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The Link Between Cardiovascular Disease and Chronic Kidney Disease: A Literature Review

Introduction

After browsing multiple scholarly sources about the link between cardiovascular disease (CVD) and chronic kidney disease (CKD), renal failure, and mild renal insufficiency, there is one pressing concern that has arisen: the healthcare system is not recognizing that cardiovascular disease risk factors need to be treated proactively when patients begin to develop CKD. This leads to an increased rate of CVD mortality, even in patients with mild renal insufficiency. Increased CVD mortality in patients with renal dysfunction must be halted; it is possible with further research into the direct mechanisms by which CKD accelerates CVD development.

There were three themes evident when browsing the available scholarly sources: first, there is a greatly enhanced risk of developing CVD in patients diagnosed with CKD, ESRD, and mild renal insufficiency; second, there are specific renal functionalities that are associated with the increase in CVD risk and mortality; and third, restoration of renal function by transplantation lowers CVD risk and mortality. Although the exact mechanisms of CVD development in relation to impaired renal function have not been explicitly defined, this literature review attempts to synopsize the previous research on the topic as well as provide new insight into what future research should entail.

Background

A few key terms should be defined for better understanding of this literature review. Chronic kidney disease is defined as either kidney damage or decreased kidney function for 3 or more months (1). Renal failure, or end-stage renal disease (ESRD), is the final stage of CKD and occurs when the kidneys can no longer provide sufficient filtration that the body requires. Mild renal insufficiency is defined as a serum creatinine concentration of 124 to 265 μmol/L (1.4 to 3.0 mg/dL) (2). This means that the kidneys are not filtering enough of this substance out of the blood, which is why elevated levels of creatinine in the blood indicate reduced renal function.

Healthcare professionals should be aware of the fact that CVD risk factor development and progression of CKD are concurrent; the best way to reduce CVD mortality is to treat the CVD risk factors as soon as possible (3). The link between kidney dysfunction and CVD is an important global epidemiological entity with an extent comparable to the link observed between CVD and diabetes mellitus (3). The annual direct costs for ESRD are around $23 billion dollars, and this cost is related to the maintenance of dialysis patients and treatment of CVD symptoms and conditions (4). Therefore, more effective treatment and preventive strategies (particularly for reducing CVD risk factor development and mortality) are necessary. Further research needs to be conducted into the link between CVD and CKD, as CKD has become a very real and relevant CVD determinant.

Decreased renal function leads to increased risk of cardiovascular disease

The increased rates of CVD risk factor development and mortality have been observed and discussed by several sources and reviews. The process of cardiovascular damage starts very early during progression of well-defined CKD, long before the dialysis stage is reached (3). Mortality from CVD in patients with ESRD is 10 to 30 times higher than in the general population (4), and a 5-fold increase in cardiovascular mortality risk is present in dialysis patients older than 75 years (3). More importantly, cardiovascular mortality is increased approximately 375 times in dialysis patients aged between 25 and 35 years (3). Even if the patient is not at the final stages of the disease yet, or has not yet been diagnosed with CKD, mild to moderate loss of renal function is strongly associated with increased risk of cardiovascular mortality (5). Treating CKD by dialysis does not decrease the risk of CVD mortality, contrary to what one would think. Cardiovascular death takes the biggest mortality toll in patients on maintenance dialysis (6). This is a clear signal that more research should be done on the effects of dialysis and dialysis medication on development of CVD risk factors.

Even with the current technological advances in medical care and dialysis treatment, morbidity and mortality remain at highly elevated levels. The five year survival rate of patients over 64 years of age when starting dialysis is worse than that of patients affected by malignant cancers (7). CVD is the leading cause of morbidity and mortality in dialysis patients, accounting for about 50% of deaths and 30% of hospitalizations (7). CVD-related deaths among dialysis patients are about 30 times higher than in the general population, and has warranted concern about the increasing rate of CKD over the past 30 years (7). Prevention of CVD should begin as early as possible during the course of CKD, and care must be taken to treat the CVD risk factors present in this population. Timely referral of CKD patients to nephrology care is of utmost importance when considering patients' prognoses. Timely referral can help to detect the early stages of CKD, when patients are technically experiencing only mild renal insufficiency. Mild renal insufficiency has a significant impact on CVD risk factor development, and the risks of death resulting from CVD were higher for individuals with renal insufficiency during 16 years of follow-up monitoring of the NHANES II study cohort (8). The increased risk of CVD morbidity and mortality due to mild renal insufficiency was not as high as the risk observed in studies on patients with ESRD (8), but is still worrisome. This observation means that the risk of CVD mortality increases with the progression of CKD. It is also alarming to note that the prevalence of mild renal insufficiency is much greater than that of ESRD (8), which indicates that mild renal insufficiency may result in a greater burden of CVD in the population than does ESRD. Another important thing to mention is that the population with mild renal insufficiency is more difficult to identify and monitor, mainly because of the lack of development and progression of CKD symptoms.

In patients with CKD, CVD is the leading cause of mortality and is more likely to cause death than the eventual kidney failure that would result from CKD (9). More research is necessary to determine more effective treatment methods and to analyze the mechanisms by which CKD accelerates the progression of CVD and development of CVD mortality risk factors. Although these exact mechanisms are not yet clear, there are certain factors that could play a role.

Specific renal functionalities associated with increased cardiovascular disease risk

Several research studies have attempted to determine the distinct physiological pathways by which CKD increases CVD risk and mortality, and multiple measurements of substances in the body and other conditions have been tied to this mechanism. CKD promotes conditions such as hypertension and dyslipidemia (elevated levels of triglycerides and cholesterol in the blood) (7), which lead to renal failure and in turn accelerate atherosclerosis (10). Accelerated atherosclerosis will then lead to increased prevalence of coronary artery disease, heart failure, stroke, and peripheral arterial disease (10). Consequently, patients with renal failure are exposed to increased morbidity and mortality as a result of cardiovascular events (10). Serum creatinine levels and microalbuminuria are also viewed as factors playing into mild renal insufficiency. Microalbuminuria refers to elevated levels of urine albumin, which means that the kidneys are leaking this protein into the urine (2); this does not occur in a normal healthy individual. Increased serum creatinine concentration in the blood and microalbuminuria were equally strong risk predictors, and may be related to the degree of generalized atherosclerotic damage (2). A decrease in glomerular filtration rate (GFR), the rate at which the kidneys filter the blood, is directly associated with an increased risk of cardiovascular death (2). Endothelial dysfunction could also possibly be linked to increased cardiovascular mortality risk. Endothelial dysfunction refers to an imbalance of vasodilating (increases blood vessel diameter) and vasoconstricting (decreases blood vessel diameter) substances produced by or acting on the endothelial tissue lining the blood vessels (10). Endothelial dysfunction appears to be the pathophysiological mechanism by which increased serum creatinine levels, microalbuminuria, or a decreased GFR can increase the prevalence of CVD risk factors such as hypertension and dyslipidemia (10). Endothelial dysfunction is caused by endothelial cell injury or damage, which (in the case of CKD, ESRD, and mild renal insufficiency patients) results from the presence of unfiltered substances in the blood.

After reviewing several studies containing over 150 000 participants, there seems to be certain substances and processes in the body during CKD that have effects on the accelerated rates of CVD development. The Hoorn Study (5) used three measurements to determine the levels of renal function: serum creatinine level (μmol/L), mean creatinine clearance (mL/min/1.73m^2), and mean GFR (mL/min/1.73m^2). The results of this study showed that: per 5 μmol/L increase in serum creatinine level, the risk of cardiovascular mortality increased by 11% (1.11 times as likely to die from cardiovascular outcomes); per 5 mL/min/1.73m^2 decrease in creatinine clearance, the risk of cardiovascular mortality increased by 15%; and per 5 mL/min/1.73m^2 decrease in GFR, the risk of cardiovascular mortality increased by 26% (5). These results show that even a slight loss of renal function increases the risk of CVD development and cardiovascular mortality. The healthcare system, if aware of these renal function impairments, would be better suited to treat and potentially reduce the risk of developing CVD. Also, researchers need to take these substances and their measurements into account before researching and developing methods to decrease the risk of CVD development and mortality.

Another cohort study reported that abnormal albumin levels in the urine are a significant predictor of cardiovascular outcomes, and albuminuria often precedes the functional deterioration that is evidenced by a decline in GFR (10). Microalbuminuria

(ACR, 30 to 300 mg/g) increases the odds of an adverse cardiac event by 10.02 (10). ACR is the albumin:creatinine ratio in the urine. There is growing evidence that relatively minor renal abnormalities such as a slightly reduced GFR, or microalbuminuria are associated with increased CVD event and mortality risks (10). The evidence of association between microalbuminuria and endothelial dysfunction has not been studied enough yet to officially correlate the two, but studies have proposed that endothelial dysfunction is a principal pathophysiological mechanism that associates renal dysfunction with increased cardiovascular risk (10). Many CVD risk factors that could affect endothelial function can be found in association with CKD. Related conditions such as diabetes, obesity, and hypertension, as well as renal dysfunction lead to activation of the renin-angiotensin system, oxidative stress, elevated ADMA, low-grade inflammation with increased circulating cytokines, and dyslipidemia (10). These conditions are all common pathophysiological mechanisms that play a role in the association of CVD and CKD. If this association is ever clearly defined, researchers and healthcare professionals would have some of the knowledge necessary to develop distinct and comprehensive treatments for the symptoms and effects of renal impairment as well as potentially prevent the development of CVD.

Another study investigated the effects of certain conditions to determine if an association existed between the conditions and their effects on renal impairment and CVD risk. Hypertension, dyslipidemia, lipoprotein (a) concentrations, microalbuminuria, homocysteine levels, acute-phase reactants, and anemia were all examined as possible contributors to the progression of renal dysfunction and CVD development. Renal impairment leads to hypertension because the blood pressure increases when GFR decreases (11). Hypertension increases the risk for cardiovascular events such as coronary artery disease and congestive heart failure (11), but hypertension can be treated with medication. Renal impairment also causes high-density lipoprotein cholesterol (HDL) levels to decrease and low-density lipoprotein cholesterol (LDL) levels to increase, mainly due to abnormal lipase function (11). These cholesterol level fluctuations can lead to coronary artery disease, but can be treated with medication. Low GFR is a direct indicator of decreased renal function, and this lower GFR also increases lipoprotein (a) concentrations (11). Increased lipoprotein (a) concentrations are unlikely to be lowered by medication, and can lead to coronary artery disease (11). Microalbuminuria, as discussed previously, is due to endothelial dysfunction caused by renal impairment. Microalbuminuria can also lead to cardiovascular events such as coronary artery disease (11). Decreases in GFR, even when in very small amounts, lead directly to increased homocysteine levels. These elevated homocysteine levels are correlated with an increased risk of developing coronary artery disease (11). Acute-phase reactants are released in response to inflammation, and include fibrinogen, albumin, and C-reactive protein. Fluctuations in the levels of these substances affect blood viscosity and coagulation ability (11). Elevated levels of fibrinogen specifically, relate to an increased risk of developing coronary artery disease (11). Anemia, resulting from decreased levels of erythropoietin produced by the kidneys, affects the amount of hemoglobin in the blood. Decreased levels of hemoglobin are directly related to increased risk of congestive heart failure, as well as left ventricular hypertrophy (11). Renal failure is associated with changes in known and suspected CVD risk factors, some of which seem to be a direct result of renal impairment.

Restoration of renal function by transplantation reduces cardiovascular disease risk and mortality

Cardiovascular disease risk factors, when detected early in the stages of renal insufficiency, can be managed or even stopped. If detected early enough, patient prognoses can be positively affected, although CVD risk factor development is difficult to stop quickly. The progression of risk factors for CVD can be halted, but only one method has definitive evidence of doing so: renal transplantation.

When a patient is diagnosed with CKD, they are likely put on a wait list for a kidney transplant. In the meantime patients are prescribed medication, and once the disease progresses far enough patients are placed on dialysis treatment. Besides transplantation, there is one other method that has reduced CVD risk in CKD patients, but it has not yet been fully proven. Some evidence suggests that angiotensin-converting enzyme (ACE) inhibitors reduce the high rates of CVD in patients with renal insufficiency (2). Although ACE inhibitors are the general medication for treating hypertension, the effects produced in CKD patients are not significant enough to warrant them as a complete treatment option. Other options for treating this increased CVD risk are currently in stages of development, as renal transplantation should not be the only option available to this population.

Renal transplantation and its effects have been studied and favorable CVD risk changes have been observed. Progression of atherosclerosis and CVD in patients with renal failure is largely due to loss of renal function, and provision of a functioning kidney through renal transplantation halts the progression of CVD and dramatically reduces mortality (4). Renal transplantation has exemplified a significant survival advantage over maintenance dialysis (4). It is highly likely that most of this survival advantage is related to decreases in both progression of CVD and cardiovascular mortality after successful kidney transplantation (4). There is a spike in CVD risk, however, during the first three months after transplantation operations are completed, due to the high dosage of immunosuppressants that the patient is placed on (6). This risk decreases significantly after the first three months, and is strongly correlated with successful renal transplantation (6). There exists a progressive decrease in cardiovascular death rates in relation to renal transplant vintage; this trend is even more significant when contrasted to the opposite trend by dialysis vintage (6). Clearly a functioning kidney transplant confers significant protection from cardiovascular death, by halting or possibly even reversing CVD progression in ESRD patients (6). Decreasing CVD progression and mortality by renal transplantation improves the quality of life and longevity for patients with CKD or ESRD, but should only be utilized when completely necessary due to the limited number of donors.

Patients with ESRD have among the highest cardiovascular event rates documented, and renal transplantation has been the only method with conclusive results showing improvement and reduction in CVD risk and mortality compared to patients that do not receive transplants (12). It has been recently noted that cardiovascular events in patients on dialysis are strongly related to vascular function and structure, aspects of the body that are directly affected by most CVD symptoms and risk factors (12). Renal transplantation is associated with marked improvements in these aspects, namely vascular structure and function (12). Improvements in these features assist in decreasing the risk

of cardiovascular events and CVD mortality, and are apparent after renal transplantation surgery. This research shows that there is a way to decrease the CVD mortality rate in patients with CKD, but unfortunately not everyone is able to receive a transplant. There exists a limited number of donors, so researchers should attempt to find other definitive methods to restore renal function to CKD patients. If third party organ development ever reaches a level where mass numbers of organs can be produced, either by growing them off of other organisms (which involves ethical issues) or by 3D printing them then renal transplantation could be a relatively stable and permanent solution. Until then, research should be continued to discover new methods and treatments to prevent the progression of CVD in patients with reduced renal function.

Conclusions

Chronic Kidney Disease, ESRD, and mild renal insufficiency all greatly increase the risk for CVD and mortality. The exact mechanisms by which decreased renal function accelerates CVD are not yet fully known, but researchers are on the right path, constantly discovering new biological markers and measurements to help determine the physiological pathway of this relationship. There are several measurements of substances in the body that are directly related to CKD, ESRD and mild renal insufficiency, and may also be linked to the increased risk of developing CVD. Some of these measurements include serum creatinine levels, glomerular filtration rate, albumin levels and homocysteine levels (2,10,11). To date, there is only one definitive method to restore renal function: renal transplantation. When a patient receives a kidney transplant, the CVD risk rates spike for the first three months after the surgery, but after that a steady decrease in the CVD rates and mortality is evident (4,6). More research needs to be conducted in relation to the exact mechanisms and pathways by which CKD increases CVD risk, and whether it is a direct or an indirect pathway. More attention along with proactivity by the healthcare system is paramount to the longevity of the patient. If CVD risk factor development is not recognized early enough in the progression of CKD or renal insufficiency, the only way the patient may be able to survive is through a transplant; this should not be the only option.