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A REVIEW ON THE PREVALENCE OF COMPLICATIONS IN CHRONIC RENAL FAILUE

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ABSTRACT

The declination of glomerular filtration (e-GFR) rate in CKD patients, eventually leads to renal failure which is the leading source to develop cardiovascular diseases. It is estimated that about 40-50% of all deaths in the end-stage renal disease population are of cardiovascular origin. The association between renal deficiencies and cardiovascular disease were conformed in large scale studies like HOPE and HOT. Even, the US Renal Data System (2013) reveals that about 43% and 15% patients with renal complications are affected with heart failure and myocardial infarction respectively. In the current article we aimed to review the literature on the prevalence rate of various types of cardiovascular complications and non-cardiovascular complications such as hypertension, arterial vascular disease, atrial fibrillation, congestive heart failure and diabetes among India community. The study also focuses on the role of novel and traditional risk factors of patients having the chronic kidney diseases. Framingham risk score supports the traditional risk factors whereas the novel risk factors include the level of homocycteine, C-reactive protein and lipoprotein.

Keywords: Chronic kidney disease, Hemodialysis, Coronary Heart Disease, Hyperlipidaemia, Hypertension, Diabetes.

INTRODUCTION

Chronic kidney disease is a worldwide public health problem, which decreases the kidney function gradually. CKD characterized by the declination of the glomerular filtration rate (GFR) where it has been staged from level 1 to level 5 according to the highest level of kidney function to the lowest level of kidney function. The level 1 CKD patient will have the GFR value more than 90ml/min/1.73m^2 whereas in level 5 the GFR value will be lesser than 15ml/min/1.73m^2[1].There is always been a correlation between chronic kidney disease and cardiovascular diseases. The trend shows that both the disease has inverse relationships where the lower the grade of kidney function, the highest the risk of cardiovascular diseases. The mortality and morbidity rates of patients having CKD worsen when they are further threatened by the CVD complications. Evidence shows that the pathophysiology and expression of CVD is differ in patient having CKD. According to the statistics, it was noted that cardiovascular disease frequently begins before the end-stage renal failure and about 40%-50% of deaths occurs due to cardiovascular complications in CKD patients. This phenomenon mainly affects the pre-dialysis and dialysis individualsand being the leading cause for death[2,3]. It was also found that the dialysis patients are having 10 to 30-folds of risk for cardiovascular disease when compare to normal populations [4].Cardiovascular diseases in kidney disease patients are treatable and potentially preventable.

The common types of CVD complications that mostly affect the populations are coronary artery

disease (CAD), myocardial infarction (MI), congestive heart failure (CHF), cerebrovascular disease, stroke, atrial fibrillation, peripheral arterial disease (PAD), and sudden cardiac death (SCD). The association between renal deficiencies and cardiovascular disease were conformed in large scale studies like HOPE [5] and HOT [6]. US Renal Data System that was published in 2013, states that 43% and 15% patients are affected with heart failure and myocardial infarction respectively. But this trend is much lower in non-renal failure patient, which is only 18.5% and 6.4% respectively. Besides, previous researchers pointed out that even 1% each 1ml/min decrease in creatinine clearance is highly influences the cardiovascular mortality. Moreover, patients with CKD and CVD contributes to the high resources expenditure, as the cost for the heart failure itself has been estimated around 2% of total amount of the health budget. In addition, 70% of cost adds in the expenditure due to readmission of patients in hospitals [7,8,9,10]. Patients with CKD will suffer cardiovascular complication due to deteriorating renal function which may ultimately leads to end-stage renal diseases. A special feature of cardiovascular disease in patients with primary renal disease is that, prevention and retardation of renal diseases can ultimately reduce the cardiac risk. Therefore, patients with renal diseases should be introduced with renal replacement therapy programmes involving either peritoneal or haemodialysis.

Progressive renal disease is actually has volume dependant mechanisms in clinical conditions like hypertension and heart failure. Normally, patients who develops anuric during the haemodialysis will accumulate around 2-3 litres of fluid between the dialysis sessions. This will eventually increases the fluid retention in the body with deteriorating renal function which leads to development of heart failure and hypertension. Thus we can conclude that hypertension and heart failure is actually volume dependant conditions. Another feature of renal disease is the nature of vascular disease in among the patients. Calcification of the vessels has lead to hyperthyroidism in renal disease patients especially on the peripheral and on the coronary vessels [11]. Even the atherosclerotic event also differs from the general populations and thus the efficacy of lipid lowering agents such as statins remain undecided.

Novel and Traditional Risk Factors

There are quite number of risk factors associated with the cardiovascular disease. These risk factors can be classified as novel or traditional risk factors. The traditional risk factors are based on the Framingham risk score. Whereas the examples of novel risk factors are the level of homocystine, C-reactive protein, and lipoprotein. Both the novel and traditional parameter categorised the asymptomatic patients into 3 reasonably distinct categories. The first category falls under lower risk for CHD that is about only 5%-in 10 years. Whereas,the second category falls in the high risk category margin, which makes more than 2 % in a year[12]**.** The intermediate patients fall under third category, this category patients lays in between both the category mentioned above. Due to their clinical complications, they can undergo counselling to follow the general dietary and life style habit advice to lower the CHD risk in future. Based on the review given in the prevention V conference, the intermediate risk patients should undergo further testing on the other risk factors such as ankle-brachial index (ABI), carotid B-mode ultrasound with emphasis in Intima Thickness (IMT), Electron Beam Tomography (EBT) to lower the risk status of CHD[13,14].

The traditional risk factor for artheroscleorsis are smoking, hypertension, elevated LDL and cholesterol, low serum of HDL, gender, diabetes mellitus and age as well. According to the Alan Wilkinson, MD and Kasiske[15], the diabetes mellitus vastly influences the kidney transplant patients. On the other hand, the biomarkers for inflammation such as C-reactive protein may also be useful to stratify risk which indicates the impaired perfusion or function [16]. Similarly, the ATP III guideline says that the major risk factor for coronary heart disease include smoking, hypertension, high LDL level, low HDL level, family history of premature coronary heart disease, age, and diabetes.

Several cross-sectional studies have suggested that the Framingham risk equation is insufficient to capture the extent of CVD risk in subjects with CKD. Therefore considering the novel risk factors are crucial in determining the risk of CVD in CKD patients. The non-traditional biomarkers include the elevated serum triglycerides, small LDL particles, elevated serum homocysteine, elevated serum lipoprotein, prothrombotic factors, inflammatory markers (Eg: C-Reactive protein & IL-6, CMV), B-type natriuretic peptide/ N-terminal pro-atrial natriuretic and aldosterone.

Traditional Risk Factors

Hypertension

Patients with renal disease have chances of 60-100% to get hypertension [17]. Treatment of hypertension should be immediate with the target range of below 130/ 80[18]. The prevalence of hypertension has been increased from 50% to 70-90% in renal patients who are on cyclosporine. Calcium channel blockers helpful in treating patients with cyclosporine

nephrotoxicity[18]. Immunosuppressant's and steroids withdrawal ameliorates also may cause hypertension [19]. In addition, the ACE inhibitors useful in protein urea patients and beta blockers are being cardio protective[18].

Hyperlipidemia

As the renal function deteriorates it will cause lipid abnormalities. For instance, high level of LDL will increase the VLDL lipoprotein level in nephritic patients. The increase in these LDL and VLDL may be due to the hyperactivity of the parathormone[20]. But an opposite trend was noticed between the parathormone and trigycerides[21]. As a consequence of these lipid abnormalities and other risk factors for ischemic heart conditions, patient with end stage renal disease have been described to be at increased risk for artherosclerotic coronary artery disease and its complications.

Hyperkalemia

It is very common in renal disease patients to experience hyperkalemia. The increased level of potassium level can be noticed in patients with ACE-inhibitors and whose serum creatinine level will be above 1.5mg/dl. Heart failure patients will have more than three times the normal level of potassium in the blood[22]. Randomized Aldactone Evaluation Study[23] also proved that the potassium level will be higher in the heart failure patients. Therefore, the physician won't be concentrating in correcting the higher level of potassium instead they will just prescribed high dose (> 25mg/day) of spironolatone to control the level [24].

Diabetes Mellitus

The vascular diseases mainly affect the individual who are having diabetes mellitus rather than the other predisposing cardiovascular diseases. The formation of advance glycosylated end products (AGE's) in diabetic patients would predispose the patients to cardiovascular complications. Inflammation will trigger at the area of AGE's deposition around the arterial wall which leads to formation of atheromata. Each artherogenesis mechanisms have the cross-linking of protein, modifications of matrix components, increased collagen deposition, platelet aggregation, defective vascular relaxation, abnormal lipoprotein metabolism, loss of elasticity and increased arterial stiffness[25,26]. Prevalence of diabetes mellitus (diagnosed and undiagnosed) in England alone is about 7.4% in people age 16 and above. However, the patients who are renal kidney disease and diabetes mellitus have the prevalence rate for CVD of 18% to 30%[27].

Lindholm and his colleagues reported that twofold higher risks of death were noticed from IHD in diabetic RTR's compared to non-diabetic patients (25% vs 11.4%). Even researcher Arend also found that there is 2.9 relative risk of mortality after the first year diabetic incidence[28]. Registry data from the United States account also for more than two-fold higher than average risk of death from CVD in diabetic RTSs[29]. A 4.3 time's increased risk of post-transplant CVD in diabetics was reported by Aker[30]. Aakhus found IHD in 24% of diabetics versus 12% of non-diabetics[31]. In Kasiske's study, diabetics RTRs had a more than threefold increased risk for IHD and for cerebrovascular disease and a 28-fold risk for peripheral vascular disease [15].

Smoking

There is a correlation between direct smoking and cardiovascular diseases in CKD patients. The nicotine intake may show a way to increase in 22% of developing coronary artery disease[32]. Direct smoking also may have an impact on the carotid artery intima [33].

Stroke

Stroke also one of the risk factor of CVD in CKD patients. In one of the study (Choices for Healthy Outcomes in Caring for ESRD) showed about the etiology of ischemic stroke involving 1041 incident [34]. The observed percentage of stroke in these patients was around 4.2 per year. Moreover, the mortality rate was almost 3 times higher (35%) than the non-end stage renal disease patients. In three randomized trials the observed percentage of strokes with high mortality rates were reported to be 43% [35], 38%[36], 36% [37]and all the strokes were noticeable ischemic in nature. The appropriate treatments for reducing the non-cardio embolic ischemic stroke are by controlling blood pressure, usage of anti-platelet agents, and statins. Whereas the use of ACE inhibitors was proven to be helpful in controlling the blood pressure and reoccurrence of stroke in stage 3-4 CKD patients.

Other risk factors include

Arterial vascular disease:

In CKD, it is useful to consider 2 subtypes of arterial vascular disease, namely, atherosclerosis and large-vessel remodelling or arteriosclerosis. Atherosclerosis is an intimal disease characterized by the presence of plaques and occlusive lesions. There is a high prevalence of atherosclerosis in CKD. In addition to intimal hyperplasia, calcification of coronary arteries is a unique striking characteristic feature noticed in chronic kidney disease patients [38]. This is evident with a comparison of post-mortem

morphology of atheromatous lesions in 27 patients with progressive renal disease (average age of 69.5 years) and appropriate controls[39]. When compared to the fibroatheromatous Plaques of control group the atheromatous plaques of chronic renal failure patients are highly calcified. This calcification of arteries is not exclusive to elderly patients with progressive renal disease, and a recent study of dialysis patients aged 20-30 years had evidence of coronary artery calcification detected by electron computed tomography[40]. In renal failure patients the Coronary artery calcification was associated with patient's length of time on dialysis, their average serum calcium × phosphate product and intake of calcium containing phosphate binders. On an average the Coronary calcification was 17.5 times that of the general population. The identification of hydroxyl apatite type of calcified plaques as an independent predictor for mortality in dialysis patients was done along ago[41].

Atrial fibrillation:

Atrial fibrillation which is associated with increased incidence of stroke in CKD patients had a prevalence rate of 51-20% among dialysis patients [42, 43, 44]. In patients with atrial fibrillation warfarin is the most effective treatment for the prevention of stroke [45, 46, 47, 48]. In the European Atrial Fibrillation Trial (EAFT), 669 patients with non-valvular atrial fibrillation (NVAF) and a prior stroke or TIA were randomized to either warfarin (INR=2.5–4), aspirin 300 mg/day, or placebo. Patients who experienced stroke, myocardial infraction/valvular death were at a rate of 17%, 8%, and 15% per year in placebo, warfarin, and aspirin treated patients respectively. This represents a 53% reduction in risk with warfarin therapy in atrial fibrillation patients[45].

Immunosuppressants usage

The adverse effects associated with the use of immunosuppressives like corticosteroids in preventing graft rejection were mostly associated with cardiovascular disorders like hypertension, hyperlipidemia, angina which leads to increased patients morbidity and mortality. Steroids are also known to increases the risk of glucose metabolism disorders [49]. Withdrawal of corticosteroids on the other hand, reduces the incidence of these metabolic disorders and post transplantation diabetes [50]. On the other hand the nephrotoxicity and hyperlipidemia associated with the use of calcineurin inhibitors led to an increase in the number of renal transplant patients dying with functioning graft, mainly because of cardiovascular disease [51].

In view of the above prevalence rates, in India a community based voluntary health screening programme "Screening and Early Evaluation of Kidney Disease" (SEEK), was started in 2006. Patients were screened of Chronic Kidney Disease using simple test to estimate GFR and proteinuria. SEEK reported a very high prevalence of 17.4% of CKD using an abbreviated modified diet in renal disease (MDRD) formula, a glomerular filtration (GFR) estimation formula[52]. Moreover in a population screening study on 4712 subjects in New Delhi, India found that 37 had a chronic renal failure with a prevalence rate of 0.78% and it accounts for about 7.85 million when applied to India's one billion populations[53]. Etiologically the percentage of patients with other co-morbid conditions who were diagnosed with chronic renal failure were found as , diabetes (41%), hypertension (22%), chronic glomerular nephritis (16%), chronic interstitial disease (5.4%), ischaemic nephropathy (5.4%), obstructive uropathy (2.7%), miscellaneous (2.7%) and unknown cause (5.4%)[53]. where as in a second prospective study which was more representative in which data were based on prospective investigations conducted over a period of 1 (33 hospitals) to 3 months (15 hospitals) comprising 4145 CKD patients. The percentage of patients with other co-morbid conditions who were diagnosed with chronic renal failure in this study were found as diabetes (29.7%), chronic glomerulonephritis (19.3%), hypertension (14%), chronic interstitial disease and vesico-ureteral reflux (12.6%), obstruction and calculus (9.3%), ADPKD and Alport Syndrome (8.4%), undiagnosed (6.2%). This study shows that the prevalence of CRF in India is ~0.8%. If we combine the two, diabetes has emerged as the most frequent cause (30–40%) followed by hypertension (14–22%)[53].

In conclusion

Diabetes mellitus is the most important co-morbid condition associated with chronic renal failure; it is followed by hypertension, glomerularnephritis, chronic interstitial disease. This article emphasizes on the roles of clinical pharmacist in hospitals to educate the patients with the above disorders to undergo a regular renal function test which may prevent them from chronic renal failure.

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