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Published paper's title : CLINICAL STUDY: Metabolic Syndrome in Chronic kidney disease and normal adults: A comparitive study

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Clinical Study

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Metabolic Syndrome in Chronic kidney disease and normal adults: A comparitive study

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Declaration

The Declaration of the authors for publication of Research Paper in Asian Journal of Modern and Ayurvedic Medical Science (ISSN 2279-0772) We Neha Srivastava[1*] , R.G.Singh[2*], Usha[3**], Alok kumar[4***], Shivendra Singh[5*], Abhishek Kumar[6****] the authors of the research paper entitled CLINICAL STUDY: Metabolic Syndrome in Chronic kidney disease and normal adults: A comparitive study declare that , We take the responsibility of the content and material of our paper as We ourself have written it and also have read the manuscript of our paper carefully. Also, We hereby give our consent to publish our paper in ajmams , This research paper is our original work and no part of it or it's similar version is published or has been sent for publication anywhere else.We authorise the Editorial Board of the Journal to modify and edit the manuscript. We also give our consent to th publisher of ajmams to own the copyright of our research paper.

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ABSTRACT :

***Background**:* Chronic kidney disease (CKD) patients have higher HOMA-IR index compared to otherwise healthy metabolic syndrome controls. The aim of this work was to compare the biochemical profile, symptoms and signs of Metabolic Syndrome (MS), between chronic kidney disease patients and non-chronic kidney disease metabolic syndrome subjects, using the World Health Organization criteria.

Methods: it is a case-control study. Among the CKD patients, 20 patients fulfilling the criteria for metabolic syndrome were included in the study and compared with the age, sex matched otherwise healthy metabolic syndrome subjects. Individuals aged > 18 years and above were included in the study. Fasting glucose, anthropometric measurements, lipid estimations, and biochemical parameters were done in all the participants, who fulfilled the WHO criteria of metabolic syndrome.

***Results**:* All the cases belonged to stages 3 & 4 of CKD. Presence of symptoms among cases were due to their CKD condition, waist hip ratio (W/H) ratio is significantly higher in cases than controls (P<0.05). Both systolic as well as diastolic blood pressure is higher in cases (M 142±19.6, F141 ± 11.3).There was significant difference in the HDL and LDL level among cases and controls HDL level being higher in females among cases(F 46.5±8.31) , whereas LDL level was higher in females among controls(F 111.3±55.9). Fasting insulin level was significantly lower among cases in both females and males (Case; M 42.6±8.3,F32.04+14.4; Controls;M56.5±6.6, F 57.5±9.4) similarly HOMA-IR values were significantly lower in cases than controls(Case M7.9±0.86, F7.4±3.7,ControlsM13.4±3.5 F12.1±3.4).None of the comparitive studies, between CKD and otherwise healthy metabolic syndrome cases have reported higher HOMA-IR levels in controls than CKD patients. HSCrp level was higher in cases than controls (case M 9.3±9.6 F5.9±7.2; Controls M2.5±3.2, F1.9±2.4). Sodium and Potassium levels were significantly higher in cases than controls. Calcium levels were higher in controls than cases, alkaline phosphatase is significantly higher in cases than controls.

***Conclusions*:** Though both the cases and controls, are insulin resistant, there is significant difference between HOMA –IR index among cases and controls , HOMA-IR value is higher among controls than CKD patients

KEYWORDS *:* Metabolic Syndrome, insulin resistance, HsCRP, Chronic kidney disease, HOMA-IR

INTRODUCTION:

Metabolic syndrome is a medical syndrome which causes increased risk of cardio vascular disease and diabetes, Metabolic Syndrome (MS) refers to a clustering of metabolic risk factors including central obesity, glucose intolerance, hyperinsulinemia, low HDL cholesterol, high triglycerides and hypertension(1). The features of metabolic Syndrome include, central obesity, hypertension, dyslipidemia , insulin resistance. The World Health Organization proposed a definition of MS in 1999(2) the metabolic syndrome was associated with kidney disease even in subjects without major classical risk factors for chronic kidney disease (3). There is twice the possibility to die, and thrice the possibility to develop myocardial infarction or stroke compared respectively with people without it (4). There is five fold greater risk of developing type 2 diabetes (If not already present) (5) CKD have been reported as, 12th leading cause of death and 17th cause of disability. (6)

CKD has also become a public health problem because it affects a considerable proportion of adult population and is a major risk factor for cardiovascular disease and premature death. Many epidemiological studies have documented diabetes and hypertension (HTN) are major risk factors for the development and progression of chronic kidney disease and microalbuminuria (7,8,9,10). It cannot be excluded that the identification of additional risk factors, such as high C-reactive protein levels (11) soon will lead to a broader definition of the syndrome in various studies.

STUDY DESIGN:

It is a case control study, conducted at the Nephrology OPD of Sir Sundar Lal Hospital, Banaras Hindu University, Varanasi. 20 CKD cases included were of age 18 years and above, BMI between, 18-25 Kg/m^2. CKD due to any cause, and Serum creatinine upto 5mg%. Patients excluded were with acute inflammatory illness e.g., AIDS, active hepatitis B or C, Malignancy, Previous kidney transplantation, current participation in drug

protocol. Patients of diabetic mellitus, and patients on dialysis, on standard criteria having metabolic syndrome as per WHO criteria, have been included in the study, and 20 otherwise normal subjects having metabolic syndrome, have been included in the study, with age of 18 years and above. Informed consent was obtained from all participants.

The World Health Organization criteria (1999) require the presence of any one of diabetes mellitus, impaired glucose tolerance, impaired fasting glucose or insulin resistance, AND two of the following

- Blood pressure: ≥ 140/90 mmHg
- Dyslipidemia: triglycerides (TG): ≥ 1.695 mmol/L and high-density lipoprotein cholesterol (HDL-C) ≤ 0.9 mmol/L (male), ≤ 1.0 mmol/L (female)
- Central obesity: waist:hip ratio > 0.90 (male); > 0.85 (female), or body mass index > 30 kg/m^2
- Microalbuminuria: urinary albumin excretion ratio ≥ 20 µg/min or albumin:creatinine ratio ≥ 30 mg/g

Fasting blood sample was taken for glucose test and same sample was used to calculate insulin levels by ELISA method, utilizing Biosource INS-EASIA KAP1251 and values were used to calculate insulin resistance by HOMA IR method. IR was defined as HOMA-IR equal to or greater than 3.8 (12)

Biochemical tests were done using, COBAS Integra 400 plus fully automatic analyzer closed system (Roche Diagnostic, GmbH, Manheim Germany), utilizing Kit Supplied by Roche Diagnostic.

HsCRP test was conducted using Nephelometry method.

Haemoglobin was measured, Five part differential count fully automatic analyzer (Span Company) utilizing Kit of Span Company.

Electrolyte was measured, using E-Lite (Na^+, K^+, Cl^- analyzer) Electronic co-operation of India.

Anthropometric measurements including weight, height, waist, and hip measurements were obtained using standardized techniques (13) The blood pressure was recorded in the right upper limb in the sitting position, to the nearest 2mmHg, using a mercury sphygmomanometer (Diamond Deluxe BP apparatus, Pune , India).

Ethical clearance:

The protocol of the study is approved by the institutional Ethical committee of Institute of Medical Sciences, Banaras Hindu University, Varanasi, and all the patients gave written consent before entering the study.

The following standard definitions were used:

Body Mass Index (BMI): Was calculated using the formula: weight (Kg)/height $(m)^2$

Waist Circumference:

The waist was measured using a non-stretchable fiber measuring tape. The subjects were asked to stand erect in a relaxed position with both feet together on a flat surface, one layer of clothing was accepted . Waist girth was measured as the smallest horizontal girth between the costal margins and the iliac crests at the minimal respiration.

Hip circumference:

Hip measure was taken as the greatest circumference at the level of

greater trochanters (the widest portion of the hip) on both the sides. Measurements were made to the nearest centimeter.

Waist and Hip ratio (WHR): Calculated by dividing waist circumference (cm) by hip circumference (cm)

Blood pressure: Recorded in the sitting position in the right arm, to the nearest 1mmHg, using the mercury sphygmomanometer. Two readings were taken 5 min apart and the mean of the two were taken as the blood pressure.

Insulin resistance: Calculated using HOMA IR method, fasting sample was collected, out of which fasting sugar and insulin was calculated. Any value above 2.5 was taken as insulin resistance.

Statistics: Statistical analyses were performed using SPSS version 16.0 software (SPSS Inc, Chicago, IIIinois). P-value <0.05 was considered significant.

Results:

Table1: Presenting symptoms in case and controls in metabolic Syndrome.

Symptoms	**Cases (n=20)** **n/%**	**Controls(n=20)** **n/%**
Increased thirst	0 (0)	20 (100)
Increased hunger	0 (0)	7 (33.3)
Frequent urination	5 (25)	20 (100)
Weight loss	13 (65)	20 (100)
Fatigue & weakness	20 (100)	6 (28.6)
Blurred vision	0 (0)	8 (38.1)
Headaches	13 (65)	3 (14.3)
Los of appetite	20 (100)	2 (9.5)

All cases in Chronic kidney disease complained of loss of appetite, weakness and fatigueness, 65 % patients reported weight loss head ache, whereas only 5 % complained of increased frequency of urination.

In the control group all the patients complained of increased thirst, weight loss whereas around 1/3rd controls complained of weakness, blurred vision, and increase in hunger, polyphagia.

Table 2: Comparison of Demographic and Clinical profile between cases and controls in males and females:

			MALES (n=8)			FEMALES (n=12)		
Characteristics	**Cases Mean (n=8) ±SD (range)**	**Controls (n=8) Mean ±SD (range)**	**t-value**	**p-value**	**Cases (n=12) Mean ±SD (range)**	**Control (n=12) Mean ±SD (range)**	**t- value**	**p- value**
Age (years)	50.25 ± 5.4 (46-60)	50.71 ± 7.7 (46-62)	0.136	NS	44.25 ± 8.0 (30 -60)	44.50 ± 11.3 (27- 60)	0.96	NS
BMI (Kg/m^2)	22.48 ± 4.9 (15.6-27.6)	23.28 ± 1.02 (20.9 – 23.7)	0.42	0.683	22.6 ± 1.7 (19.5 – 25.4)	22.59 ± 4.1 (16.4 – 26.7)	1.6	0.129
W/H	0.93 ± 0.1 (0.8-1.1)	0.94 ± 0.04 (0.85 – 0.9)	0.34	0.743	0.97 ± 0.15 (0.84 – 1.2)	0.81 ± 0.07 (0.73 - 0.89)	3.5	P<0.05
SYSTOLIC BP (mm Hg)	142 ± 19.6 (116-180)	123 ± 6.2 (118 – 135)	2.4	P<0.05	141 ± 11.3 (130 – 160)	114.30 ± 15.4 (88 – 135)	4.9	P<0.001
DIASTOLIC BP (mmHg)	90.25 ± 10.7 (72-106)	80.14 ± 5.5 (80 – 94)	2.3	P<0.05	88 ± 6.2 (80 – 94)	77 ± 7.8 (60 – 89)	3.9	P<0.01

Waist hip ratio was noticed to be higher in patients of CKD, and where as blood pressure, both diastolic and systolic was found to be higher in male patients, which was statistically significant in patients of CKD.

Table III: Comparison of biochemical profile among cases and controls in males and females:

	MALES (n=8)				FEMALES (n=12)			
Characteristics	**Cases Mean (n=8) ±SD (range**	**Controls (n=8) Mean ±SD (range)**	**t-value**	**p-value**	**Cases (n=12) Mean ±SD**	**Control (n=12) Mean**	**t-value**	**p-value**

	)				(range)	±SD (range)		
TG (mg/dl)	117.65 ± 70.6 (61-277.1)	124.9 ± 17.8 (84.5 – 131.7)	0.3	0.795	108.3 ± 27.6 (70.9 – 142.4)	105.5 ± 63.5 (59.9 _ 187.7)	0.14	0.891
CHO (mg/dl)	155.3 ± 35.0 (115.0-224.0)	180.9 ± 35.8 (99.8 – 194.4)	1.4	0.185	147.3 ± 19.3 (114 – 187)	175.2 ± 66.4 (127.5 – 261.1)	1.4	0.173
HDL(mg/dl)	42.8 ± 9.4 (32.2 – 57.0)	42.3 ± 7.7 (24.8 – 45.2)	0.104	0.919	46.35 ± 8.31 (32.2 – 58.7)	39.6 ± 7.3 (34.3 – 49)	2.2	P<0.05
LDL(mg/dl)	80.5 ± 40.5 (23.6 – 152.5)	115.3 ± 27.4 (53.2 – 125.6)	1.9	0.077	82.18 ± 27.8 (38 – 121.8)	111.3 ± 55.9 (71.1 – 183.7)	2.2	P<0.05
VLDL(mg/dl)	24.6 ± 13.7 (12 – 55.4)	24.9 ± 3.5 (16.9 – 26.3)	0.6	0.954	23.5 ± 6.8 (14.1-31.6)	21.04 ± 12.7 (11.9 – 37.5)	0.6	0.547
Na(mmol/lit)	135.2 ± 5.2 (128.2-144.2)	137.43 ± 4.2 (128 – 139)	0.19	0.382	140.2 ± 4.0 (134 – 145)	137.14 ±0.54 (137-139)	3.03	P<0.05
K (mmol/lit)	4.5 ± 0.86 (3.3 – 5.7)	3.14 ± 0.15 (2.8 – 3.2)	4.1	P<0.001	4.8 ± 0.7 (3.9 – 6.2)	3.8 ± 0.1 (3.8 – 4.2)	5.6	P<0.01
P (mg/dl)	3.8 ± 1.1 (2.4 – 5.6)	3.8 ± 0.38 (2.9 – 3.9)	0.012	0.990	3.8 ± 1.1 (2.4 – 5.6)	3.8 ± 0.1 (3.8 – 4.2)	0.317	0.754

Ca (mg/dl)	8.6 ± 1.1 (7.2 – 10.2)	9.6 ±0.38 (8.7 – 9.7)	2.1	P<0.05	7.7 ± 1.7 (5.3 – 10.2)	8.7 ± 0.13 (8.7 – 9.2)	2.3	P<0.05
B-Urea (mg/dl)	84.6 ± 1.7 (51.8 - 127.0)	16.3 ± 1.7 (13.8-17.3)	7.7	P<0.001	71.3 ± 16.5 (47 – 90)	20.4 ± 7.3 (13.9 – 36)	10.31	P<0.001
S-Cr (mg/dl)	3.2 ± 0.5 (2.3 – 3.6)	0.7 ± 0.1 (0.64 – 0.78)	13.7	P<0.001	3.1 ± 0.7 (2.1 – 4.3)	0.5 ± 0.17 (0.29 – 0.82)	13.1	P<0.01
Alk Phosphatase (mg/dl)	329.1 ± 144.3 (81 – 535)	88.5 ± 27.8 (72.2 – 129.2)	4.3	P<0.01	169.4 ± 71.6 (68 – 243)	96.3 ± 10.1 (84.6 – 109.2)	3.8	P<0.001
Hb (gm %)	11.1 ± 1.5 (9.7 ± 13.5)	13.8 ± 1.2 (11 – 14.5)	3.7	P<0.05	8.32 ± 1.1 (7 – 10)	12.66 ± 1.1 (10 – 14)	10	P<0.001
TP (gm/dl)	7.4 ± 1.6 (3.7 – 8.9)	7.6 ± 0.5 (6.9 – 7.9)	0.24	0.814	7.2 ± 1.2 (6.2 – 8.5)	7.6 ± 1.8 (5.05-9.17)	0.40	0.694
Albumin (gm/dl)	4.2 ± 0.46 (3.5 – 4.7)	4.1 ± 1.4 (1.9 – 4.9)	0.17	0.867	4.3 ± 0.25 (4.0-4.7)	3.9 ± 0.70 (2.92 – 4.95)	0.78	0.449
Globulin (gm/dl)	3.3 ± 1.4 (0.2 - 4.7)	1.4± 0.4 (3.99 – 4.91)	1.7	0.120	2.7 ± 0.97 (1.9 – 4.2)	3.7 ± 1.1 (2.13 – 4.6)	1.8	0.086

Triglyceride, cholesterol, VLDL, phosphorus, total protein , albumin, globulin did not show any significant change in both groups in both sexes . However HDL was found to be significantly higher in patients of CKD, whereas LDL was significantly higher in subjects without CKD. Similarly Serum Na and K was found higher in females in CKD cases than non-CKD case.

The S.Calcium, was significantly low in CKD patients males as well as females. The blood urea and serum creatinine , alkaline phosphatase was significantly higher in CKD cases as expected.

Table IV: Insulin resistance in cases and controls:

	Males(n=16)				**Females(n=24)**			
Characteristics	**Cases (n=8) Mean ±SD (range)**	**Controls (n=8) Mean ±SD (range)**	**t-value**	**p-value**	**Cases (n=12) Mean ±SD (range)**	**Control (n=12) Mean ±SD (range)**	**t- value**	**p- value**
FBS (mg/dl)	95.11± 7.4 (82 – 106)	93.9 ± 16.5 (81.7 – 117.7)	0.2	0.864	89.63 ± 11.5 (78.2 – 117.2)	91.1 ± 6.9 (75.6 – 102.4)	0.4	0.695
FI (µU/mL)	42.6 ± 8.3 (33 – 58)	56.5 ±6.6 (48.5 – 64)	3.6	P<0.05	32.04 ± 14.4 (0.5 – 53.5)	57.5 ± 9.4 (35 – 72.5)	5.4	P<0.001
HOMA IR	7.9 ± 0.86 (7.3 - 18.5)	13.4 ± 3.5 (10.62 – 18.5)	2.2	P<0.05	7.4 ± 3.7 (0.1 - 15.05)	12.1 ± 3.4 (6.2 – 16.82)	3.4	P<0.05
HSCrp (mg/l)	9.3 ± 9.6 (0.6 – 26.2)	2.5 ± 3.2 (0.44 – 7.16)	1.8	0.098	5.9 ± 7.2 (0.4 – 26.2)	1.9 ± 2.4 (0.3 – 5.9)	1.9	0.064

The fasting blood sugar did not show any statistical change in both the sexes and groups, whereas fasting insulin level was found to be low in both the group and both sexes which were statistically significant. Whereas, HOMA-IR was noticed to be higher in control groups in both the sexes.

HsCRP which is one of the markers of inflammation, was found to be apparently high in CKD patients compared to groups, though the difference between cases and controls was not statistically significant.

Discussion:

The definition used in the WHO report centers on diabetes and insulin resistance, the WHO definitions identify people at risk of developing CVD and all the causes of mortality and for developing diabetes (15).As per WHO criteria, the polyphagia and polydipsia are features in non-CKD patients of metabolic Syndrome because they all had evidence of uncontrolled diabetes in form of insulin resistance, and raised blood sugar. The polyuria or increase frequency of micturation may be because of increased level blood sugar in these patients, leading to diuretic effect of glucose, blurred vision, and may be because of change of diabetic retinopathy in these patients.

The patients of CKD had loss of appetite, headache, weight loss and fatigue more because of their existing uraemia, GI upsets and because of breakdown of urea leading to liberation of ammonia in GI tract, that causes decreased appetite and unpleasant taste in patients, which leads to poor food intake and appetite which is a cause of weight loss in these patients. This has been reported by other workers also, such as uremia is consequence of kidney failure, its signs and symptoms often occur concomitantly with other signs and symptoms of kidney failure, such as hypertension due to volume overload, hypocalcemic tetany, and anemia due to erythropoietin deficiency (16). These, however, are not signs or symptoms of uremia (16), still it is not certain that the symptoms currently associated with uremia actually are caused by excess urea, as one study showed that uremic symptoms were relieved by initiation of dialysis, even when urea was added to the dialysate to maintain the blood urea nitrogen level at approximately 90 mg per deciliter (that is, approximately 32 mmol per liter)(16).

HTN is one of the criteria for qualifying for metabolic syndrome and significantly more HTN was noticed both in systolic blood pressure and diastolic blood Pressure in CKD group than the control group, this is because of nephronal loss in patients of CKD leading to ischaemia, triggering up of renal angiostensin system thereby more aldosterone production and which results in sodium retention, thus both hyper anaemic situation and salt retention are the other additional factors for HTN in these patients, this has been observed by other workers also, hypertension is a frequently observed disorder in these individuals, ranging in prevalence from 60% to 100% and is associated with significant cardiovascular morbidity and mortality. The presence of hypertension in CKD is widely believed to be a manifestation of positive sodium balance (17). Many previous studies suggest that even mildly elevated blood pressure (≥ 130/85 mm Hg) or serum glucose levels (≥110 mg/dl) are associated with an increased risk for CKD and microalbuminuria.(10)

The major mechanism underlying for the development of glucose intolerance in uraemia is resistance of peripheral tissues, particularly muscle, to insulin. Metabolic studies both in-vivo and in-vitro have uncovered impaired insulin mediated glucose uptake in muscle, many such studies have quoted the presence of higher HOMA-index in CKD patients. The state Insulin resistance and hyperinsulinemia are present in patients with CKD, without clinical diabetes (18).

In present study there is significant difference between case and control

HOMA-IR values, whereas in work done by other studies, the prevalence of abnormal HOMA did not differ significantly between CKD patients (98%) and BMI matched control subjects (94%) (19). In some other similar studies, having comparisons between chronic kidney disease patients and, otherwise healthy subjects the HOMA-IR value for CKD group was significantly higher (3.59 ± 3.55 *versus* 1.39 ± 0.51 $P < 0.01$) (20); higher mean HOMA index (6.0 ± 2.7 *versus* 2.9 ± 2.2 μU/ml x mmol/L; $P < 0.001$ (21).

It has been shown that a serum Hs-CRP level below 1ml/l indicate low risk, 1-3mg/l average risk, and 3-10mg/l very high cardiovascular risk. In a study, Compared with healthy subjects with normal renal functions, chronic kidney disease patients had higher blood pressure, waist circumference, higher triglyceride, and lower HDL Levels, higher insulin levels as well as higher mean HOMA index, these patients showed increased levels of Hs-Crp (22). C-reactive protein (CRP) correlates with generalized and abdominal adiposity(23) , and robustly predicts future risk of coronary heart disease (CHD) and type 2 diabetes mellitus (T2DM) (24, 25). Higher CRP levels in Asian Indians than white Caucasians, may contribute to a high prevalence of CHD and T2DM in this ethnic group. Further study is needed in the field, with larger sample size.s

Disclosures- There is no conflict of interest.

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