Ischemic Heart Disease in Patients with End-Stage Kidney Disease

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Key Words
Coronary artery disease · Oxygen supply · Oxygen demand · Anemia · Left ventricular hypertrophy · Type 2 myocardial infarction

Abstract
Background: It was recently reported that the severity of coronary and carotid atherosclerosis in patients with end-stage kidney disease (ESKD) has improved over the last two decades. However, the frequency of coronary artery events observed at the initiation of dialysis remains high. Summary: Recently, 5 different clinical types of acute myocardial infarction (MI) were introduced in the third universal definition of MI. Type 2 MI, known as secondary MI, is a more heterogeneous entity, where a condition other than coronary artery narrowing contributes to an acute imbalance in oxygen supply and demand. In patients with chronic kidney disease, it has been demonstrated that type 2 MI is more common than type 1 MI, which is associated with coronary occlusive disease. It is suspected that patients with ESKD also often have type 2 MI. Factors associated with incremental increases in oxygen demand may cause myocardial ischemia in ESKD. Key Messages: Significant epicardial coronary narrowing might not be a necessary precursor of myocardial ischemia in ESKD. To prevent ischemic heart disease and improve prognosis in patients with ESKD, we need to pay attention not only to coronary stenotic lesions, but also to the factors associated with the induction of an imbalance in myocardial oxygen supply and demand.

Introduction
Ischemic heart disease (IHD) is prevalent in patients with end-stage kidney disease (ESKD) and has a marked impact on prognosis [1, 2]. In clinical studies of ESKD patients, IHD is variously referred to as coronary artery disease, coronary heart disease, and myocardial infarction (MI), among other terms. Many of these terms seem to reflect the commonly held concept that myocardial ischemia or myocardial necrosis is due to a significant coronary stenotic lesion and/or coronary occlusion in the epicardial arteries. We are also inclined to believe that the presence of significant coronary stenosis is a necessary precursor of myocardial ischemia and infarction.

It has been reported that the risk of cardiovascular events, including MI, is higher in patients with more advanced stages of chronic kidney disease (CKD) [3, 4]. This implies that coronary atherosclerosis progresses rapidly and severely in the course of advanced-stage CKD because of an increase in traditional and non-traditional risk factors for atherosclerosis, and that the prevalence of...
significant coronary stenotic lesions is higher in more advanced stages of CKD. Indeed, it was reported 20 years ago that about 60% of ESKD patients had significant, complicated angiographic coronary narrowing lesions at the initiation of hemodialysis (HD) [5]. Naturally, however, clinical practice has changed substantially since CKD was first identified as a risk factor for atherosclerotic cardiovascular disease, and recently it was reported that the severity of coronary and carotid atherosclerosis at the initiation of dialysis has improved over the last two decades [6, 7]. However, despite a tendency toward less severe coronary atherosclerosis in ESKD patients, a high proportion of patients still have IHD at the initiation of dialysis [8]. In this review, we discuss IHD in ESKD patients with reference to recent evidence in the literature.

The High Frequency of Coronary Events in Early-Phase Dialysis Patients

Every year, about 10% of CKD patients in the United States experience MI [9] and about 5% of Japanese dialysis patients die of MI [10]. Interestingly, the incidence of MI tends to be higher in the early period after starting chronic HD. In a large population study conducted in the United States, Herzog et al. [11] found that 29% of MIs occurred within 1 year of starting HD. Similarly, in a cohort study conducted in Okinawa, Japan, Iseki and Fukiyama [12] revealed that 24% of MIs occurred within the first year. Even in more recent data from 2007 to 2009, coronary event rates were found to be higher in the first year of dialysis than in the second year [8]. Such findings raise the question of whether HD itself is associated with rapid progression of atherosclerosis or the onset of coronary events after starting HD.

Does Coronary Atherosclerosis Progress Rapidly after Initiation of HD?

Several studies have focused on the relationship between the duration of HD and the severity of atherosclerosis in various parts of the vasculature. No association was found between the duration of HD and wall thickness of the carotid or femoral arteries (evaluated by ultrasonography) by Kawagishi and colleagues [13, 14], or with arterial stiffness or the extent of stiffness, which is one of the surrogate indexes of early atherosclerosis, by London et al. [15]. Similarly, a histological study by Vincenti et al. [16] showed no association between the duration of HD and the severity of atherosclerosis in the iliac artery. Thus, to our knowledge, there is no evidence of an association between the two factors. Moreover, in longitudinal observational study, Shoji et al. [17] confirmed the lack of an association between the duration of HD and the occurrence of cardiovascular events. Taken together, it would seem reasonable to conclude that HD itself does not promote the acceleration of coronary atherosclerosis, although this remains to be confirmed. Through multiple regression analysis, Shinohara et al. [18] demonstrated that aortic stiffness is positively correlated with the presence of renal failure but inversely correlated with HD independent of other confounding variables. These findings indicate that the high frequency of IHD in the early phase of HD is due to coronary lesions from the predialytic phase of CKD.

Is the Prevalence of Coronary Artery Disease at Initiation of HD Decreasing?

Around 20 years ago, several studies exploring the prevalence of cardiovascular abnormalities at the initiation of dialysis attempted to clarify whether the phase before or during HD is more important for progression of cardiovascular disease in CKD patients. It has long been known that the prevalence of IHD [2], congestive heart failure [19], left ventricular systolic dysfunction [20], and angiographic coronary atherosclerosis [5, 21] is much higher in CKD patients at the initiation of HD than in the general population. At that time, such information suggested that the uremic milieu, rather than HD itself, contributes to the acceleration of atherosclerosis in CKD patients.

The medical management of patients with predialytic phase of CKD to retard the progression of CKD and to prevent cardiovascular disease has changed remarkably over the past two decades [22]. Actually, we have recently demonstrated that the prevalence of significant coronary artery stenotic lesions as evaluated by angiography or single photon emission computed tomography at the start of dialysis has declined remarkably over this period, from 54% to 15% in ESKD patients without any history of cardiac disease in the predialytic phase. Concurrent with this phenomenon is the favorable change that has been seen in high density lipoprotein cholesterol and C-reactive protein levels with the use of medications such as erythropoiesis-stimulating agents, angiotensin receptor blockers/angiotensin-converting enzyme inhibitors, and statins, all of which are potentially protective against cor-

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Imbalance in Myocardial Oxygen Supply and Demand

IHD is typically caused by a decrease in coronary blood flow due to an epicardial coronary stenotic lesion. However, it is well recognized in clinical practice that MI can be induced by an increase in oxygen demand by the myocardium without any coronary artery narrowing [23]. Rostand et al. [24] reported the remarkable finding that 27% of HD patients’ ischemic symptoms were not caused by a significant coronary stenotic lesion. In ESKD patients, we often find factors associated with an incremental increase in oxygen demand, which can potentially cause myocardial ischemia.

Hypertension and Overhydration

Myocardial oxygen demand is defined by three major factors: left ventricular wall tension, contractility, and heart rate. Wall tension is estimated by the following formula: ventricular pressure \times ventricular radius / ventricular wall thickness. In other words, high blood pressure (high ventricular pressure) with volume overload (large ventricular radius), which is often seen in ESKD patients in the clinical setting, will lead to high wall tension of the left ventricle, thereby increasing myocardial oxygen demand. This suggests that patients with stage 4 and 5 CKD, including those on dialysis, are always susceptible to an incremental increase in myocardial oxygen demand, and by extension, that myocardial ischemia or infarction is possible without epicardial coronary narrowing. Of course, should tachyarrhythmia occur simultaneously, an imbalance between myocardial oxygen supply and demand would readily develop.

Cardiac Hypertrophy

Left ventricular hypertrophy (LVH) is reported to be an independent risk factor for the development of de novo ischemic heart disease in HD patients [2]. In particular, LVH is associated with a reduction in capillary density [25], which creates an imbalance in oxygen demand and supply, causing ischemia [26]. Ischemia promotes myocardial cell apoptosis, as well as extracellular matrix and collagen accumulation, leading to interstitial fibrosis, which in turn induces LV stiffness, increased LV filling pressure, impaired diastolic filling, and diastolic dysfunction [27, 28]. Moreover, myocardial fibrosis aggravates ischemia by reducing capillary density and coronary reserve [29]. Thus in ESKD, LVH may, in part, predispose patients to myocardial ischemia by reducing capillary density and coronary reserve, in addition to the increased oxygen demand for cardiac work, regardless of the presence of obstructive coronary artery disease. As is well known, LVH is highly prevalent in ESKD patients [30].

Anemia

Hemoglobin carries oxygen from the lungs to other tissues in the body, including the heart. Uncontrollable renal anemia has a negative effect on maintaining the balance in myocardial oxygen supply and demand. In an animal study, it was reported that in the presence of even mild anemia in dogs, electrocardiographic signs of ischemia and relative subendocardial underperfusion were observed with aortic stenosis—a typical situation in which myocardial oxygen demand is increased [31]. This means that the combination of anemia with increased oxygen demand, such as hypertension and/or volume overload, readily leads to an imbalance in myocardial oxygen supply and demand. It is of interest that correction of hemoglobin level improves the severity of myocardial ischemia in HD patients with stable angina pectoris. Hase et al. [32] demonstrated that partial correction of renal anemia from a hemoglobin level of 7.9 to 10.4 g/dl by treatment with recombinant human erythropoietin resulted in a significant increase in exercise duration and maximum pressure-rate product. Moreover, the maximum exercise-induced ST segment depression was significantly decreased after treatment.

Type 2 MI in ESKD Patients

In the third universal definition of MI [23], 5 different clinical types of acute MI (AMI) were introduced (table 1). Type 2 MI, also known as secondary MI, is a more heterogeneous entity, where a condition other than coronary artery narrowing contributes to an acute imbalance in oxygen supply and demand, such as coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachyarrhythmias or bradycardrhythmias, anemia, respiratory failure, hypotension, and hypertension with or without left ventricular hypertrophy. Baron et al. [33] recently compared the clinical characteristics of type 1 MI with those of type 2 and, as expected, the prevalence of eGFR <60 ml/min/1.73 m² associated with CKD was...
about 1.7 times higher in patients with type 2 MI compared with those with type 1 MI. Moreover, Sandoval et al. [34] speculate that type 2 MI often occurs in patients with ESKD. Together, these reports are consistent with the specific situation in ESKD where multiple factors are often found to be associated with an imbalance in myocardial oxygen supply and demand. Therefore, we need to be aware that significant epicardial coronary narrowing is not a necessary precursor of myocardial ischemic necrosis in ESKD patients.

Conclusion

Major improvements in the management of the pre-dialytic phase of CKD have been attained over the past two decades. Also, treatment and interventional procedures for coronary events have dramatically changed. Several studies suggest that the severity of atherosclerosis in ESKD has improved significantly in parallel with these changes. However, the prognosis of ESKD patients has not significantly changed. The pathophysiology of IHD in ESKD is probably due to an imbalance in myocardial oxygen supply and demand, rather than a remarkable decrease in oxygen supply caused by significant narrowing of the coronary artery. Indeed, it was reported that two-thirds of MI events in patients with CKD 4–5 were the non-ST-elevation type, whereas two-thirds of MI events in patients with CKD 1–3 were the ST-elevation type [35]. Therefore, to prevent IHD and improve prognosis in ESKD patients, we need to pay attention not only to coronary stenotic lesions, but also to the factors associated with inducing an imbalance in myocardial oxygen supply and demand.

Conflicts of Interest

None of the authors have any conflicts of interest or financial disclosures associated with this study.
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