	III	1.78	LVH	HID	160/110	2+
28	CS	49	F	112	168	9.6	4.6	II	0.29	N	D	150/100	1+
29	CS	54	M	108	196	8.6	8.3	III	1.09	LVH	HID	170/120	2+
30	CS	31	F	118	178	9	8.9	II	0.13	N	N	160/100	1+
31	CS	46	F	98	132	9.6	3.9	II	0.14	N	N	170/100	1+
32	CS	27	M	104	154	8.8	13.8	III	2.16	LVH	HID	150/120	3+
33	CS	52	M	108	130	8	9.1	II	0.16	N	N	130/100	1+
34	CS	50	M	110	160	6.4	9.3	II	3.02	N	ID	140/100	2+
35	CS	46	M	118	136	8.4	4.8	II	1.33	LVH	HID	170/100	2+
36	CS	40	M	108	164	9.3	6.3	III	2.13	LVH	HE	170/100	2+
37	CS	60	M	73	184	9.5	5.9	II	2.08	LVH	HE	160/100	3+
38	CS	48	F	117	78	7	4.7	II	1.76	LVH	HID	170/100	2+
39	CS	36	F	110	106	9.8	6.8	II	0.3	LVH	N	150/100	1+

Sl. No.	Case Control	Age	Sex	Blood Sugar	Urea	Hb%	Sr.Cr	Retinopathy Gr	CRP	ECH	Echo	BP.(on Adm)	Urine Alb
40	CS	45	M	96	176	8.6	8.8	II	1.83	LVH	HD	170/100	1+
41	CS	53	M	104	98	9.6	4.2	I	1.57	LVH	HE	150/100	1+
42	CS	48	F	112	94	9.8	6.2	II	0.26	N	N	140/100	2+
43	CS	53	M	118	124	8.2	6.8	II	2.11	LVH	HD	160/110	2+
44	CS	42	F	87	242	5.8	9.1	III	2.07	LVH	HD	170/100	2+
45	CS	40	F	98	163	6.8	7.8	II	2.23	LVH	HED	150/100	1+
46	CS	54	M	96	205	7.2	7.6	II	2.71	LVH	HED	160/100	1+
47	CS	44	F	96	154	9.2	6.8	II	0.12	N	N	150/100	1+
48	CS	38	M	118	120	7.8	4.3	I	0.26	LVH	N	160/100	2+
49	CS	58	M	119	103	8.6	4.5	II	1.66	LVH	HD	180/100	1+
50	CS	46	M	108	168	10.2	6.8	II	0.13	N	N	160/100	1+
51	CS	51	M	118	204	9.6	11.3	III	1.95	LVH	HID	170/120	1+
52	CS	56	M	98	146	10.4	5.6	II	0.16	N	N	160/100	1+

CN – control
CS - Case

ECG

N- Within normal limits

H - LVH

Echo

N- Normal LV function
I - Ischaemic changes (Wall motion anomaly / Global hypokinesia)
D - LV Dysfunction
H - LVH
E - Pericardial Effusion

PROFORMA

(CRP in CRF with cardiovascular complications)

Name : **IP.No:**

Age/Sex:

Address:

Admitted for: **duration**

Chest pain **Y/N** **Past History**

Palpitation **Y/N** **HT**

Dyspnoea **Y/N** **DM**

Pedal oedema **Y/N** **P.TB**

Others **IHD**
Others

Personal History **Smoking** **Y/N** **Alcohol Y/N**

Family History

Vitals (on adm) **PR** **/ mt** **BP** **/ mmHg** **RR** **/mt** **temp**

CVS

RS

ABD/

CNS

Investigations

Urine ALB - **Sug** **Dep** **spot PCR (Pr** **: Cr)**

Blood – TC **DC-P:** **L:** **M:** **E** **Hb%**

Blood sugar **Urea** **CR** **Electrolytes** **Na^+** **K^+** **Cl^-** **HCo3-ECG**

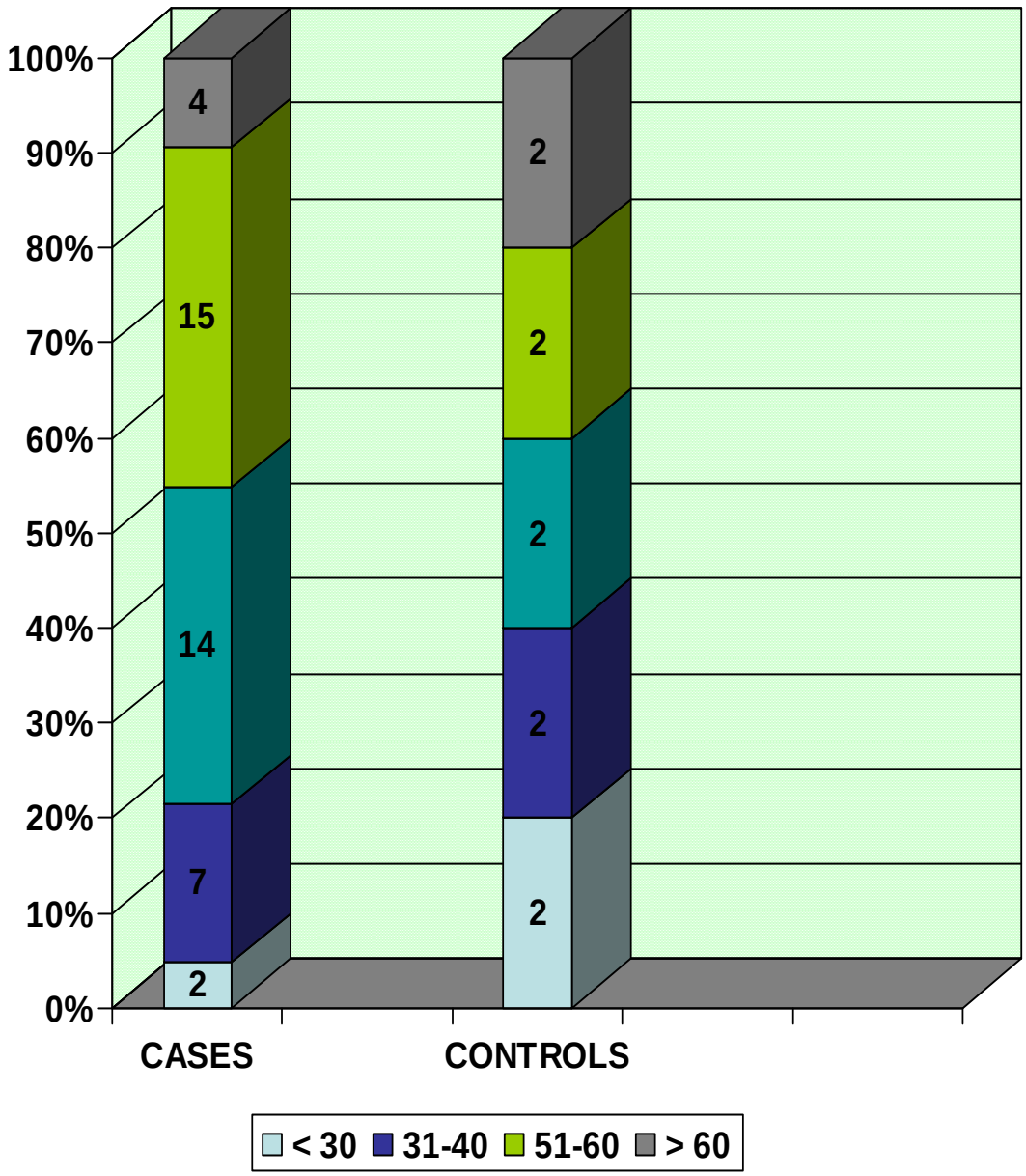
ECHO

USG Abd **hs-CRP -**

Ophthalmology

Others

AGE DISTRIBUTION IN CASES AND CONTROLS



SEX DISTRIBUTION IN CASES AND CONTROLS

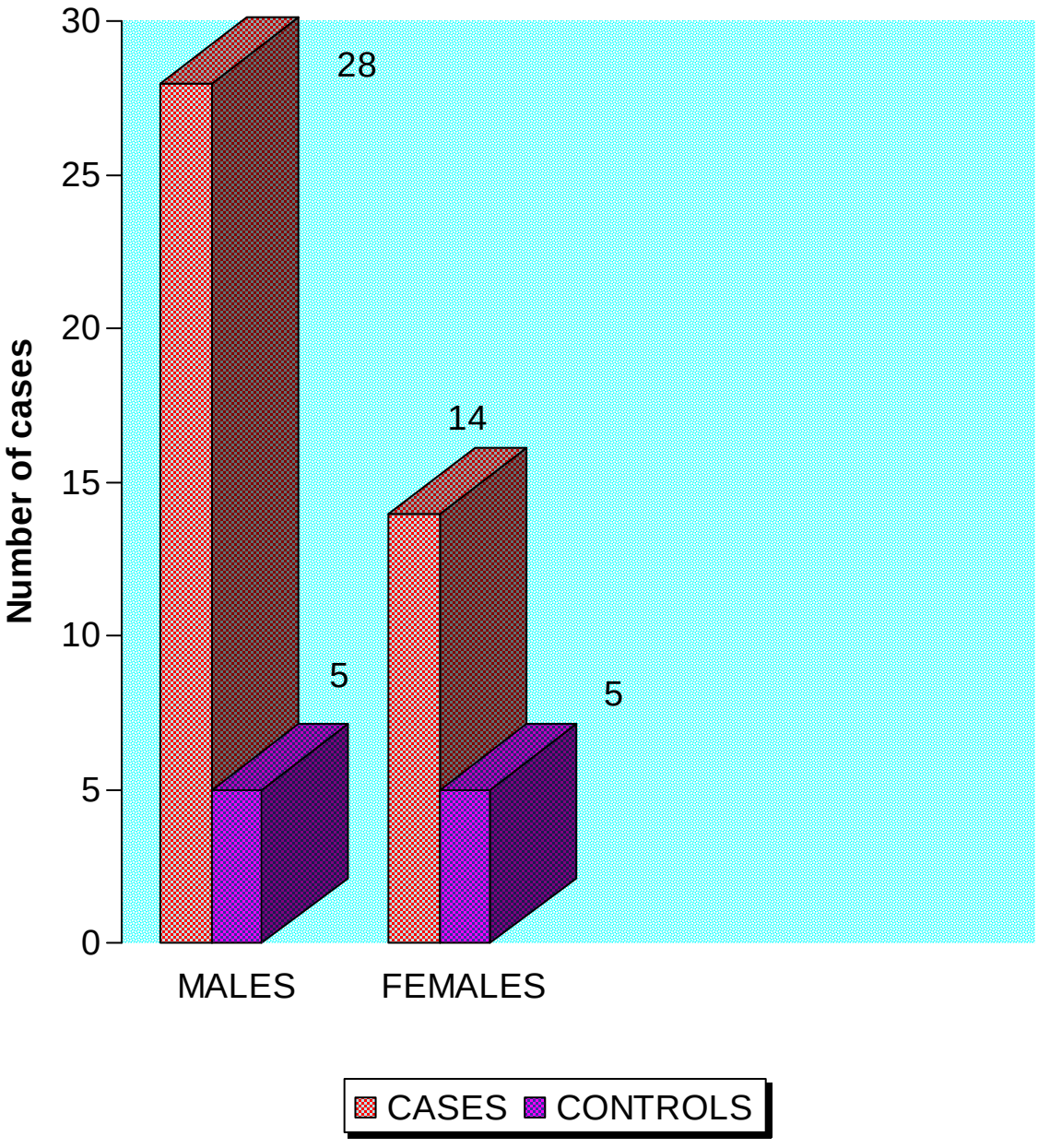


Figure – 3

CRP LEVELS IN CASES AND CONTROLS

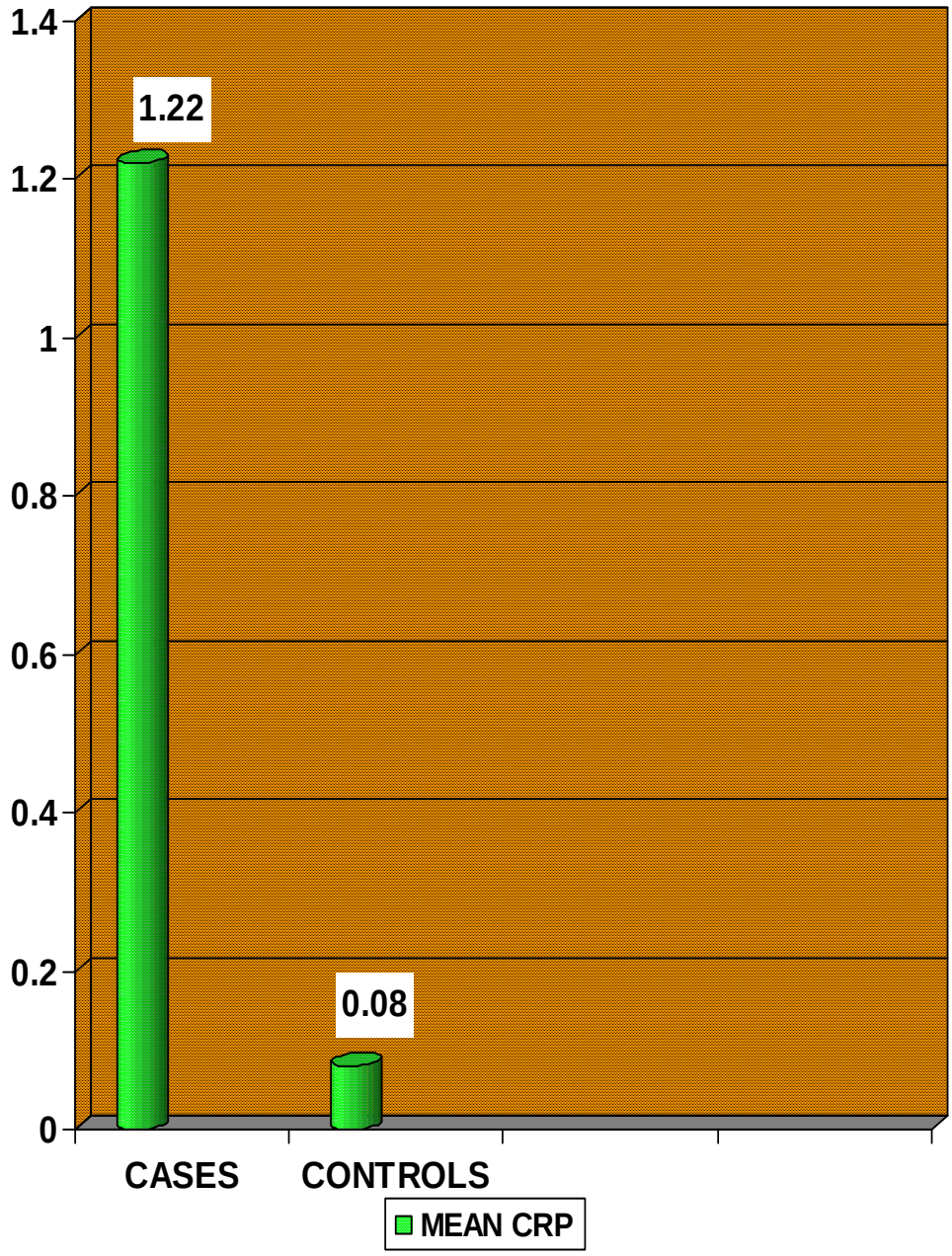


Figure – 4
RETINOPATHY AND MEAN CRP LEVELS IN CASES

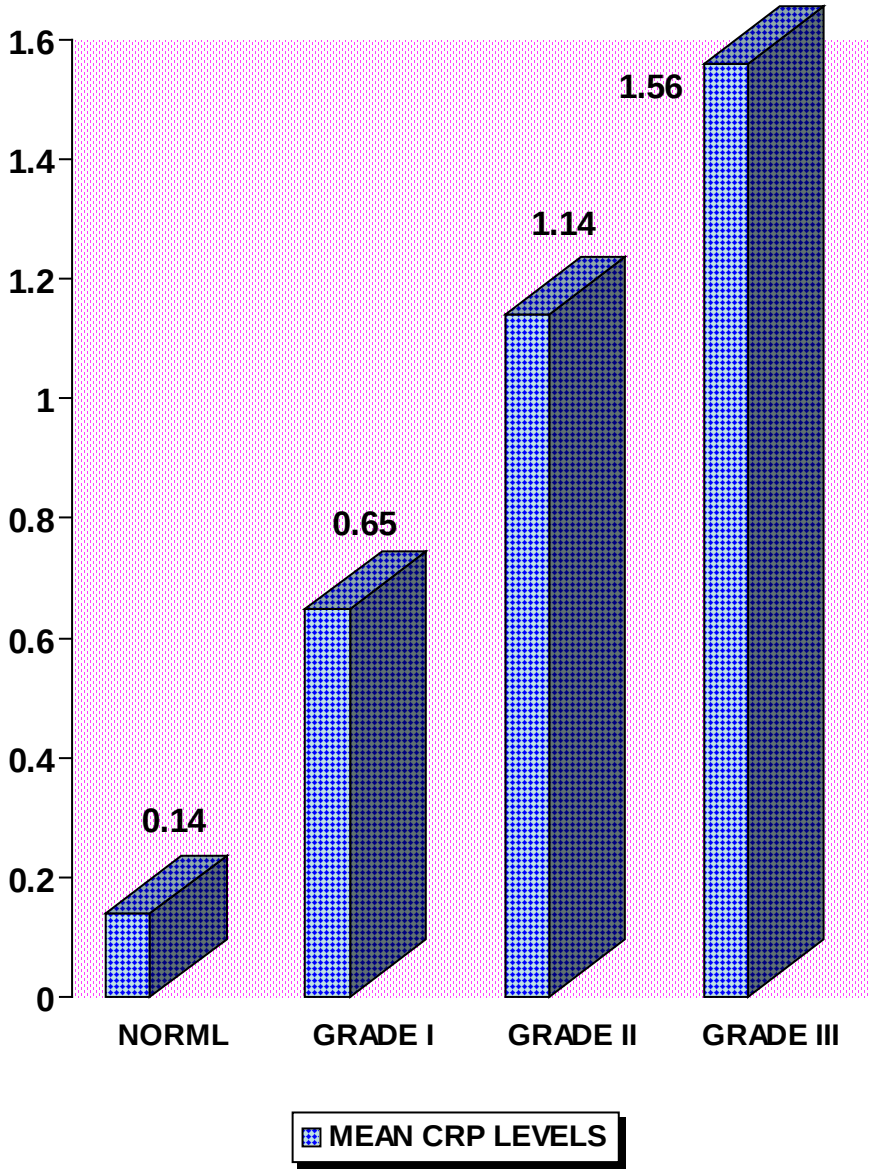
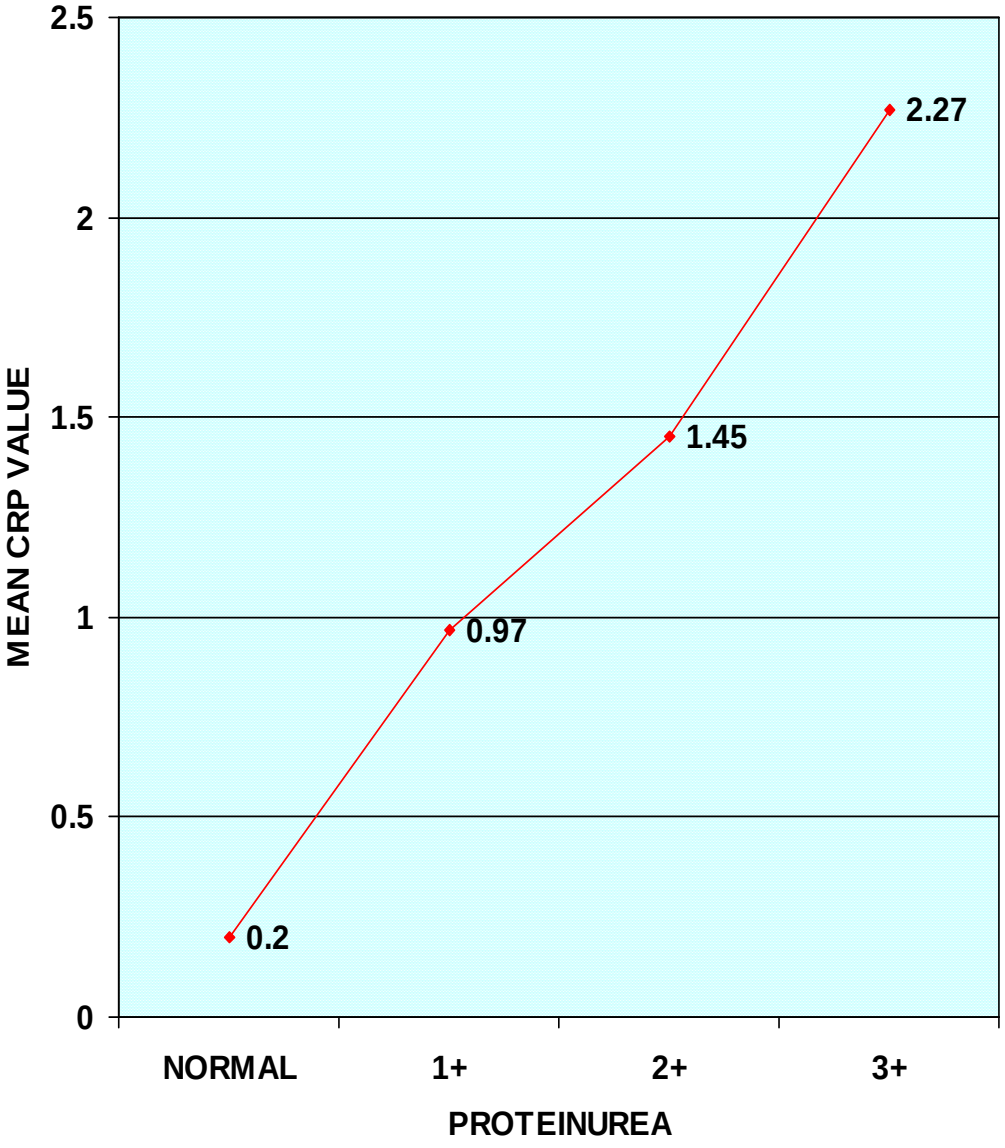


Figure – 5
PROTEINURIA AND MEAN CRP LEVELS IN CASES



ANAEMIA AND CRP LEVELS