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RESEARCH ARTICLE

Assessment of Risk Factors for Ischemic Kidney Disease in Patients with Impaired Renal Function

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ABSTRACT

The present study was planned primarily to investigate the risk factors associated with renal ischemia in chronic kidney disease and secondarily to measure the incidence of disease. Observational study conducted in collaboration with a tertiary care hospital. All patients visiting nephrology unit meeting basic criteria of having at least 5 year diabetes mellitus, 10 year hypertension, dyslipidemia, age >55 year were recruited for kidney ischemia through Doppler scan. Written consent was obtained on a questionnaire inquiring about personal family medical history. Mean age was 48.2 ± 11 year. Male gender was significant factor ($p<0.001$) comprising 73.8%. The most prevailed risk factors were diabetes mellitus (61.2%), hypertension (43.7%), smoking (34.8%), raised cholesterol (52%), low HDL-C (35.4%) and increased triglycerides (61.4%) who contributed significantly in developing ischemic changes with ($p<0.01$, 0.0001, 0.0005, 0.0005, 0.05, 0.05) respectively. The calculated odd ratios at 95% confidence interval, for age>46 year (OR 0.5902, $p<0.01$), diabetes mellitus (OR 0.6677, $p<0.05$), hypertension (OR 4.1339, $p<0.0001$), male gender (OR 0.5320, $p<0.001$), smoking (OR 0.4862, $p<0.0005$), hypercholesterolemia (OR 2.1004, $p< 0.0005$), low HDL-C (OR 1.4567, $p<0.05$), obesity (OR 1.6345, $p<0.05$). While IHD, oral tobacco consumption, use of alcohol remained non-significant. It was observed that IKD positive had relatives with diabetes, hypertension, stroke, obesity and renal disease, significant as individual risk factor. Renal ischemia incidence was 11.5% among CKD. More large scale multi-centre studies are required to get the true prevalence and actual picture of disease.

KEYWORDS

Ischemic Kidney Disease, Diabetes Mellitus, Hypertension, HDL-C, LDL-C

INTRODUCTION

Ischemic nephropathy (IN) is recognized as distinct cause of renal disease in 1980s[1]. It is a disease of kidney hypo-perfusion mainly described as a significantly reduced glomerular filtration rate (GFR), more often reported in kidney patients with hemodynamically pronounced disease of occlusive renal blood-vessel. It progressively affects the entire functional renal parenchyma leading to severe renal sufficiency[2]. This clinical entity has alternatively been stated as ischemic renal disease, ischemic kidney disease, chronic renal ischemic disease, azotemic RVD, atherosclerotic RVD, renal insufficiency of renovascular hypertension by many authors[3]. It is suspected in patients who have sudden worsening of the kidney function with non-responsive hypertension to the angiotensin-

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converting enzyme (ACE) inhibitor or angio-reception blockers (ARB). The primary factor causing renal ischemia is a marked reduction in kidney blood flow, that can be result of low systemic blood pressure as observed in pre-renal acute renal failure, or it may be developed by large renovascular occlusion for instance renal artery thrombosis, embolism, or atherosclerosis[4]. The signs & symptoms develop when the obstruction in the renal blood supply reaches 70%-80% of the luminal area and there is development of pressure gradients and changes in blood flow occur. If kidney fails to regulate perfusion pressure by itself, there is renal ischemia forwarding to glomeruli collapse, atrophied tubules, and fibrosis in interstitium. The major risk factors and clinical findings are similar as for ischemic heart disease (IHD) including old age (>50 year), male gender, smoking, hypertension, diabetes mellitus, family history of artery disease and hypercholesterolemia[3].

A difference of > 1.5 cm or shorten renal size may serve as diagnostic clues to the ischemic renal disease. Flash pulmonary edema recurrence, low plasma potassium and metabolic alkalosis duebecause of hyper-renin, hyper-aldosterone state are also commonly observed findings[5]. Since, its identification as a separate disease, it has earned special significance as it is initially silent, prospectively harmful but potentially reversible cause of kidney function impairment. Based on the various retrospective studies, it has been established that it could be the sole cause of end-stage renal failure in 5-16% patient and the ratio increase as the age advances[6].

The exact prevalence of the disorder is yet debatable and the available data represents the local picture in selected population, most of the reported studies are either conducted on elderly people, retrospective biopsies or on specific ethnic group, but among all these the common finding is its increasing percentage worldwide. Further randomized studies are required not only to assess its exact prevalence but also to outline the factors that accelerate the disorder and related abnormalities[6,7]. The purpose of current study is to calculate its frequency in local population and to report the prevailed causes and associated complications in this group of renal insufficiency patients.

MATERIALS AND METHOD

The study was conducted in collaboration with Department of Nephrology, Jinnah Post Graduate Medical Centre, Karachi, Pakistan. It was an observational study and all patients coming to the outpatient department were recruited initially by filling up a questionnaire inquiring about personal and family history. As basic inclusion criteria, individuals with more than ten year hypertension and/or at least five year diabetes mellitus and/or age >55 years and/or using lipid lowering medicines were requested to give an informed consent. The exclusion criteria included age less than 18 more than 70, renal transplantation, liver cirrhosis, plasma cholesterol > 300mg/dl and chemical induced nephrotoxicity.

The functional definitions were pre-identified used for various risk factors and considered positive when either of description found; diabetes mellitus: fasting blood glucose>140 mg/dl, intake of hypoglycemic medicines, hypertension: systolic blood pressure>140 mmHg, diastolic blood pressure>90 mmHg, using antihypertensive medicines, obesity: body mass index >25kh/square meter, current smoker: smoking for at least 2 year minimum 5 cigarettes per day, Ex-smoker: quit smoking at least 6 months ago, oral tobacco: consuming *gutka, pan, naswar* for at least 2year, hypercholesterolemia: plasma cholesterol >240 mg/dl, low HDL-C: <40mg/dl, increased triglycerides: >150mgdl, alcohol use for at least two year and protein urea >150mg/24 hour.

Blood samples were collected following 12-hour fasting in heparinized tubes from agreed upon patients and immediately centrifuged at 3000rmp for 5-minute. The plasma was kept frozen at -80^{0}C till used for biochemical estimation of lipid profile and glucose done spectrophotometrically using kits from Randox on PRIM Light & Advanced Spectrophotometer, Schott Instruments,

Germany. Person weight and height were also recorded in light clothing without shoes and blood pressure was measured by taking three consecutive reading in comfortable position. As a diagnostic tool to investigate the presence and intensity of ischemia, renal artery Doppler scan was performed by skilled person. The scan result was considered positive if there was turbulence before and after stenosis, maximum flow velocity > 180 cm/sec at stenosis, end-diastolic velocity >50cm/sec, post-stenotic drop in velocity, acceleration time > 0.07 seconds and slope of systolic upstroke < 3 m/s^2 or resistance index associated with stenosis or occlusion of the segmental arteries < 0.5[8], though the final decision regarding the presence of ischemic changes in kidneys was solely taken by the nephrology consultant. Collected information was analyzed through SPSS. Mean values, percentage, frequency were estimated as required. While chi square, odd ratio and relative risk were calculated[9] to assess the retrospective impact of various factors in person and in close relatives respectively.

RESULTS

1280 patients meeting the fore-mentioned initial criteria registered in the tertiary care hospital outpatient unit. Among these 1190 patients showed the consent to become the part of study while remaining refused. 25 individuals did not turn back following Doppler scanning from radiology department hence the final findings were reported for 1165 patients. These all are suspected for the presence of ischemic nephropathy.

Table 1 showed the demographic information of renal impairment patients meeting the inclusion criteria and was recruited for presence or absence of ischemic changes in kidneys. The mean age was 48.2 ± 11 years ranging 36-65 year. Patients were categorized into three slabs of advancing age and it was observed that majority (48.8%) falls in 56+ year with 59.2% cases positive for IKD. Male gender was found a significant factor ($p<0.001$) comprising 73.8% of total population. The most prevailed risk factors were diabetes mellitus (61.2%), hypertension (43.7%), smoking (34.8%), raised cholesterol (52%), low HDL-C (35.4%) and increased triglycerides (61.4%) who contributed significantly in developing IKD with ($p<0.01$, 0.0001, 0.0005, 0.0005, 0.05, 0.05) respectively. While other less common factors, that we observed in our population were obesity (10%), IHD (24%), use of alcohol (3%); among these only obesity showed significant relation with IKD ($p<0.05$). Approximately half of the patients were addicted by oral tobacco but its ling with IKD found insignificant.

A linear regression model was used to measure the precise contribution of all fore-mentioned risk factors in ischemic renal disease by calculating odd ratios and respective level of significance at 95% confidence interval illustrated in table 2. The findings remained significant for age >46 year (OR 0.5902, $p<0.01$), diabetes mellitus (OR 0.6677, $p<0.05$), hypertension (OR 4.1339, $p<0.0001$), male gender (OR 0.5320, $p<0.001$), smoking (OR 0.4862, $p<0.0005$), hypercholesterolemia (OR 2.1004, $p< 0.0005$), low HDL-C (OR 1.4567, $p<0.05$), obesity (OR 1.6345, $p<0.05$). While IHD, oral tobacco consumption, use of alcohol remained non-significant when assessed as individual risk factor. IKD presence was confirmed in 135 of total recruited patients (11.58%). The family history for associated ischemic risk factors was also noted. Graph I expressed their frequency in close relatives of mother or father side. It was observed that in patients with compromised renal function who diagnosed with kidney ischemia had relatives with diabetes, hypertension, stroke, obesity and renal disease. However, when they analyzed together to estimate their role as independent risk factor, IHD ($p<0.05$), hypertension ($p<0.0005$), obesity ($p<0.01$) on mother side and hypertension ($p<0.005$), diabetes ($p<0.0001$), renal disease ($p<0.0001$), obesity ($p<0.001$) at father side found significant in the IKD development (table 3).

Table 1: Demographics and Risk Factors in Renal Patients Recruited For Ischemic Kidney Disease

Variable	Frequency (%)	IKD Frequency (%)	p-value<
Age in years			
36-45	216 (18.5)	25 (18.5)	NS
46-55	380 (32.6)	30 (22.2)	0.01
56-65	569 (48.8)	80 (59.2)	0.05
Gender	860 (73.8)	81 (60)	0.001
Diabetes Mellitus	714 (61.2)	71 (52.5)	0.01
Hypertension	510 (43.7)	103 (76.2)	0.0001
Obesity	118 (10.1)	21 (15.5)	<0.05
IHD	290 (24.8)	26 (19.2)	NS
Current Smoker	406 (34.8)	34 (25.1)	0.0005
Ex-Smoker	216 (18.5)	14 (10.3)	0.05
Oral Tobacco	580 (49.7)	70 (51.8)	NS
Hypercholesterolemia	608 (52.1)	94 (69.9)	0.0005
Low HDL-C	413 (35.4)	60 (44.4)	0.05
Increased TG	716 (61.4)	95 (70.3)	0.05
Alcohol Use	36 (3.0)	02 (1.4)	NS
Proteinurea	613 (52.6)	86 (63.7)	0.01

IHD: Ischemic Heart Disease HDL-C High density lipoprotein cholesterol
TG: Triglycerides NS: Statistically non-significant

Table 2: Assessment of Observed Risk Factor Impact in the Development of Renal Ischemia from Recruited Patients of Impaired Kidney Function Using Logistic Regression Model at p<0.05, 95% Confidence Interval

Risk Factor	Odd Ratio	95% Confidence Interval	z-statistics	p-value<
Age (36-45)year	0.9985	0.6312-1.5797	0.006	NS
Age (46-55)year	0.5902	0.3863-0.9018	2.438	0.01
Age (56-65) year	1.5236	1.0608-2.1882	2.280	0.05
Gender	0.5320	0.3681-0.7688	3.359	0.001
Diabetes Mellitus	0.6677	0.4656-0.9576	2.195	0.05
Hypertension	4.1339	2.7347-6.2491	6.732	0.0001
Obesity	1.6345	0.9885-2.7025	1.915	0.05
IHD	0.7197	0.4599-1.1264	1.439	NS
Current Smoker	0.4852	0.3265-.7210	3.579	0.0005
Ex-Smoker	0.5083	0.2867-0.9013	2.316	0.05
Oral Tobacco	1.0862	0.7604-1.5516	0.454	NS
Hypercholesterolemia	2.1004	1.4300-3.0850	3.784	0.0005
Low HDL-C	1.4567	1.0162-2.0880	2.047	0.05
Increased TG	1.4894	1.0106-2.1949	2.013	0.05
Alcohol Use	0.4716	1.026-0.3049	1.026	NS
Proteinurea	1.5805	1.0926-2.2862	2.430	0.01

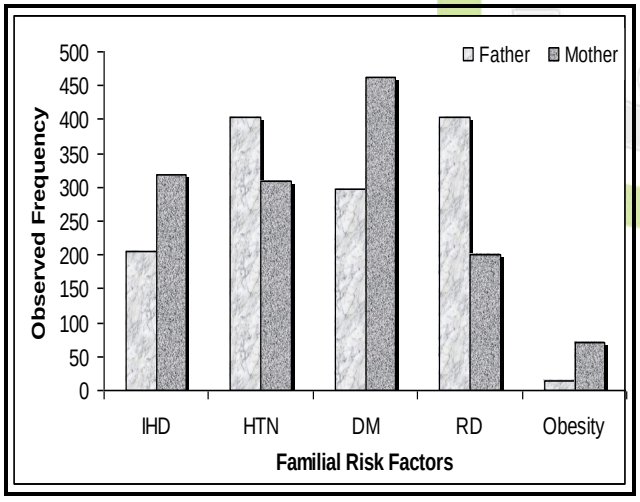
IHD: Ischemic Heart Disease HDL-C High density lipoprotein cholesterol
TG: Triglycerides NS: Statistically non-significant

R.D.: Renal Disease

Table 3: Estimation of Relative Risk Associated With Maternal and Paternal History for Potentially Significant Contributor of Ischemic Kidney Disease Development in Studied Patients of Impaired Renal Function at p<0.05

Risk Factor	Relative Risk	95% Confidence Interval	z-statistics	p-value<
FATHER				
Ischemic Heart Disease	0.6730	0.4162-1.0793	1.646	NS
Hypertension	1.3490	1.1080-1.6426	2.981	0.005
Diabetes Mellitus	1.5929	1.2708-1.9962	4.040	0.0001
Renal Disease	0.4497	0.3012-0.6714	3.907	0.0001
Obesity	4.3148	1.7726-10.5033	3.221	0.001
MOTHER				
Ischemic Heart Disease	0.7056	0.4933-1.0092	1.910	0.05
Hypertension	1.5311	1.2230-1.9168	3.716	0.0005
Diabetes Mellitus	0.8592	0.6725-1.0979	1.213	NS
Renal Disease	0.4732	0.2644-0.8436	2.534	0.01
Obesity	1.8696	1.1202-3.1202	2.395	0.01

NS: Statistically non-significant



Graph 1: Presence of Ischemia Associated Risk Factors in Close Relative of Chronic Kidney Disease Patients; Suspected And Recruited For Renal Ischemia.

Considered only if established before age of 70year

IHD: Ischemic Heart Disease

HTN: Clinical hypertension

DM: Diabetes Mellitus

DISCUSSION

The study estimated the incidence of renovascular related kidney ischemia in local population of chronic kidney disease in presence of any of the initial risk factors i.e. hypercholesterolemia, diabetes mellitus and hypertension. 11.58% patients had renal artery occlusion of varied degree that was unilateral in most of the cases. Univariate analysis suggested gender difference with more frequent in males as with other conditions of atherosclerosis. Increasing age, elevated blood pressure, chronic smoking, overweight, raised cholesterol and low HDL-C also demonstrated significant and independent association with IKD as shown in table 2.

The true prevalence of renovascular disease in not well established because mostly it remains asymptomatic and not included in general screening plans of renal patients unless clinical signs developed in the strong presence of risk factors[10]. Substantial data suggested it as a disease of increasing prevalence and the onset is

much higher as reported[11,12,13]. Autopsy findings showed its prevalence between 4-50% in different age groups with an increasing incidence in old age[14], so called disease of aging in developed countries with better life standards and health systems[15], partially in accordance with our findings as we observed even at lesser age (ref table 1). This difference may be due to lack of/expensive health facility, overall poverty, illiteracy and low living standards in general population.

Hypertension is the leading cause of IKD development in CKD patients. We found it as independent risk factor (OR 4.1139, p<0.0001) that is in agreement with reports published by Alcazar [15] from a large Spanish survey observed hypertension in more than 70% of renovascular disease patients and Dutch Renal Artery Stenosis Intervention Cooperative study[16]. Hypertension plays significant role in the progression of CKD to irreversible renal failure[17]. Moreover, pre-hypertensive state is known to be associated with raised in inflammatory mediators of atherosclerosis[18]. Generally, hypertension primarily causes increase in hyaline thickening of small arteries and arterioles in the renal vasculature leading to dysfunctional endothelium facilitating attachment of macrophages, chemotaxis and inflammatory cells aggregation. On the other side, in large blood vessels, hypertension progresses atherosclerosis promoting conversion of fatty streaks into lesions[19]. Finally, these vascular lesions can turn into necrosis and hyperplastic arteriolosclerosis extending necrotizing glomerulitis[20].

Other significant contributors were diabetes, raised cholesterol and low HDL-C values (ref. table 2) in our study which is supported by previous findings by many investigators in different region of world[15,16]. Published data suggested its positive correlation and increasing incidence rate in presence of generalized atherosclerosis, peripheral vascular disease and aortic disease[21,22] that is in contrast to what we observed in our study as non-significant contributor (19.25%, OR 0.7197), this dissimilarity may be justified by the different age (65 VS 45) of patients.

Dyslipidemia is common finding in renal disease present either as cause or complication. It speeds up atherogenic mechanism resulting in vascular disease[23]. Atherogenesis favoring oxidized LDL-C can accelerate glomerulosclerosis in compromised renal function. The other lipid metabolism abnormalities also develop in these patients more often raised plasma triglycerides and suppressed HDL and apolipoprotein A-1 levels that further work to stimulate atherosclerosis and associated complications of ischemic heart and kidneys[23,24].

Most prevailed complication of diabetes is atherosclerosis that progresses quicker and sooner in these patients and damages the small and large systemic and renal blood vessels. Key mechanism of dyslipidemia leading to vascular changes involve advanced glycation end products (AGEs) generation following long-term exposure of proteins to glucose or species derived from glucose. It seems there is a mutual link between renal efficiency and atherosclerosis in diabetes: diabetes promotes atherosclerosis and CKD both, suppressed renal performance further promotes atherosclerosis[25].

Obesity is currently found as common feature of metabolic syndrome corresponding with increasing CKD burden[26,27]. Lab reports show a high prevalence of microalbuminuria in these patients, that is an early renal endothelial damage marker particularly for renal disease, for endothelial dysfunction in general and atherosclerosis[28]. Furthermore, abnormalities observed in various vascular beds macro- and microvascular may potentially result in kidney ischemia[26].

All above discussed factors along with smoking also cause inflammatory changes and oxidative imbalance leading to raised oxidants & reduced antioxidants that further promote the process of atherosclerosis in the patients of impaired renal function who are already at strong risk.

CONCLUSION

We found a high incidence (11.5%) of ischemic kidney changes in the patients of CKD bearing hypertension, diabetes, dyslipidemia either as cause or complication of renal disease. The other affecting factors were male gender, advancing age, overweight and smoking. Further studies with greater sample size are required to calculate the actual prevalence and to mark true picture of renal ischemia in this part of world.

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