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Heavy Metal Accumulation in Cardiovascular Tissues: Rethinking Pathogenesis and Treatment Paradigms

Kardiyovasküler Dokularda Ağır Metal Birikimi: Patojenez ve Tedavi Paradigmalarını Yeniden Düşünmek

PERSPECTIVE
GÖRÜŞ

Cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality worldwide. While traditional risk factors such as elevated cholesterol, hypertension, and lifestyle choices have been well-documented, a growing body of research suggests that environmental and dietary exposure to heavy metals may also contribute to the pathogenesis of CVD. This editorial synthesizes findings from recent studies examining the elemental composition of cardiovascular tissues in patients with atherosclerosis, aortic stenosis, and carotid artery disease. These studies reveal that concentrations of magnesium, potassium, calcium, phosphorus, iron, bromine, zinc, aluminum, arsenic, chromium, platinum, and mercury are significantly elevated in diseased tissues. These findings imply a potential role for heavy metals in inflammation, calcification, and tissue degeneration.

Heavy Metals in Coronary Arteries: A Paradigm Shift in Atherosclerosis

A recent epidemiological study in U.S. adults found that urinary metal levels are associated with an increased risk of CVD and related mortality.[1] Another study showed that exposure to various metals is generally associated with the extent of coronary artery calcification, both at baseline and during follow-up assessments.[2] Previous analyses of coronary artery tissues from autopsy cases have revealed that metals such as magnesium, calcium, phosphorus, iron, zinc, arsenic, chromium, platinum, and mercury are present in significantly higher concentrations in atherosclerotic coronary artery tissues compared to non-diseased controls. Yolay et al.[3] highlighted these findings for the first time in their investigation of coronary tissues, suggesting that non-essential metal accumulation may contribute to chronic inflammation, tissue stress, and plaque formation in the coronary arteries. These results challenge the cholesterol-centric view of atherosclerosis by introducing a new hypothesis: that metal toxicity, possibly resulting from chronic environmental exposure, is an underexplored contributor to the disease. This emerging perspective opens new avenues for future research to explore the pathophysiological mechanisms through which heavy metals exacerbate vascular disease.

Stenotic Aortic Valves and the Selenium Deficiency Hypothesis

In studies on aortic stenosis, researchers have, for the first time, identified a notable deficiency of selenium along with elevated levels of metals such as sodium, magnesium, phosphorus, copper, zinc, chromium, and mercury.[4,5] Selenium, a well-known antioxidant, plays a crucial role in reducing oxidative stress in cardiovascular tissues, and its deficiency may promote chronic inflammation in the aortic valves. Olcay et al.[5] proposed a "toxic inflammation hypothesis" to explain these findings, suggesting that heavy metal accumulation disrupts cellular homeostasis and activates inflammatory pathways similar to those observed in atherosclerosis. We hypothesize that heavy metals create a toxic insult in tissues, leading to the alteration of three-dimensional protein structures through metal binding. These altered protein structures may trigger a chronic autoimmune inflammatory response, which could explain our study findings. In particular, elevated levels of mercury and chromium, along with selenium deficiency, may serve as initiators of aortic valve protein structural changes, ultimately triggering an autoimmune inflammatory response. High levels of zinc and

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copper in aortic tissue may represent residual components of the Cu-Zn superoxide dismutase enzyme, which scavenges superoxide ions generated during chronic autoimmune inflammation in calcific aortic tissues. The toxic inflammation hypothesis should replace passive degeneration concept in the pathogenesis of aortic stenosis, and new preventive and therapeutic strategies should be developed accordingly. This hypothesis suggests that selenium supplementation, targeted antioxidant therapies, or heavy metal chelation could serve as novel interventions to delay or mitigate the progression of calcific aortic stenosis.[6]

Carotid Plaques: Elemental Composition and Implications for Stroke Risk

The accumulation of non-essential metals in carotid plaques has also been observed in studies analyzing surgically removed carotid endarterectomy specimens. In a 2019 study, Olcay et al.[4] were the first to report that concentrations of magnesium, potassium, calcium, phosphorus, iron, bromine, zinc, aluminum, arsenic, chromium, platinum, and mercury were markedly elevated in carotid plaques compared to normal carotid tissues. The authors propose that these metals may represent a missing link in the pathogenesis of atherosclerosis, contributing to plaque vulnerability and increasing the risk of stroke and transient ischemic attacks. This study highlights the role of non-essential transition metals, such as aluminum, chromium, cadmium, and arsenic, in the pathogenesis of carotid atherosclerosis, proposing that their accumulation contributes to oxidative stress, DNA damage, and plaque formation. Key findings include:

Metal-Induced Oxidative Stress: Redox-active metals (e.g., iron, copper, chromium) generate reactive oxygen species (ROS), while redox-inactive metals (e.g., cadmium, arsenic, lead) impair protein function.

Plaque Composition: Elevated levels of calcium and phosphorus in carotid plaques resemble hydroxyapatite, suggesting an ongoing accumulation process.

Clinical Correlations: Increased aluminum and chromium concentrations in atherosclerotic plaques may serve as independent markers of cardiovascular risk. Cadmium has been linked to ischemic stroke and plaque vulnerability, although its postmortem accumulation can complicate accurate interpretation.

These findings in carotid plaques mirror observations from studies of coronary and aortic tissues, supporting the hypothesis of a systemic pattern of metal accumulation in atherosclerotic lesions. This pattern may be addressable through novel preventive and therapeutic strategies, such as chelation therapy, aimed at reducing metal-induced toxicity and inflammation.

Clinical Implications for Diagnostic Challenges and Future Directions

Diagnosing heavy metal intoxication is challenging due to several factors:

1. Lack of Standardized Protocols – There are no universally accepted guidelines for screening or diagnosing heavy metal exposure, resulting in inconsistent detection and management.
2. Short Detection Window in Blood and Urine – Heavy metals are detectable in biological samples only for limited periods:
   - **Blood:** Detectable for days to weeks, reflecting recent exposure.
   - **Urine:** Detectable for weeks to months.
   - **Hair (Scalp or Pubic):** Can reflect exposure for up to a year, but it is not widely used in clinical practice.
3. Chronic Tissue Deposition Is Difficult to Assess – Metals accumulate in various organs (e.g., brain, liver) over time, but routine medical tests do not reliably measure these long-term tissue deposits.
4. Chelation Challenge Tests Are Not Standardized – Some centers employ ethylenediaminetetraacetic acid (EDTA) or dimercaptosuccinic acid (DMSA) challenge tests with 24-hour urine collection to evaluate chronic metal burden. However, these methods are not endorsed by official clinical guidelines, which makes the diagnosis of long-term exposure challenging.
5. Current Testing Primarily Detects Acute Exposure – Traditional blood and urine tests are effective in identifying recent metal exposure, but they fail to detect chronic metal intoxication, where metals have already been deposited in tissues.[7]

A previous American Heart Association (AHA) scientific statement reviewed the evidence linking chronic exposure to low and low-to-moderate levels of three contaminant metals—lead, cadmium, and arsenic—to coronary and peripheral artery atherosclerosis, including stroke. The statement emphasized the clinical and public health implications for healthcare professionals, researchers, and the general public. However, the review was limited to only three heavy metals, whereas our previous findings suggest that additional metals, such as iron, bromine, zinc, aluminum, chromium, platinum, and mercury, also require inclusion and further investigation. The AHA review discussed several mechanisms, including impaired vascular endothelial function, chronic inflammation, hypertension, kidney toxicity (primarily affecting the proximal tubule), oxidative stress, lipid metabolism disruption, myocardial electrical disturbances, cardiotoxic effects, and epigenetic changes. We propose that the "chronic autoimmune inflammation hypothesis" should be added to the list of potential causative mechanisms. Furthermore, aortic stenosis should be included in the spectrum of heavy metal-associated cardiovascular diseases, which the AHA review restricted to coronary and peripheral arterial disease. Our pathologic tissue analyses provide strong preliminary evidence to support a causal relationship, and we urge the cardiology community to recognize chronic heavy metal exposure as a significant cardiovascular risk factor. There is a critical need to standardize diagnostic methods and implement heavy metal screening protocols in clinical guidelines.[8]

A recent review article strongly emphasizes that molecular investigations have provided insights into the complex interplay between environmental factors and CVDs, underscoring the urgent need for comprehensive preventive measures and environmental policies to safeguard public health.[9]

Conclusion

This body of research invites a shift in our understanding of cardiovascular disease pathogenesis. The accumulation of heavy metals in coronary, aortic, and carotid tissues suggests that these elements may play a contributory role in vascular inflammation and plaque stability, potentially representing the long-sought missing pathophysiologic link.

The findings from these studies present a compelling case for re-evaluating the role of heavy metals in cardiovascular diseases, proposing that chronic heavy metal accumulation be recognized as an independent risk factor in official clinical guidelines. They also highlight the need for standardized diagnostic and screening methods for chronic heavy metal exposure. The novel toxic autoimmune inflammation hypothesis presented here challenges the traditional focus on cholesterol and lipids, urging the medical community to consider environmental and dietary sources of metal exposure as potential modifiable risk factors in the prevention and treatment of CVD. Further research is essential to validate these findings, and to explore therapeutic interventions targeting metal accumulation particularly in the context of atherosclerosis and aortic stenosis.

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