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Roles of Metabolic and Endocrinological Alterations in Atherosclerosis and Cardiovascular Disease in Renal Failure: Another Form of Metabolic Syndrome

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Patients with end-stage renal disease have markedly increased risk for death from cardiovascular disease. Renal failure is associated with multiple metabolic and endocrinologic abnormalities, and these alterations are involved in advanced atherosclerosis and high cardiovascular risk. Increased insulin resistance index by homeostasis model assessment (HOMA-IR), a simple index of insulin resistance, was an independent predictor of cardiovascular mortality in nondiabetic patients on maintenance hemodialysis. Renal failure impairs lipoprotein metabolism leading to the atherogenic lipoprotein profile characterized by increased triglyceride-rich remnant lipoproteins such as intermediate-density lipoprotein, an independent factor of increased aortic stiffness. Non–high-density lipoprotein cholesterol, the sum of cholesterol of intermediate-density lipoprotein and other apoB-containing lipoproteins, is an independent factor associated with increased arterial thickness and a predictor of cardiovascular death in hemodialysis patients. The risk for cardiovascular death in hemodialysis patients is associated closely with hypertension and malnutrition, but not with obesity. The constellation of insulin resistance, dyslipidemia, hypertension, and malnutrition in renal failure suggests the presence of another type of metabolic syndrome promoting cardiovascular disease. In addition, vitamin D deficiency and abnormalities in calcium, phosphate, and parathyroid hormone levels increase the death risk from cardiovascular disease in renal failure. It is expected that treatment of these metabolic and endocrinologic alterations would improve the survival of patients with renal failure.

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The risk for death from cardiovascular disease is increased markedly in patients with end-stage renal disease receiving hemodialysis.[1] The presence of renal failure is associated with deterioration of multiple factors that may promote atherosclerosis and cardiovascular disease. Among well-known metabolic abnormalities developed in renal failure are insulin resistance,[2] dyslipidemia,[3] hypertension,[4] malnutrition,[5] vitamin D deficiency, and impaired calcium-phosphate homeostasis.[6] Studies from our laboratory and others have shown that these metabolic and endocrinologic abnormalities are associated closely with atherosclerosis and cardiovascular death in hemodialysis patients.

Insulin Resistance and Hyperglycemia

Patients with diabetes mellitus have decreased glucose use in response to insulin.[2] The reduced insulin action is termed *insulin resistance* and is found not only in diabetic patients but also in obesity and renal failure. The gold standard method for evaluation of insulin resistance is the euglycemic hyperinsulinemic glucose clamp, but it is time-consuming and re-

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quires special equipment. The HOMA-IR level can be calculated from fasting glucose and insulin levels,[7] and correlates significantly with the insulin resistance index obtained by the glucose clamp method in those with and without renal failure.[8] In a cohort of nondiabetic patients on maintenance hemodialysis, insulin resistance as shown by increased HOMA-IR levels was a predictor of cardiovascular mortality independent of other major risk factors.[9] This suggests that insulin resistance is associated with poor outcome of renal failure patients directly and/or indirectly via some nonclassic risk factors such as the presence of low-grade inflammation and increased homocysteine level.

In hemodialysis patients with diabetes mellitus, hyperglycemia appears to be a predictor of poor outcome. The studies by Wu et al[10] and Morioka et al[11] showed that an increased level of glycosylated hemoglobin was associated with a higher risk for death. However, these studies do not show which is more important, hyperglycemia itself or insulin resistance.

Lipoprotien Metabolism

Renal failure impairs lipoprotein metabolism,[3] causing the atherogenic lipoprotein profile characterized by increased remnant lipoproteins such as intermediate-density lipoprotein,[12] an independent factor of increased aortic stiffness.[13] Increased aortic stiffness also showed a positive correlation with cholesterol of very low density lipoprotein, low-density lipoprotein, but not high-density lipoprotein. The sum of cholesterol of non–high-density lipoproteins is an independent factor associated with increased arterial stiffness and thickness,[14] and an independent predictor of cardiovascular death in hemodialysis patients.[15]

There is a controversy regarding the role of plasma lipids in atherosclerosis in hemodialysis patients.[15] Previous studies showed that a high plasma total cholesterol level was associated with a reduced risk for all-cause and cardiovascular mortality.[16] In contrast, a high level of apoB, the major protein component of non–high-density lipoproteins, was increased in dialysis patients having a history of myocardial infarction.[17] The current understanding of the paradoxic relationship between plasma lipids and cardiovascular disease is that such a complicated and reversed epidemiology presumably is caused by the interaction of malnutrition, inflammation, and atherosclerosis.[5] Therefore, the true role of dyslipidemia should be clarified by interventional studies such as the 4D study.[18]

Hypertension

High blood pressure is associated with arterial thickness[14] and stiffness[13] in hemodialysis patients. Blood pressure is associated with risk for death in hemodialysis patients. But the association is not simple, and the U-shaped relationship is known in hemodialysis patients,[19] presumably because of the pre-existence of impaired cardiac function in those with low blood pressure. The use of antihypertensive medications is associated with better outcome, with β-blockers having the greatest benefit on survival in the analysis adjusted for other major confounders.[20] The major pathogenesis of hypertension in renal failure is excessive extracellular fluid. In addition, metabolic and endocrinologic alterations, such as insulin resistance and increased plasma endothelin concentration,[21] may play important roles.

Malnutrition

In contrast to the epidemiology in the general population, a lower body mass index previously was shown to be an independent predictor of increased all-cause and cardiovascular death rates in hemodialysis patients.[16] The coexistence of malnutrition, inflammation, and atherosclerosis is termed *MIA syndrome*[5] and may explain the unusual association between malnutrition and cardiovascular death. Although malnutrition predicts poor outcome of hemodialysis patients, it is unclear whether malnutrition promotes arterial changes. Because the risk for death from cardiovascular disease is determined by the risk for cardiovascular events (incidence of events) and the risk for death after the events (fatality), malnutrition may be more important in the risk for fatality than that of incidence of events.

Vitamin D Deficiency

Suppressed 1α-hydroxylase activity in renal failure causes deficiency of the active form of vitamin D_3, 1,25$(OH)_2$ vitamin D_3. Deficiency of vitamin D may cause a variety of uremic manifestations because the receptor for the hormone has broad distribution in many organs and tissues including the classic target organs (the bone, intestine, kidneys, and parathyroid glands) and other nonclassic targets (the heart, arteries, and the immune system).[6] Active forms of vitamin D analogues usually are used to treat secondary hyperparathyroidism and bone mineral abnormalities in renal failure. In addition, other beneficial effects of treatment with vitamin D are known such as reversal of left ventricular hypertrophy[22] and improved cardiac performance.[23] We showed the normalized immune function after administration of oral 1α(OH) vitamin D_3 (alfacalcidol)[24,25] that is to be converted into 1,25$(OH)_2$ vitamin D_3 by the liver. Furthermore, the expression of the macrophage scavenger receptor gene in vitro is suppressed in the presence of 1,25$(OH)_2$ vitamin D_3.[26] We recently found that the users of oral 1α(OH) vitamin D_3 had a significantly lower risk for death from cardiovascular disease than the nonusers in a cohort of hemodialysis patients.[27] The reduced risk for cardiovascular death in the vitamin D users remained significant after adjustment for other major confounders. Another recent study[28] compared the outcomes between 2 groups of hemodialysis patients, one group treated with 1,25$(OH)_2$ vitamin D_3 (calcitriol) and the other group treated with paricalcitol, a vitamin D analogue having a lower calcium-increasing activity than calcitriol. Paricalcitol is reported to be better than calcitriol in terms of survival advantage.

Calcium, Phosphate, and Parathyroid Hormone

Epidemiologic data indicate that hyperphosphatemia is a predictor of higher risk for death in hemodialysis patients,[29] whereas serum calcium level has no apparent correlation with mortality.[30] The parathyroid hormone level shows a U-shaped association with mortality.[30] Increased levels of serum phosphate and parathyroid hormone level were associated significantly with increased arterial thickness of hemodialysis patients.[31] Reduction of serum phosphate levels with the phosphate binder sevelamer slowed the progression of arterial calcification in patients with renal failure.[32]

Conclusions

As reviewed earlier, uremia-related metabolic and endocrinologic alterations are associated closely with vascular changes and cardiovascular mortality in patients with renal failure. The clustering of insulin resistance, dyslipidemia, hypertension, and malnutrition (not obesity), and an increased risk for cardiovascular disease suggest the presence of another form of metabolic syndrome in patients with renal failure. In addition, vitamin D deficiency and abnormalities in calcium, phosphate, and parathyroid hormone levels increase the death risk from cardiovascular disease in renal failure. These previous and recent observations warrant further studies to improve the outcome of renal failure patients by correcting the metabolic and endocrinologic alterations.

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