Fat expansion with obesity leads to chronic inflammation in adipose tissue itself caused by a local hypoxic state that triggers hypoxia-inducible factor 1α. The inflammatory response promotes adipose tissue fibrosis with excessive extracellular matrix accumulation, which leads adipose tissue into metabolic dysfunction (Figure). Visceral adipose fibrosis contrib-
EAT to slowing down the expansion of tissue volume, because of limited physical and metabolic flexibility, but overflow of free fatty acids from adipose tissue with inflammation and excessive serum lipids that have nowhere to go will result in ectopic lipid deposition in non-adipose peripheral tissues, such as liver or muscle. Ectopic fat depots and visceral fat are associated with increased risk of cardiovascular disease. Furthermore, we should know that ectopic fat accumulation has been reported to occur more easily in Asian populations, including Japanese, compared with Caucasians.

Epicardial adipose tissue (EAT) has been a focus because of its unique and multifaceted characteristics. EAT is located between the myocardium and the visceral layer of pericardium, contiguous with the myocardium. It is more active in fatty acid metabolism than other ectopic adipose tissues, thermogenic like brown adipose tissue, and secreting cytokines that may modulate myocardial and endothelial functions directly. EAT may secrete cardioprotective cytokines such as adiponectin under normal conditions, but secretes pro-atherogenic or pro-inflammatory cytokines such as tumor necrosis factor or interleukin-6 with obesity.

The presence of EAT is associated with coronary atherosclerosis, increased left ventricular mass, and development of atrial fibrillation. It is noteworthy that the volume of EAT is eligible as a marker of coronary atherosclerosis even with a coronary artery calcium score of zero on coronary computed tomography angiography.

The study by Tsushima et al suggests that EAT can predict a previously invisible group with lipid-rich vulnerable plaque independent of the high-risk group with coronary calcification. Recent research reconfirmed that segmental precoronary EAT volume evaluated with multidetector computed tomography was associated with the severity of coronary atherosclerosis and may be a determinant of plaque vulnerability.

Chronic kidney disease (CKD) is now an emerging global cardiovascular risk that affects up to 15% of the population. The absolute cardiovascular risk of patients with CKD is similar to that of patients with established coronary artery disease, and the severity of CKD is associated with increased cardiovascular risk. Several mechanisms have been proposed for the increased cardiovascular events with CKD: high prevalence of insulin resistance, high blood pressure, disturbed lipid metabolism, chronic inflammation, vascular calcification etc. The main lipid abnormalities seen in patients with CKD are metabolic disturbances in triglyceride-rich lipoprotein with fatty acid metabolism and high-density lipoprotein function. Statins clearly reduce the cardiovascular risk in the general population, but do not provide enough efficacy among patients with endstage CKD. Understanding the mechanism of CKD-induced cardiovascular disease will lead us to conquering the residual risk in this era of statins.

In general, obesity is simply associated with visceral fat accumulation. On the other hand, body mass index (BMI) is an inverse predictor of mortality in patients with CKD, mainly because low BMI means protein-energy wasting stage in this group. Nevertheless, ectopic fat deposition appears and is associated with coronary atherosclerosis in non-obese patients with CKD. Visceral adipose accumulation in non-obese patients should be described as “normal weight obesity”, but may also represent metabolic risk accumulation.

It has been recently reported that moderate to severe CKD patients (ie, stages 3–5) have epicardial fat accumulation, which is associated with increased cardiovascular events independent of general adiposity. Those reports indicate that EAT may have pathogenic roles independent of visceral fat accumulation and other cofounders.

In this issue of the Journal, Nakanishi et al report that epicardial fat accumulation is associated with renal dysfunction even among mild CKD patients with estimated glomerular filtration rate >30 ml/min/1.73 m2, and with vulnerable plaque evaluated by multidetector computed tomography. This is the first report on EAT and coronary atherosclerosis in the mild CKD group, and this study may provide a lost piece of the puzzle.

Interestingly, similar analysis in the Framingham Heart Study with a general population showed the association between epicardial fat accumulation and cardiovascular events was not independent of visceral fat accumulation. This discrepancy suggests that epicardial fat accumulation in the CKD group seems to be more linked with “normal weight obesity” and pathogenesis of this unique ectopic fat depot. Nakanishi et al report that the presence of high-risk plaque is associated with epicardial fat tissue volume even in a multivariate analysis including age, sex, hypertension, diabetes mellitus, hypercholesterolemia, smoking, and BMI. The association between EAT volume and coronary risk in the mild CKD group should be weak compared with advanced CKD groups, but the Japanese population with a tendency of ectopic fat accumulation may be suitable for conducting this study.

With these studies reporting a strong and independent association between EAT and coronary atherosclerosis, the intriguing hypothesis will lead to the idea that EAT itself can be a target of cardiovascular risk reduction. There are reports that significant weight loss in severely obese subjects can be associated with significant reduction in the epicardial fat thickness, but weight reduction could not be the main therapeutic method in CKD patients without general adiposity to improve their prognosis. As EAT is more functional, theoretically it can secrete protective cytokines and stop pro-inflammatory cytokines directly to the myocardium and vasculature under “normalized” conditions. As it directly contacts the vasculature, EAT may affect vascular remodeling or angiogenesis in the adventitia. Already some cardiovascular drugs, including renin-angiotensin-aldosterone system inhibitors and lipid-lowering agents, have shown anti-inflammatory properties in metabolic syndrome. More specific anti-inflammatory therapy, including targeting adipose infiltrating macrophages, could be effective for ectopic fat-induced metabolic disturbance.

As the authors describe themselves, the present study was a single-center preliminary study, not big enough to discuss the absolute coronary events, so further large-scale studies are necessary to confirm these intriguing findings.

Epicardial fat accumulation in CKD may elucidate the role of ectopic and visceral adipose tissue dysfunction in the development of coronary atherosclerosis. Comprehension of the mechanisms underlying atherogenesis and vascular protection in patients with CKD should provide new therapeutic targets that we do not now have in our hands.

References
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