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Relation between Alkaline Phosphatase and Cardiovascular Disease: Review Article

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ABSTRACT

Background: In human tissues, alkaline phosphatase (ALP) is a membrane-bound glycoprotein with the highest activity reported in kidneys, bone as well as in liver. In recent years, it has emerged as a risk factor for cardiovascular disease. ALP has been linked to increased vascular inflammation as well as calcification in both laboratory and clinical trials. Blood ALP activity has been associated with an increased risk of death or significant adverse cardiovascular events such as stroke, myocardial infarction, coronary revascularization, coronary slow flow phenomenon, and peripheral artery disease in epidemiological studies. Patients with chronic renal disease may benefit from medication therapy aimed at improving bone AP, according to new research.

Objective: This review article aimed to evaluate the Potential relationship between cardiovascular disease and alkaline phosphatase.

Methods: The databases were searched for articles published in English in 3 data bases [PubMed, Google scholar and science direct] and Boolean operators (AND, OR, NOT) had been used such as [alkaline phosphatase AND cardiovascular disease OR CVD] and in peer-reviewed articles between June 2005 and October 2021.

Conclusion: Diagnosis of cardiovascular disease (CVD) is not based on ALP measurement. According to recent research, heart disease and CVD-related death are both more likely in people with higher levels of AP activity.

Keywords: Alkaline phosphatase, Cardiovascular disease.

INTRODUCTION

As a plasma membrane-anchored enzyme, alkaline phosphatases can be found in a wide range of organisms, from bacteria to humans. Catalyzing the hydrolysis and transphosphorylation reactions, the enzymes can be applied to a wide range of substrate phosphate monoesters and acceptors [(1)]. The biochemical characterisation of AP and the postulation of its physiological role were greatly aided by a series of experiments conducted by **Robison and Kay** [(2)] in the 1920s. Hexosephosphoric ester hydrolyzed in the presence of rabbit and rat bone extracts, but not in the absence of non-ossifying cartilage, was reported to liberate phosphate by Robison in 1923. Robison and Soames later termed the enzyme found in bone "monophosphoric esterase. Elevated AP levels have been linked to cardiovascular disease (CVD) and mortality in population-based research, according to epidemiological evidence. In patients who had suffered an acute myocardial infarction, **Tonelli and colleagues** [(3)] looked at the correlation between AP and cardiovascular disease risk. A stronger connection was shown between AP and death as the concentration of phosphate increased [(3)].

Structure and function:

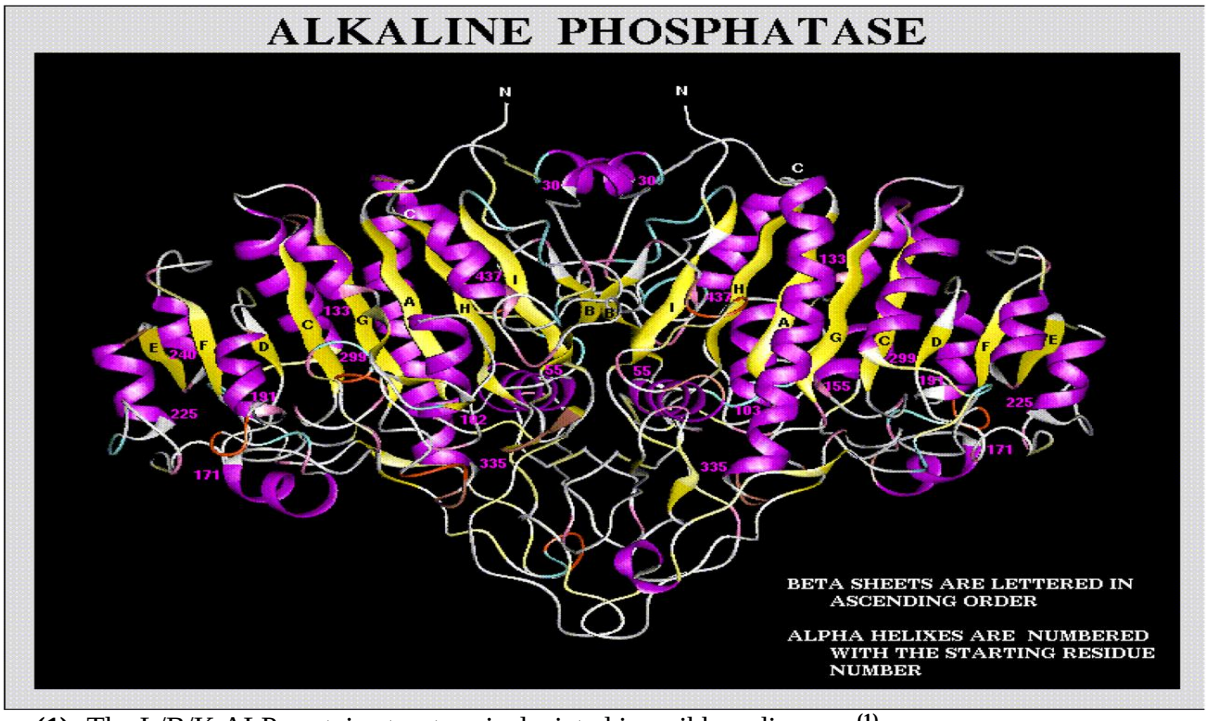

Figure (1): The L/B/K ALP protein structure is depicted in a ribbon diagram [(1)].

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It is important to note that there are four distinct forms of AP in humans: tissue non-specific (intestinal, placental and germ-cell types). It's in bone, liver, and kidneys (the AP type of these three organs) that TNAP is most active. Its homology to the other three tissue-specific APs is just 50 percent compared to those APs [(1)].

To date, there is no established mechanism for the release of AP from tissues into bloodstreams; however, several mechanisms have been proposed, including: C or D phosphatidases, lipolysis, cellular turnover, membrane breakage or proteolysis [(4)].

Alkaline phosphatase and cardiovascular disease:

Using data from the Prevention of Renal and Vascular End-stage Disease project, **Kunutsor and colleagues** [(5)] evaluated the correlation of AP with cardiovascular disease risk in 6,974 participants**.** AP was associated with a number of risk variables for cardiovascular disease, including age and CRP.

CVD developed in 727 patients throughout the course of a median follow-up of 10.5 years. Cardiovascular disease risk was shown to be "J-shaped" in relation to AP (CVD) [(5)].

Epidemiological studies show a clear connection between rising AP activity and an increased risk of death from any cause. People with elevated AP levels have been found to have a higher risk of cardiovascular disease, although the evidence supporting a relationship between elevated AP and CVD or CVD-related mortality is less clear. Men and women do not appear to have an elevated risk of death or cardiovascular disease (CVD) as a result of using AP. AP with atherosclerosis, coronary heart disease, and acute coronary syndromes such acute myocardial infarction have only been examined in a few studies (AMI). High AP levels seem to be associated with a reduced life expectancy in patients with chronic renal disease [(6)].

(CHD):

Patients with established coronary artery disease (CAD) are at greater risk of death from CVD-related causes, and biomarkers are useful in assessing risk in these patients. Prognostic value of AP has been studied in a variety of subsets of CHD patients. In the context of the CARE trial, 4115 patients with a prior myocardial infarction were investigated for the connection between AP and subsequent outcomes [(3)].

With regard to acute coronary syndrome (ACS) and ST-segment elevation infarction (STEI), numerous studies have been conducted (STEMI) . Our recent study examined the 3-year prognostic value of AP in 2134 individuals who had percutaneous coronary intervention for acute coronary syndromes [(6)]. Studying 847 individuals with acute STEMI, researchers found that AP was the best predictor of serious cardiovascular events in the hospital [(7)].

A poorer 5-year survival rate was shown to be associated with higher AP in diabetic patients who suffered an acute myocardial infarction in another investigations [(8)].

In patients with stable coronary artery disease or acute coronary syndromes, higher AP has been linked to an increased risk of mortality. Many parts of this relationship remain unanswered. According to a lack of comparative studies, whether the existence of coronary artery disease (CAD) is associated with an increased risk of death remains unanswered. It's not clear why AP is less strongly associated with cardiac mortality than all other causes of mortality in individuals with CHD, despite this being the most common cause of death. The link between AP, coronary calcium, and acute coronary syndromes is still up for debate till now. If coronary angioplasty or contemporary cardiovascular medicines (especially statins) have an effect, it's possible, but further research is needed to confirm this [(6)].

Alkaline Phosphatase and congestive heart failure:

There is a high prevalence of abnormal liver tests, such as abnormal AP values, in individuals with congestive heart failure. These abnormalities are caused by liver congestion and destruction [(9)]. This condition has been linked to extremely high AP levels [(10)].

Putative mechanisms of the association between AP and CVD risk and mortality:

Mechanisms underlying the link between AP and an increased risk of cardiovascular disease (CVD) and death outside of clinically overt bone or liver illness are still being studied. It's possible, though, to name a few other theories. A high AP level is linked to a wide range of cardiovascular and metabolic risk factors. There are at least two possible outcomes to this correlation: An important part of higher AP risk is mediated by cardio-metabolic risk factors. According to this connection, concerns have been raised over whether AP directly influences the pathogenesis of cardiovascular disease and mortality, or if it is just an epiphenomenon of CVD risk factors that tend to cluster in patients with elevated AP levels. A significant correlation exists between AP and inflammatory indicators such as C-reactive protein (CRP). Inflammation is hypothesised to affect all stages of atherosclerosis, including the formation of plaques, their progression, and the transition from stable to unstable plaques, as well as the resulting clinical effects [(11)]. According to population-based research and dialysis patients with chronic kidney disease, increased AP has been linked to low levels of vitamin D in the bloodstream [(12)].

No clear link between AP and CVD or CHD pathophysiology can be found in the above-mentioned pathways, despite their importance in understanding the relationship between AP and CVD or mortality. Since AP has been shown to be involved in calcification, it has been hypothesised that AP contributes to an increased risk of cardiovascular disease and a negative prognostic impact. The mechanisms of calcification in the arteries have been studied [(13, 14)].

In people who live in the community, coronary calcium also predicts mortality. The question of whether calcification of atherosclerotic plaques contributes to plaque instability is still open. Some researchers believe that calcium destabilises the plaque either by exerting a physical load on calcified nodules or by the tendency of plaques to rupture at the interface of high and low density tissues. Atherosclerotic plaque rupture might be predisposed by splotchy calcification, according to some researches [6, 15].

CONCLUSION

Diagnosis of cardiovascular disease (CVD) is not based on ALP measurement. According to recent research, heart disease and CVD-related death are both more likely in people with higher levels of AP activity.

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REFERENCES

1. **Sharma U, Pal D, Prasad R (2014):** Alkaline phosphatase: an overview. Indian Journal of Clinical Biochemistry, 29 (3): 269-278.
2. **Robison R, Kay H (1924):** The possible significance of hexosephosphoric esters in ossification. Part iii: the action of the bone enzyme on the organic phosphorus compounds in blood. Biochemical Journal, 18 (3-4): 755-764.
3. **Tonelli M, Curhan G, Pfeffer M *et al.* (2009):** Relation between alkaline phosphatase, serum phosphate, and all-cause or cardiovascular mortality. Circulation, 120 (18): 1784–92.
4. **Whyte M (2010):** Physiological role of alkaline phosphatase explored in hypophosphatasia. Annals of the New York Academy of Sciences, 1192 (1): 190-200.
5. **Kunutsor S, Bakker S, Kootstra-Ros J *et al.* (2015):** Serum alkaline phosphatase and risk of incident cardiovascular disease: Interrelationship with high sensitivity c-reactive protein. PloS One, 10 (7): 822-28.
6. **Ndrepepa G, Holdenrieder S, Xhepa E *et al.* (2017):** Prognostic value of alkaline phosphatase in patients with acute coronary syndromes. Clinical Biochemistry, 50 (15): 828-834.
7. **Huseynov A, Baumann S, Becher T *et al.* (2016):** Liver and cholestatic parameters as prognostic biomarkers of in-hospital MACE in patients with STEMI. European Journal of Clinical Investigation, 46 (8): 721-729.
8. **Nunes J, Melão F, Godinho A *et al.* (2016):** Plasma alkaline phosphatase and survival in diabetic patients with acute myocardial infarction. Annals of Translational Medicine, 4 (11): 210-215
9. **Samsky M, Patel C, DeWald T *et al.* (2013):** Cardiohepatic interactions in heart failure: an overview and clinical implications. Journal of the American College of Cardiology, 61 (24): 2397-2405.
10. **Shamban L, Patel B, Williams M (2014):** Significantly elevated liver alkaline phosphatase in congestive heart failure. Gastroenterology Research, 7 (2): 64-68.
11. **Hansson G (2005):** Inflammation, atherosclerosis, and coronary artery disease. New England Journal of Medicine, 352 (16): 1685-1695.
12. **Jean G, Charra B, Chazot C (2008):** Vitamin D deficiency and associated factors in hemodialysis patients. Journal of Renal Nutrition, 18 (5): 395-399.
13. **Schoppet M, Shanahan C (2008):** Role for alkaline phosphatase as an inducer of vascular calcification in renal failure?. Kidney International, 73 (9): 989-991.
14. **Zhu D, Mackenzie N, Farquharson C *et al.* (2012):** Mechanisms and clinical consequences of vascular calcification. Frontiers in Endocrinology, 3: 95-99.
15. **Mehta V, Paterick T (2021):** Coronary artery disease risk assessment in sedentary and active patients: medical risk, behavioral psychology, and the standard of care. Cardiovascular Disease, 4: 1-9.