Levels of C-reactive protein, LDL, IL-1α, and IL-1β as Potential Indicators of Heart Disease

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ABSTRACT

C-reactive protein, interleukin-1α, and interleukin-1β are biomarkers that are important in the early detection of heart disease and atherosclerosis. There are many different types of heart diseases, but coronary artery disease is the most common. Heart disease kills hundreds of thousands of people every year because it is usually detected late and its general complications at the later stages. Often, by the time a patient is diagnosed, the heart disease has progressed to its later stages where treatment is not as effective. One of the current diagnostic tests that are conducted is called an electrocardiogram (EKG), and it is very expensive, reducing cost-effectiveness. In this paper, the relevance of C-reactive protein, interleukin 1α, interleukin 1β, and low-density lipoprotein to the indication of heart diseases and the use of those in early detection is discussed. In addition, there is an in-depth review of the correlations between each of the biomarkers and the severity of atherosclerosis within patients.

Introduction

Heart disease is the collection of heart conditions. The most prevalent type of heart disease is coronary artery disease (CAD) as it affects about 365,914 Americans annually. CAD is characterized by the buildup of plaque alongside the walls of arteries, which are vessels that transport blood to the rest of the body. This process is known as atherosclerosis (refer to Figure 1). The plaque builds up on arterial walls usually containing cholesterol and other waste products of the cell. This buildup leads to less space in these vessels for blood transport, causing difficulty within blood flow in the body.

Heart disease is an important area of study because of its fatality, causing it to be the leading cause of death in America as 1 in every 4 Americans die due to heart disease. Also, the death tolls extend across all genders and racial and ethnic groups, implying that the need of research to be conducted to prevent such conditions from continuing to affect the population is growing (CDC, 2020).[1]
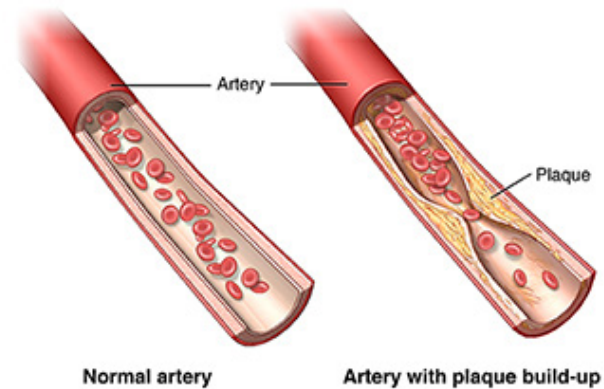
Figure 1. Normal Artery compared to Artery with plaque build-up (Hopkins)[2]

The current method of identifying heart disease is reliant on several blood tests and diagnostic tests. These blood tests include a Total cholesterol (TC) test, a High-density lipoprotein (HDL) test, a Low-density lipoprotein (LDL) test, and several other tests. A TC test is used to measure cholesterol levels since high levels of cholesterol can lead to a buildup in blood vessels, increasing risk of heart disease. A HDL test is used to measure the level of HDL, with higher levels being better for the body since high-density lipoproteins absorb cholesterol and take it to the liver to remove from the body. A LDL test is important because LDL can also build up in the walls of blood vessels, leading to narrowing (Cleveland Clinic).[3] Electrocardiograms (ECGs), Nuclear cardiac stress tests, and coronary computed tomography angiograms (CCTAs) are the main diagnostic tests used for identifying CAD in patients.

By detecting heart disease early, doctors can effectively prescribe treatments and carry out procedures, leading to significant positive results. Recent studies have shown an overwhelming amount of evidence relating the levels of specific proteins in the human body to signals of abnormal behavior causing heart disease. Proteins are a crucial part of the human body, carrying out many processes within a cell and attributing themselves to the regulation of a body's organs. Inflammation is the central response to the body's fight against the development of CAD, atherosclerosis, and many other heart diseases. This response causes fluctuation in protein levels which, if properly detected, can be the most indicative of heart complications. The early detection of CAD would greatly increase the rate of successful treatment, limit the need for substantial treatment, and reduce deaths from heart-related diseases.

There are several biomarkers, molecules found in the body that signify normal or abnormal conditions, responsible for detecting if one could be affected by CAD (NCI).[4] A few of these biomarkers include C-reactive protein (CRP), interleukin-1α (IL-1α), and interleukin-1β (IL-1β). When there are elevated levels of any of these biomarkers in the body, it generally indicates a higher risk of having heart disease (Journal of Cardiology, 2009).[5] Since there is no one specific cause of CAD, several factors such as smoking, having high blood pressure or cholesterol, and having diabetes can increase the chance of obtaining heart disease (Mayo Clinic, 2020).[6]

C-reactive protein

C-reactive protein (CRP) is the most commonly studied inflammatory biomarker related to CAD (Journal of Cardiology, 2009).[5] CRP is a ligand for FcγRII (CD32) and is made by the liver in response to inflammation (NCBI, 2021).[7] This protein can help identify systemic inflammation, elevated in response to injury, infection, inflammatory process of atherogenesis, and several other inflammatory responses. From a study done, it was concluded that CRP is found where there is either plaque or an injury to the vessel wall. This can either lead to the activation of the Mac-1 gene or restenosis which is the narrowing of the previously treated artery.

CRP levels can vary in individuals. Several factors play a role in this variety including genetics, parents who suffered a heart attack (MI), and cardiovascular risk factors like obesity, smoking, high blood pressure, serum triglycerides, and increased blood glucose levels. Additionally, having certain diseases such as chronic stable angina have been shown to have extremely high levels of CRP. After studying patients with acute coronary syndrome (ACS), a correlation between the levels of CRP and the risk of having an early death or repeating cardiac events was found.

Interleukin-1 (IL-1)
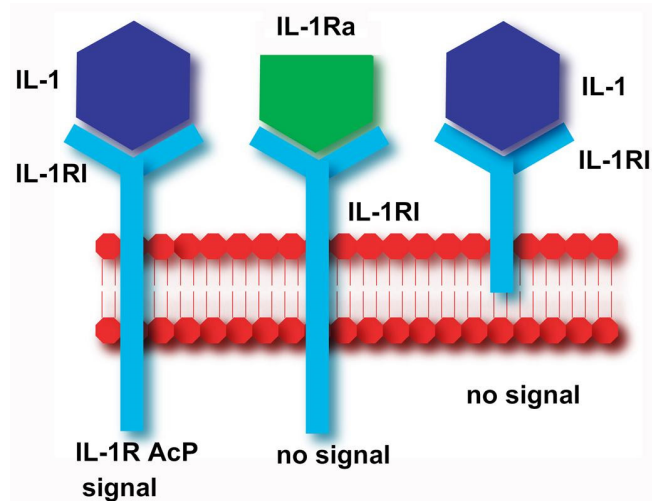
Figure 2. IL-1 Signaling Pathway (NCBI, 2009)[8]

Interleukin (IL)-1 is a group of ligands and receptors in the inflammatory cytokine family that is made by cells because of the recognition of several stimuli (NCBI, 2018).[9] IL-1 plays an important role in the detection and recognition of inflammation in the body. When there is a decrease in the IL-1β level, a decrease in the severity of the disease follows. Since inflammation has some significance in several cardiovascular diseases, interleukin-1 is being studied more extensively (NCBI, 2018).[9] In a study focusing on CAD, the underexpression of IL-1β or the overexpression of IL-1Ra has been shown to help protect against atherosclerosis. Even though there have been countless studies about the role of IL-1 in CAD, the exact role is still not known other than its importance for atherogenesis which is the formation and buildup of plaque in the arteries (AHA Journals, 2004).[10]

Both IL-1a and IL-1b play a role in activating inflammatory processes. First, IL-1α or IL-1β will bind to its receptor, type 1 IL-1R1 (NCBI, 2018).[11] Second, the additional protein (IL-1RAcP), which is the co-receptor chain, induces the binding of MyD88 to the Toll-IL-1 receptor (TIR) domain of each receptor. Finally, several kinases go through phosphorylation, the nuclear factor-κB (NF-κB) translocates to the nucleus, and several genes responsible for inflammation like the IL-1 gene are activated such as chemokines, pro-inflammatory cytokines, adhesion molecules, and colony-stimulating factors. Through this process, IL-1 stimulates inflammation which can be used to trigger plaque destabilization in blood vessels (NCBI, 2018).[9]

IL-1 is known to play an important role in the stimulation of post-infarction inflammatory response, the response caused by the death of cardiomyocytes in an infarcted heart leading to inflammation. It also plays a role in the pathogenesis of remodeling the heart. To understand more about IL-1, when studied in a mouse model, IL-1α was released by dying cardiomyocytes and IL-1β synthesis was increased after infarction. It was localized in leukocytes (white blood cells that are important in fighting pathogens), fibroblasts (aid with maintaining the structure of the myocardium) (Oxford Academic, 2005)[12], and cardiomyocytes (cells responsible for contracting the heart) (The International Journal of Biochemistry & Cell Biology, 2005)[13], showing us that targeting the IL-1 signaling cascade could lead to

promising effects in patients with myocardial infarction. Finding ways to block IL-1 isoforms in the future can help prevent the pathogenesis of cardiovascular diseases (NCBI, 2018).[9]

IL-1α and IL-1β are large precursor proteins. Pro-IL-1α is an active protein that is responsible for making mature proteins when it is cleaved by calpain which is a protein that degrades cell membranes (NCBI, 2011).[14] The two forms of IL-1α are known to stay inside of a cell unless a dying cell releases it. On the other hand, pro-IL-1β is in the inactive form until it is cleaved by the IL-1β-converting enzyme. Some of the IL-1β protein combines with procaspase-1 while the majority of it is found in the cytosol. Procaspase-1 is converted to caspase-1 when the IL-1β inflammasome, a molecular complex, is triggered. Once the caspase-1 is in its active form, it results in the production of the IL-1β precursor and of active IL-1β (NCBI, 2009).[15]

Current Treatments for CAD

Two main classifications of treatments for CAD are drugs and surgical procedures (Mayo Clinic, 2020).[16] Some common medications that are used to treat CAD include cholesterol-modifying medications, aspirin, beta-blockers, calcium channel blockers, ranolazine, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers (ARBs). Generally, medications are used when CAD is not very aggressive in patients, but in the case it is very aggressive, surgical procedures such as percutaneous coronary revascularization (also known as angioplasty and stent placement) or a coronary artery bypass surgery are conducted.

Cholesterol-modifying medications work to help treat CAD by reducing the plaque buildup in coronary arteries. This causes cholesterol levels, but more specifically low-density lipoprotein (LDL) levels to decrease. LDL is cholesterol that builds upon the walls of blood vessels blocking the flow of blood in the human body. This raises the risk of heart attacks and strokes which are fatal (WebMd, 2020).[17] Other specific examples of these drugs include niacin, statins, and fibrates.

Aspirin is another drug that can be taken to help with CAD since it thins the blood which decreases the chance of blood clotting. Reducing the chances of a blood clot helps reduce obstruction in the coronary arteries.

There are several drugs that can be taken together or separately to help reduce pain symptoms such as chest pain (angina). Beta-blockers are medications that are used to decrease the chance of heart attacks, reduce heart rate and reduce blood pressure. Calcium channel blockers are medications that can be used in conjunction with beta-blockers to synergize the effect of the drugs. Both of these drugs are used to manage pain such as chest pain rather than directly aiding in reducing the chance of CAD. In addition to this, ranolazine also helps with angina and can be used with beta-blockers.

Angioplasty and stent placement (percutaneous coronary revascularization) is a procedure where the medical professional will put a catheter into the part of the artery that is blocked. Then, another tool with a balloon is put through the catheter to reach the affected area of the artery. Following this, the balloon is filled so that it can push the deposits against the walls of the artery. Before the procedure is completed, a stent is left in the artery which lets out medicine that aids in keeping the artery open.

Another surgical procedure called coronary artery bypass surgery (CABG) is used to treat CAD. This procedure is not commonly used since it requires open-heart surgery which tends to cause many problems. In this procedure, the doctor will make a graft to bypass the part of the coronary artery that is blocked via a vessel from a separate area of the body. This will allow the blood to flow past the blocked area of the artery.

Methods

The following resources were used to obtain information needed for this review. National Center for Biotechnology Information (NCBI), Mayo Clinic, PubMed, Centers for Disease Control and Prevention (CDC) and WebMD. The keywords used to search the information included: CRP, of "Coronary Artery Disease", "Biomarkers for Coronary Artery Disease", and "Uses of C-reactive Protein". Coronary Artery Disease and its effects. Heart Disease Facts

Discussion

The diagnosis of heart disease risk is insufficient because a majority of the cases are detected in later stages of the complication's development in a patient. This is also many times the result of a lack of checkups for people who have a high risk for heart disease as a result of family history. Studies have shown there to be a 40% risk increase for patients who have siblings with cardiovascular disease (CVD), while a 60% to 75% risk increase for those whose parents have CVD. Usually, there are some symptoms such as chest pain or irregular heartbeats which indicate that someone should contact their medical professional (Mayo Clinic, 2021).[18] Doctors then conduct tests such as electro-cardiograms (ECGs) or blood tests in order to determine if a patient has a heart complication. Later stages of the disease are a result of the preemptive plaque buildup before symptoms are first identified (WebMd, 2020).[19] Essentially, this is a late detection of heart disease in which treatments can attempt to help the patient but are ineffective. As a result, many of the current tests to determine the presence of heart disease are incapable of early detection. This makes us consider what can be done to prevent the relatively quick progression of atherosclerosis. Treatment is much more effective when heart disease is detected at its earliest stages. Normally, the battery of tests for cardiac workup are ECGs, Exercise Stress Tests, Nuclear Stress Tests, Cardiac catheterizations, and Cardiac CT scans (Mayo Clinic, 2020).[16] A novel method to carry out early detection involves the analysis of C-reactive protein, LDL, IL-1α, and IL-1β levels together. This proposition costs less than the normal testing procedures and can be made more readily available.

CRP is directly associated with the fundamental process of atherosclerotic lesion (Oxford Academic, 2006).[20] The protein co-localizes with monocytes and lipoproteins which suggests that it triggers the caspase cascade and apoptosis—the programmed death of cells (NCBI, 2018).[21] Apoptosis is used to get rid of damaged cells and helps control the growth of cancer cells. Without an apoptotic mechanism, uncontrolled cell growth can occur, leading to the development of a tumor (NHGRI).[22] The interaction of CRP with inducing gene expression is highly correlative to atherosclerotic severity.

Alongside CRP, there is a presence of two primary cytokines involved with the IL-1 pathway, IL-1α, and IL-1β, which can indicate a higher risk of development or aggravation of heart complications. IL-1α and IL-1β play direct roles in the perceivable inflammation as a result of atherosclerosis (Frontiers in Immunology, 2020).[23] Specifically, IL-1α plays an important role in the inhibition of atherosclerotic development at its earliest stages (NCBI, 2009).[15] Two of the outcomes of this particular inhibition are thrombosis and plaque rupture. Thrombosis is the development of a blood clot within blood vessels that can induce a heart attack or stroke (Hopkins).[24] Plaque ruptures are followed by clotting as a result of platelets attempting to cover the rupture. The severity of the clotting can cause artery blockage which will induce a heart attack (NHCS).[25] The involvement of IL-1α in such pathways makes it a candidate for close observation in the study of early detection possibilities for heart diseases. Concurrent with IL-1α activity, IL-1β is another mediator involved with inflammatory responses (NCBI, 2013).[26] Increased serum levels of IL-1β have been associated with a cascade of events that lead to a heart attack. Studies have shown a significant increase of IL-1β levels in hearts with atherosclerotic coronary arteries compared to nonischemic hearts (J Galea et. al., 1996).[27] The increase

was found to be proportional to the severity of atherosclerosis. These outcomes highlight the importance of IL-1β serum levels in relation to heart disease.

Additionally, it is important to mention the Canakinumab Anti-Inflammatory Thrombosis Outcome Study (CANTOS), a trial that investigated the effectiveness of antibody inhibition of IL-1β in preventing vascular events (Syed Raza Shah et. al., 2018).[28] The premise of the study was on the hypothesis that reducing inflammation through direct inhibition of IL-1β would be a crucial step forward in combating cardiovascular events. The results of CANTOS were statistically significant, amounting to the conclusion that directly lowering IL-1β levels, in turn, lowered recurrent cardiovascular events when compared to a placebo group. The aforementioned molecules relevant to inflammation, alongside IL-1β, should be monitored in a patient to predict the onset of cardiovascular conditions or identify the existence of such complications at their earliest stages.

Implications

The crucial role of CRP in the pathway to developing coronary artery disease is the reason for it being an important component of detecting such a complication. Given that CRP is a result of inflammation, its abundance in a patient's blood is an indicator of severe or upcoming risk of heart disease. CRP is not only produced by inflammation but also plays a role in inducing the genes that cause the adhesion of monocytes (NCBI, 2018).[29] The adhesion is one of the novice stages of plaque formation (Cor et Vasa, 2015).[30] It is given that there can be up to a ten thousandfold increase in the concentration of CRP during the response to serious issues in the body (NCBI, 2010).[31] The data sets, providing a healthy serum level of CRP in patients, also give depth into the levels which are considered to be a result of atherosclerosis. The increase in CRP levels is a sufficient indicator for risk of ensuing cardiovascular conditions, but its combination with a few highly present proteins in cases of heart disease can make tests more effective. Testing for one or the other protein individually will provide results that have low accuracy in relation to the entire population of affected patients. Through proper evaluation of multiple protein levels, chances of accurate diagnosis are significantly increased. For example, in current tests for just LDL, it is seen that around 50% of all heart disease patients experience levels of LDL which are considered to be indicative of risk. In comparison, a study from 2006 has shown that even a minor elevation in CRP levels, present in a third of Americans, effectively had negative prognostic implications (AMJMED, 2006).[32] The increased CRP levels were found to be very high within diseased and healthy people. The union of the levels of CRP and LDL in a patient then increases statistical predictions by a significant amount because a greater range of cases are covered. However, although evidence points to the significant association of increased levels of CRP and LDL with cardiovascular conditions, the IL-1 pathway involved with inflammation is a notable factor in the direct cascade of vascular events. Often overlooked, the IL-1 pathway has insight to offer regarding the ongoing prognosis of vascular complications.

Seeing the vital roles each of the proteins or lipoproteins play in either stimulating, inhibiting, or contributing to the formation of plaque on the interiors of artery walls, makes them an important subject to study for the diagnosis of heart conditions. Current methods of detecting a heart disease or even its risk is a matter of luck or the conspicuousness of a symptom. In order to make the process of diagnosing a patient much more effective, the usefulness of these proteins can be extracted by having levels of these proteins tested on a regular basis. Using previously published empirical data giving exact measurements of levels at which the given proteins are normal and in which they are higher can be a step forward towards eliminating the current death rate of heart disease patients. CRP, LDL, IL-1α, and IL-1β all play roles, supported by much evidence, in the process of initial plaque formation. Already, doctors order CRP tests in order to learn more about inflammation due to infections or evaluate heart disease risk (Mayo Clinic, 2021).[33] Cholesterol tests are generally recommended to be conducted every 4 to 6 years, in some cases more or less due to underlying heart disease risk (Health.gov, 2021).[34] However, health care providers are not making use

of IL-1α and IL-1β tests for preventative measures. Through regular testing for levels of these proteins, as soon as multiple proteins have abnormal levels, any medical professional will have the apt amount of time to plan a treatment that is suited to preventing the progression of plaque formation. Such testing is progressive and eliminates reliance on symptoms as the only method of identifying the progression of CAD.

Additionally, the relative cost-effectiveness of testing for protein levels makes them a better heart disease diagnosis process than standard testing procedures. The national average price for an EKG (Electrocardiogram) procedure is $1,750 which is expensive for the average person (NewChoiceHealth).[35] Additionally, many EKGs have inconclusive results, prompting doctors to order other tests that hold health risks, such as coronary angiography which exposes patients to radiation (Choosing Wisely, 2012).[36] Comparatively, the price to test for cholesterol, CRP, and other substances is around $12 to $16 which is over one hundred times cheaper than an EKG (Harvard Health, 2017).[37] At the price of an EKG, a patient could get numerous protein level tests that could be used as indicators of heart disease. The ability to diagnose heart disease at a more inexpensive rate makes it widely accessible and facilitates its access for the average patient.

Conclusion

Overall, CAD is the most common heart disease in the United States and as more people are dying from heart diseases each year, it has become the leading cause of death. The need for early detection of heart disease is extremely important now more than ever. Hundreds of dollars are spent on expensive tests such as EKGs and more while a more cost-effective and simplistic approach can be used to diagnose heart diseases. This approach consists of the conjunctional use of CRP, LDL, IL-1α, and IL-1β levels. Research and studies all point to the direct involvement of these proteins and lipoproteins in high concentration and in the inflammatory response within atherosclerotic cases. Current techniques of diagnosing heart disease in patients are highly inefficient and are late in their detection. Comparatively, the array of the four molecules (CRP, LDL, IL-1α, and IL-1β) will allow for sufficient risk assessment before a complication reaches a fatal stage which in turn reduces deaths from heart-related diseases.

Acknowledgments

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