Commentary

Atherosclerosis in chronic kidney disease: Striking while the Iron is labile

Cardiovascular disease (CVD) due to atherosclerosis is a leading cause of morbidity and mortality in both developing and developed world. This holds true for patients with all stages of the chronic kidney disease (CKD) so much hence that it has been remarked that "only the lucky reach dialysis" since the majority of the pre-dialysis subjects experience cardiovascular events before progressing to end stage renal disease. It is well-known that even on dialysis cardiovascular disease is the most important cause for mortality. In fact, a recent study endorsed the long prevailing perception that CKD, like diabetes, should be considered as a coronary artery disease (CAD) equivalent.[1]

The understanding of pathogenesis of atherosclerosis has grown immensely and it is now known that inflammation in all its hues is plays a significant role in addition to conventional risk factors. Oxidative stress is ubiquitous in all cellular activities and its role has been implicated in a host of the disease conditions including atherovascular disease. However, unfortunately, exogenous anti-oxidant therapy has so far delivered very limited therapeutic success in most conditions.

This issue of the journal carries an article about serum catalytic iron as a biomarker for coronary artery disease in

patients on maintenance hemodialysis. The results of this study as well as another publication on a similar theme in subjects without CKD present impressive data about a distinct and substantial association of serum catalytic iron with prevalent CAD as well its ability to predict short-term mortality in acute coronary syndromes.[2] This study unequivocally lends strength to the existing literature on the role of iron and CAD/atherosclerosis.

However, the role of iron in the pathogenesis of atherosclerosis is still far from settled. Essentially, iron is an essential dietary component, necessary for a number of cellular functions. The importance of iron resides in its capacity to participate in electron exchange reactions. However, this nature also endows it with a capacity to catalyze free radical generation. The two main oxidative states are the divalent, Fe (II), and the trivalent, Fe (III). Because of the extremely low aqueous solubility of iron, biologic systems have evolved proteins that are able to bind Fe (III) and keep it thermodynamically stable, and proteins that are able to catalyze the reduction of Fe (III) to Fe (II) to make it kinetically available for biological processes. Through the Fenton reaction, under biologically relevant conditions, Fe (II) is capable of transforming molecular oxygen to the superoxide radical (O_2^-), and weak oxidant hydrogen peroxide (H_2O_2) into hydroxyl radical (OH), the major damaging reactive species in nature.[3]

Epidemiological studies initially suggested that low iron stores due to menstrual loss afforded protection from cardiovascular disease in women, safety that was ceded with menopause.[4] Other associations of body iron with carotid intima media thickness and acute coronary syndromes have also been reported. However, data on the role of iron in atherosclerosis is conflicting with numerous other reports that refute this association. Hemochromatosis, a condition of iron overload has not been associated with premature atherosclerosis. A very recent population based study on the associations of serum ferritin and percentage transferrin saturation (TS%) with all-cause, cancer, and cardiovascular disease mortality actually found no correlation with serum ferritin and an inverse correlation of TS% with CVD.[5]

Nevertheless, from a pathophysiological perspective, the role of iron as a potential atherogen is plausible given its susceptibility to oxidation and association with inflammatory stress. The authors report on the association of catalytic iron and not ferritin or TS% with a significant atherosclerotic coronary artery disease. The former is likely to be a better way of examining the association of iron with its inflammatory effect, a measure of the body iron that can participate in oxidative injury.

Reactive oxygen species play a central role in endothelial damage and generation of oxidized low density lipoprotein (LDL), a key determinant of the atherosclerotic plaque.[6] Earlier studies have identified catalytic iron in human atherosclerotic plaques. Animal studies in cholesterol fed rabbits have demonstrated a decrease in plaque iron content with the use of the iron chelator, desferrioxamine.[7] More recently, using dual energy computed tomography and three-dimensional tomography, researchers at Mayo identified iron in unstable plaques.[8]

However, cross-sectional data can at best be considered hypothesis generating as it is impossible to establish causality. Intra-plaque hemorrhage is well-known and iron deposits in macrophages could reflect a secondary phenomenon of plaque inflammation and healing following an initial injury. The etiopathogenesis of coronary artery disease is complex and truly multi-factorial with different clinical and biochemical pathways culminating in the development of the atherosclerotic plaque. Even in the current study, it would have been helpful to have some information of inflammatory status of the subjects, the exact timing of blood sampling with respect to coronary angiogram, the indication of angiography in each subject, total iron received exogenously on dialysis and serial titers of catalytic iron, to establish their stability or time course. It is well-accepted that the pathogenesis of atherosclerosis in CKD and uremia has additional variables than in the general population. In the current study, many of the well-established associations of CAD fell out on multivariate regression arguing for the possibility of a non-representative cohort of subjects. Furthermore, the association of serum catalytic iron did not show a "dose-response" with the magnitude of CAD. Despite all these limitations, a role of iron in CAD remains plausible and even more so in CKD subjects who receive intravenous iron preparations which are known to have a measurable albeit small proportion of free iron. Further, intravenous iron has been shown to escalate oxidative status of subjects.[9] The association of iron with CAD/atherosclerosis is causative or it is just marker or a covariate can only be established by longitudinal studies. Then only, we will be able to establish the role of iron metabolism in the genesis of the coronary plaque and its therapeutic implications, if any. Until then, three decades after it was first postulated, the role of iron in atherosclerosis/CAD remains to be fully established.

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