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ORIGINAL ARTICLE

Glomerular hyperfiltration: An independent risk factor and predictor of advanced coronary artery disease.

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ABSTRACT… Objective: To determine frequency and patterns of coronary artery disease in patients with glomerular hyper filtration (GHF), presented with acute coronary syndrome (ACS). **Study Design:** Cross Sectional, Retrospective study. **Setting:** Tertiary Healthcare Centre, Karachi. **Period:** July 2018 to July 2021. **Material & Methods:** Twelve hundred and sixty seven patients undergone Coronary angiography (CAG) for ACS having estimated glomerular filtration rate (eGFR) calculated through Cockcroft-Gault equation >90ml/min were selected. They were divided into two groups on the basis of eGFR, group A with normal eGFR (90-120ml/min) and B with eGFR i-e >120ml/min with glomerular hyper filtration (GHF). Variables like age, gender, BMI, Diabetes mellitus (DM), Hypertension, Smoking, history of previous cardiovascular diseases (CVD) and family history of CVD and obesity were studied. Findings of CAG results from Cath lab were also noted down. All the relevant data was analyzed through SPSS 16. **Results:** Out of 1267 patients 807 patients had normal eGFR and 460 had GHF. Mean age in two groups was 45± 8.5years and 45.6± 7.8years, mean eGFR 102ml/min and 146ml/min and mean B.P was 110/80 and 135/90 mmHg respectively. Association of GHF with younger age, mean B.P, BMI, and family history of obesity was significant P value <0.05. Patients with GHF had significant Coronary artery disease (CAD) P-0.036. Patients with eGFR between 145-175ml/mid had worst angiographic results, 80% of those had CAD. **Conclusion:** GHF has strong association with CVD and is a predictor of severity of disease.

Key words: Cardiovascular Disease, Coronary Angiography, Estimated Glomerular Filtrartion Rate, Glomerular Hyper Filtration.

INTRODUCTION

Association of chronic kidney disease (CKD) with cardiovascular disease (CVG) is well known and is one of the important cause of morbidity and mortality worldwide. More than 50% deaths in patients with End stage renal disease (ESRD) are because of CVD including fatal Myocardial infarctions and Angina.[1] The measurement of kidney function is Glomerular filtration rate (GFR) and by definition, normal GFR ranges from 90ml/min per 1.73m^2 to 120 ml per minute per 1.73 m.^{2} GFR <60ml/min per 1.73m^2 indicates chronic kidney disease.[2] While GFR >120 ml per minute per 1.73 m is called as Glomerular hyperfiltration.[3] according to newer studies GHF is also important due to its Pathophysiologic role and clinical implications in CVD.

Stage of GHF occurs in the early phases of kidney disease, before significant loss of nephrons and this results from primary increase in sodium and glucose reabsorption from proximal convoluted tubules. This rise in reabsorption, reduces sodium chloride delivery to the macula densa and in turn afferent arteriole vasodilatation and eventually a rise in GFR occurs through tubuloglomerular feedback system. (Figure-1)[4]

A-normal glomerulus with balance normal intraglomerular pressure balanced through afferent and efferent arteriolar pressures. B-Glomerular hyper filtration results from dilatation of afferent arterioles and vasoconstriction of efferent arterioles lead to raise in intraglomerular pressures and thus glomerular hyper filtration.

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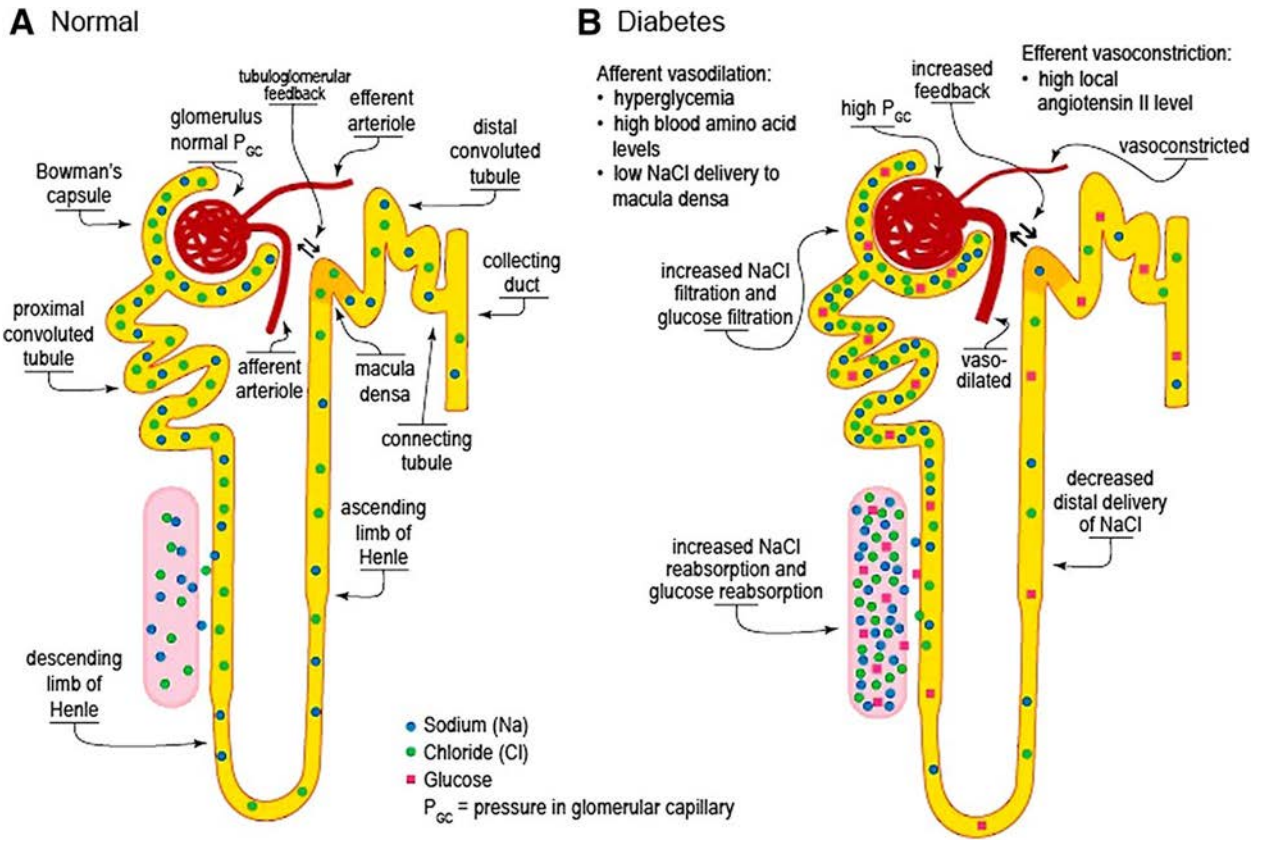

Figure-1. Mechanism of glomerular hyper filtration

Mechanism is mediated by decreased delivery of sodium chloride to the distal tubular macula densa via tubuloglomerular feedback. Factors like hyperglycemia causes high filtered load of glucose results in increased reabsorption of glucose and sodium chloride in proximal tubule.

GHF is also found in CVD risk factors like obesity, Diabetes Mellitus, Hypertension, pre diabetes and hypertension is[4]

It is yet to establish whether GHF is an independent risk factor for CVD or not. However early identification of GHF can guide clinicians for risk assessment and timely measures for fatal outcomes.

Rationale of this study is to explore the association of GHF with CVD in local population and if hypothetically it is correct then it may be introduced in risk assessment strategies and early detection of CVD. This will help in improving quality of life and expectancy.

MATERIAL & METHODS

This was a retrospective, cross sectional study performed at tertiary cardiac care center, Karachi. Study period was of 3 years ranging from July 2018 to July 2021. Total 1267 patients were enrolled in study through Consecutive sampling. The study was approved by an institutional review committee number ERC-12/ 2018. Inclusion criteria included all the patients who undergone coronary angiography at cardiac Cath lab from 1st January 2019 to 31st December 2020 for evaluation of CVD. All those patents having eGFR more than 90 ml/min including both genders were enrolled for study. All Patients with eGFR <90 ml/min by Cockcroft-Gault formula including CKD, were excluded from study. Patients with concomitant severe disease, such as neoplasm that was likely to limit life expectancy were

excluded.

GFR (eGFR) of each patient was measured using Cockcroft-Gault equation (The Modification of Diet in Renal Disease (MDRD).[6]

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times [0.85\ if\ Female]}{72 \times \text{Serum Creatinine (in mg/dL)}}$$

Patients were divided into two group one with normal eGFR (90-120ml/min) and other with GHF having eGFR >120ml/min. Information regarding variables of these patients like; Age, gender, BMI, (height in meters and weight in Kg), Diabetes Mellitus and its medications, Hypertension, history of smoking, previous history of CAD and family history of Obesity and CAD were taken from medical records. Findings of Coronary angiogram were noted down by tracing Angiographic reports in each case. All the above information were collated on a written proforma. Results of coronary angiography were interpreted into 4 categories; none (Normal Coronary arteries), Single vessel disease (SVD), Double vessel disease (2VD) and Triple vessel disease (3VD).

All the angiographies was performed by skilled interventional cardiologists. Stenosis of greater than 70% for Left anterior descending (LAD), Left Circumflex (LCX), Right coronary artery (RCA) and 50% for left main artery was taken as the diagnostic criterion to label as "vessel disease"[7] Data was analyzed by using SPSS 16. Continuous and categorical variables were presented as frequencies and percentages with 95% confidence interval and Mean + SD. comparison between two groups were made using Student t-test, Spearman correlation test and the Chi square test. P value of less than 0.05 were considered statistically significant.

RESULTS

Out of 1267 patients 807 had normal eGFR while 460 were in GHF group. Mean eGFR of the two groups was 102ml/min and 146ml/min, respectively. Subjects with GHF were more likely to be younger (mean age=45.6±7), males, had higher average BMI (30.9± 5.3), relatively high mean blood pressure (mean B.P135/90mmHg). Family history of obesity and CVD were statistically significant in this group (p-value <0.05). (Table-I & II)

The association of GHF with CAD was statistically significant (p-0.036). (Table-III)

	eGFR(90-120ml/min) Normal eGFR	eGFR > 120ml/min GHF	P-Value
Total	N= 807	N= 460	
Gender (Male)	666(82.5%)	395(85.9%)	0.133
Gender (Female)	141(17.5%)	65(14.1%)	
Age in years	49.5± 8.5	45.6± 7.8	<0.001
BP in mmHg (Mean)		135/90	<0.001

Table-I. Demographic and physical findings of patients at time of presentation and association with eGFR

	eGFR(90-120ml/min) Normal eGFR	eGFR > 120ml/min GHF	P-Value
	N= 807	N= 460	
Diabetic	203 (25.15%)	120 (26%)	0.875
1. Total	181 (22.4%)	108 (23.5%)	
2. Oral hypoglycemic	11 (1.4%)	5 (1.1%)	
3. Insulin	11(1.4%)	7 (1.5%)	
4. Diet controlled			
BMI	28.1± 4.4	30.9± 5.3	<0.001
Smoking	230 (28.5%)	139 (30.2%)	0.853
Hypertension	342 (42.4%)	209 (45.4%)	0.117
Previous history of ACS	224 (27.7%)	123 (26.7%)	0.863
FH of cardiac disease	142 (17.6%)	101 (22%)	0.064
FH of Obesity	103 (12.8%)	87 (18.9%)	0.004

Table-II. Association of eGFR with Risk factors of CAD

	eGFR(90-120ml/min) Normal eGFR	eGFR 120ml/min GHF	P-Value
	N= 807	N= 460	
1. NONE	210 (26%)	128 (27.8%)	
2. SVD	176 (21.8%)	128 (27.8%)	0.036
3. 2VD	191 (23.7%)	90 (19.6%)	
4. 3VD	230 (28.5%)	114 (24.8%)	

Table-III. Association of eGFR with CVD

On further evaluation it was noted that subjects with elevated eGFR between the ranges of 150 ml/min- 175ml/min had worst angiographic findings. 80% of them had CVD. 30.5% of whom had had 3VD, 19% had 2VD and 30.5% had SVD. While only 20% had normal coronaries. (Figure-2).

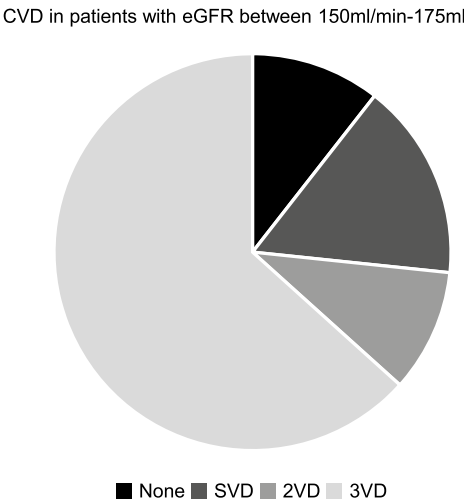

Figure-2. CVD in patients with eGFR 150-175ml/min (GHF)

DISCUSSION

Several studies, such as the HOPE trial The Second National Health and Nutrition Examination Survey (NHANES II), The Hypertension Optimal Treatment (HOT and the Atherosclerosis Risk in Communities (ARIC) have shown decreased GFR to be associated with increased risk for cardiovascular events. However, the prognostic impact of GHF is yet to decide.

A study by Inrig et al[8] in 8,941 patients with atherosclerotic cardiovascular disease reported an elevated risk of cardiovascular outcomes (MI, stroke, CHF and all-cause mortality) in patients with increased eGFR (estimated by Cockcroft-Gault formula and MDRD). This study showed that among subjects with an eGFR ≥ 100ml/min per 1.73 m^2, each 10ml/min per 1.73 m^2 increase in eGFR was associated with an increase of 9% of that risk. In Inrig's study the population with eGFR>120ml/min were younger, females and non-white while in our study the subjects were younger and males. CVD associated with GHF in relatively younger population (p-<0.001) mean age in this group was 45.6± 7.8 years. Though gender distribution in two groups was statistically insignificant (p-0.133) but it can be observed that over all proportion of male patients enrolled in study were more in normal eGFR group as compare to GHF this finding is possibly because ACS/CVD predominantly affects males.

Various studies suggest that GHF is associated with target organ damage. In 111 patients with essential hypertension and normal renal function, GHF was associated with a significant increase in left ventricular mass index, suggesting that elevated GFR may be an indicator for early target organ damage in these patients.[9] Similarly in our study GHF was also associated with hypertension (Diastolic > 100mm Hg) and a mean recorded blood pressure of 135/90 mm Hg. (P- <0.001). This strong association of hypertension with GHF increases the risk of adverse CVEs. In addition loss of diurnal variation and nocturnal dip in blood pressure is also a feature of GHF which further potentiates this risk. Another study has reported that GHF in hypertensive patients increases the risk of micro albuminuria which is another predictor of worsening cardiovascular outcome.[10]

In diabetic patients, GHF predicts the subsequent development of nephropathy, irrespective of the degree of metabolic control.[5] In our study percentage of patients presented with ACS having normal eGFR were predominantly suffering from

DM. 120 (26%) vs 203 (25.15%), though the association of GHF with DM was statistically insignificant. (P-0.875). Majority of these diabetics were on oral Hypoglycemic. Here it is important to highlight that effects of anti-diabetic medications on GFR should also be investigated. Not only this but for better understanding of association between GHF and CVEs in DM and Hypertension or syndrome X, other emerging markers of severity like Glycated Hemoglobin/Albumin, microalbuminoria, Uric acid level, dyslipidemia, Vitamin D3, C-reactive protein and upcoming inflammatory markers need to study.

Obesity has also been associated with GHF. A study by Wuerzner G et al[11] suggested that rise in metabolic risks in young healthy males is associated with a 6.9-fold increase in likelihood of GHF before the overt manifestations of cardiovascular disease10. Indeed our subjects with GHF (group B) had mean BMI of 31 which by international standards is borderline Obese. Our study also proved that association of GHF with Obesity in patients with CVD is statistically significant. (P- <0.001). Our patients who presented with GHF also reported with positive family history of Obesity 87 (18.9%) vs 103 (12.8%) and its statistically significant (P- 0.004).

Though association of family history of CVD with GHF was in significant statistically (P-0.064) but overall percentage of patients in this group were more than the group with normal GFR. 101 (22%) vs 142 (17.6%). Our study also concluded that smoking in patients with ACS had some impact on eGFR though statistically insignificant (p-.0.853)

The association of GHF with vessel disease came as significant. Our study showed that those with GHF mostly presented with single SVD. Involvement of more than one vessels at the time of presentation were less as compare to group with normal eGFR. These finding could be justified by the fact that due to the greater CVD risk in these patients, they presented earlier in course of disease with ACS, though number of coronary vessels involved in obstruction/ atherosclerosis, were minimum (SVD) but significant enough to cause MI and unstable angina. On the other hand patients with normal eGFR presented late in the course of disease when they had more advanced/ multi vessel disease (2VD and 3VD). The association of GHF and atherosclerotic CVD was significant statistically (P-0.036).

It was also found that majority of patients with normal eGFR) had previous episodes of CVD 224 (27.7%) while patients with GHF presented for the first time with clinically significant disease and less previous episodes 123 (26.7%). (Table-II) though this association of GHF with previous episodes of CVD was statistically insignificant (P-0.863)

On further stratification it was observed that GHF had strong association with advanced CVD by the fact that patients with GHF group having eGFR between 150 ml/min- 175ml/min had worst angiographic findings and most severe disease. 80% of them had CVD out of which 30.5% had 3VD the most severe form, 19% had 2VD and 30.5% had SVD while minimum number had normal coronaries (20%) (Figure-2)

Above results were compare with a prospective study by Reboldi G1 et al.[1] the also compared association of eGFR and major CVEs. Their results were more or less same our study results.

It can be suggested that GHR is an early marker of population at risk for CVEs. However due to retrospective nature of our study it could not be determined whether GHF was an independent risk factor for the CVD or a predictor of worst outcome, nevertheless the association is too strong to be negated.

CONCLUSION

Being a retrospective analysis, our study had many limitations of recording bias however this study has proved that GHF has strong association with CAD. Relatively younger age, male gender, obesity, raised mean blood pressure and family history of obesity all are associated with GHF and CVD risks. Extent and severity of atherosclerotic CVD is directly proportional to GFR. As CVD is one of the major health burden and leading cause of death all over that's why all measure

should be taken to reduce its incidence via effective preventive strategy. GHF need to be considered as target for therapy and glomerular decompression as main stay of treatment. Weight reduction and dietary modification can provide synergetic effects in GHF reduction and thus CVEs. More prospective studies are required in this regards for further prove of association and individualized risk stratification of CVD.

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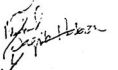
4	Muhammad Saqib Habib	Statistical analysis, paper writing.	
5	Khuwaja Muhammad Areej	Data collection.	
6	Shahana Arshi	Discussion, paper writing.