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The Role of Neutrophils, Lymphocytes and Monocytes in Ischemic Heart Disease: Friend or Foe?

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Ischemic heart disease (IHD) remains a leading cause of morbidity and mortality globally. In recent years research has increasingly focused on the interplay between the white blood cells and the development and progression of IHD. Neutrophils, lymphocytes, and Monocytes play an important role in the immune system and were found to have dual roles in both protective mechanisms and harmful effects. Neutrophils are traditionally viewed as first responders to tissue injury. Their rapid infiltration aids in the clearance of cellular debris and pathogens, while the release of reactive oxygen species and inflammatory mediators can exacerbate tissue damage. Additionally, neutrophils participate in intercommunication with endothelial cells and platelets, influencing the

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progression of atherosclerosis and thrombosis. Lymphocytes, a key player in adaptive immune response, similarly exhibit a dual role in IHD. Their involvement extends beyond immune surveillance. Monocytes contribute to phagocytosis and tissue repair while some of their actions cause atherosclerotic plaque instability. This review provides an overview of IHD, covering its prevalence, pathogenesis, risk factors, clinical manifestations, diagnosis, and the involvement of white blood cells, including neutrophils, lymphocytes, and monocytes, in the disease process.

Keywords: Ischemic heart disease; white blood cells; neutrophils; lymphocytes; monocytes.

1. INTRODUCTION

Ischemia can be described as reduced blood flow (circulation) to a particular organ due to obstruction of blood vessels supplying that area [1]. Ischemic heart disease (IHD), commonly known as coronary artery disease (CAD) or coronary heart disease, stands as a prevailing and formidable global health challenge [2-4]. Characterized by an impaired blood supply to the myocardium, IHD results from the progressive narrowing or complete occlusion of coronary arteries, typically due to the formation of plaque, called atherosclerosis. This vascular condition leads to an inadequate delivery of oxygen and nutrients to the heart muscle, instigating a cascade of events that profoundly impact cardiovascular function [5].

Globally, around 620 million people deal with heart and circulatory disorders. On a global scale, it is estimated that one in every thirteen persons has a heart or circulatory disorder. The most prevalent cardiovascular disorder is IHD with a global prevalence indicated at 200 million in 2019 with 9.14 million deaths [6,7]. The significance of IHD lies not only in its prevalence but also in its repercussions on public health and individual well-being. According to the World Health Organization (WHO), IHD remains the leading cause of death worldwide, accounting for a prevalence rate of 3820 cases per 100,000 population worldwide. Its pervasive nature transcends geographical boundaries, affecting individuals across diverse demographics and socioeconomic strata [8,9]. Cardiovascular disease is the leading cause of death in Asia, and it is considered a growing epidemic. In 2019, 10.8 million people died from heart and circulatory disorders, the majority of which were caused by ischemic heart disease (47%), accounting for approximately 35% of all deaths in the Asian continent [10]. In Sri Lanka, coronary heart disease deaths were reported as 26,304, or 22.66% of all deaths in 2020 [11,12]. According to a study conducted in 2005, the prevalence of IHD in Sri Lanka was found to be 9.3%, with a higher prevalence among females (11.3%) compared to males (7.2%) [13].

2. PATHOGENESIS OF IHD

The pathogenesis of IHD is intricately linked to atherosclerosis, a chronic inflammatory process characterized by the deposition of cholesterol, lipids, and cellular debris within the coronary arteries. Over time, these atherosclerotic plaques can undergo rupture or erosion, triggering thrombotic events that further compromise blood flow to the heart muscle [5,14]. The clinical manifestations of IHD encompass a spectrum of conditions, ranging from stable angina to acute coronary syndromes such as myocardial infarction, each posing distinct challenges in terms of diagnosis, management, and prevention.

As shown in Figure 1, IHD is linked to inflammation, atherosclerosis, vasospasm, and coronary microvascular dysfunction [15]. Risk factors of atherosclerosis such as aging, diabetes mellites, arterial hypertension, dyslipidemia, genetic predisposition, and smoking contribute to the progression of plaque development and eventually lead to CAD or Angina. Prolonged or sudden severe obstructions can cause Acute Myocardial Infarction (AMI). Tumor Necrosis Factor-alpha, C-reactive protein, Neutrophils, and Interleukins (IL-6R) collectively contribute to the local inflammatory response during AMI. Stenosis marks the advanced and ultimate phase of the intricate atherosclerotic progression. In IHD, apart from the local inflammation, systemic inflammation also takes place releasing cytokines, Angiotensin II, and triggering oxidative stress. This will lead to endothelial dysfunction and eventually deregulated excessive inflammation. Vasospasms refer to sudden, intense contractions of the coronary arteries. These spasms can lead to temporary narrowing or complete closure of the vessels leading to IHD. Coronary microvascular dysfunction (CMD) involves structural and functional changes in the

small blood vessels (microcirculation) within the heart. It affects the arterioles and capillaries that regulate blood flow. CMD can impair coronary autoregulation, leading to inadequate blood supply to the heart muscle. Endothelial dysfunction, risk factors like hypertension, diabetes mellitus, Myocardial Infarction with Non-Obstructive Coronary Artery Disease (MINOCA), Ischemia and No Obstructive Coronary Artery Disease (INOCA), cardiotropic viruses increase CMD risk. On the other hand, CMD can worsen the ischemia-reperfusion injury (IRI): i.e. blood flow to an organ (such as the heart) is temporarily interrupted (ischemia) and then restored (reperfusion). This can lead to microvascular injury worsening the outcomes in patients with IRI [15].

3. RISK FACTORS OF IHD

IHD encompasses a range of conditions caused by reduced blood flow to the heart muscle, often due to coronary artery disease. Several risk factors contribute to its development, including age, gender, hypertension, smoking, particulate matter pollution, diabetes, unhealthy dietary habits, overweight, physical inactivity, and a family history of IHD. These factors can lead to the buildup of plaque in the arteries, restricting blood flow and oxygen delivery to the heart [16,17,18]. According to findings from a study conducted at the Teaching Hospital Peradeniya in Sri Lanka, there is evidence suggesting a progressive development of ischemic heart disease in association with smoking and alcohol consumption [19]. A study conducted at the Teaching Hospital Jaffna in Sri Lanka found evidence that physical inactivity, unhealthy dietary habits, alcoholism, and smoking are lifestyle risk factors among patients with IHD [20].

4. SIGNS AND SYMPTOMS OF IHD

The signs and symptoms of ischemic heart disease occur when the heart does not get sufficient amounts of oxygenated blood [21]. Symptoms of IHD vary but commonly include chest pain or discomfort (angina), shortness of breath, fatigue, nausea, and sweating. However, some individuals, particularly women and older adults, may experience atypical symptoms or no symptoms at all, complicating diagnosis. In severe cases, IHD can lead to a myocardial infarction or sudden cardiac death [22,23]. Early recognition of risk factors, regular monitoring, and prompt medical intervention are essential for managing IHD and reducing the risk of complications.

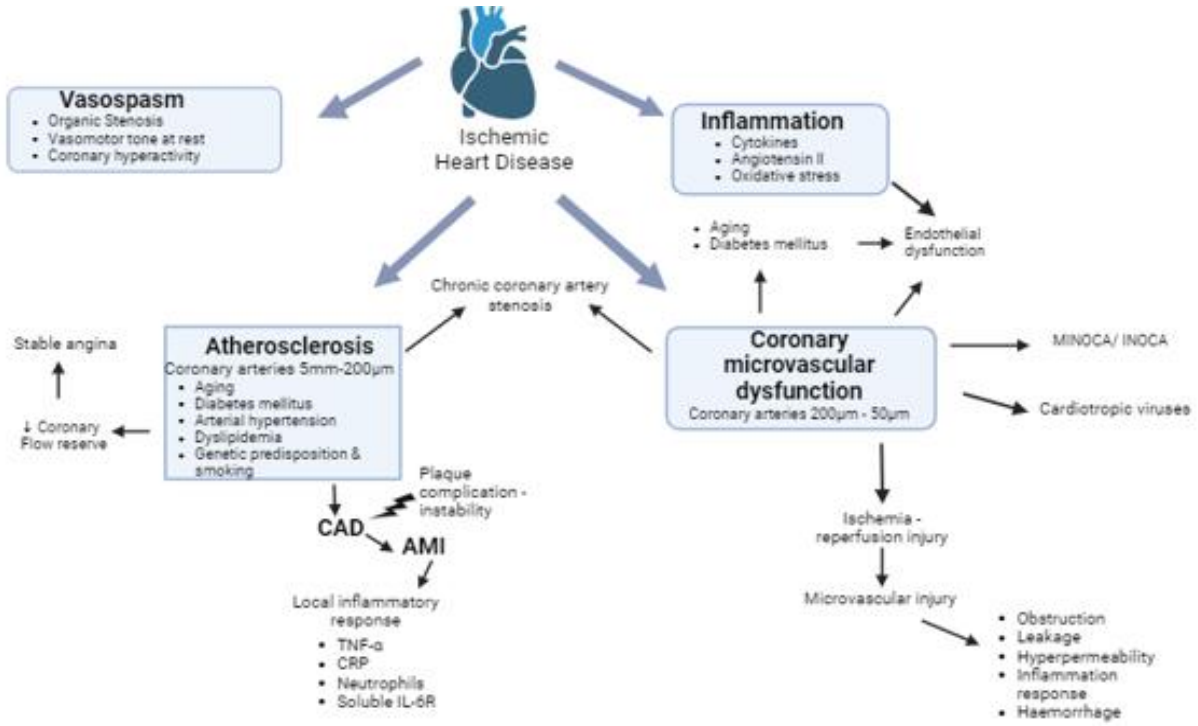

Fig. 1. Mechanisms of pathophysiology in ischemic heart disease. adapted from [15].

5. DIAGNOSIS OF IHD

Accurate and timely diagnosis is paramount in the effective management of IHD. The diagnostic process for IHD involves a comprehensive clinical assessment and patient history, imaging techniques, and laboratory tests. Clinicians utilize a combination of these tools to not only confirm the presence of IHD but also to determine its severity, guide appropriate interventions, and mitigate the risk of complications [22,23]. In clinical evaluation, healthcare professionals gather information about a patient's medical history, risk factors, and presenting symptoms which were formerly discussed.

Various imaging techniques play a crucial role in diagnosing IHD and evaluating its impact on cardiac function. Non-invasive imaging modalities include electrocardiography (ECG or EKG), stress testing (exercise or pharmacological), echocardiography, and nuclear imaging. ECG provides valuable information about the heart's electrical activity, helping identify abnormalities indicative of ischemia or previous heart damage. Stress testing involves monitoring the heart's response to physical or pharmacological stress, revealing changes that may not be apparent at rest. Echocardiography uses ultrasound to assess cardiac structure and function, while nuclear imaging provides detailed information about blood flow to the heart muscle [24].

Laboratory tests contribute to the diagnosis of IHD by assessing cardiac biomarkers. Troponins (T or I), creatine phosphokinase-MB (CK-MB), and myoglobin are commonly measured to detect myocardial damage [25,26]. Ischemia modified albumin (IMA), Brain natriuretic peptide (BNP), and N-terminal pro b-type natriuretic peptide (NT-proBNP), ST2, copeptin, galectin-3,Whole Blood Choline, Unesterified Free Fatty Acids are some of the markers of ischemia where elevated levels of these biomarkers suggest ongoing or recent cardiac injury or ischemia [27,28]. Additionally, lipid profile assessments aid in evaluating cardiovascular risk by measuring cholesterol levels [29].

Invasive procedures, such as coronary angiography, provide a direct visualization of the coronary arteries. This procedure involves injecting contrast dye into the coronary arteries, allowing for the identification of blockages or narrowed segments. Coronary angiography is often performed in conjunction with percutaneous coronary intervention (PCI), commonly known as angioplasty, to open narrowed arteries and restore blood flow [30,31].

5.1 Hematological parameters

Hematological parameters, which encompass a variety of blood components and characteristics, can provide valuable information in the diagnosis and management of IHD. While these parameters are not specific to IHD, certain hematological markers can offer insights into the underlying pathophysiological processes and contribute to risk assessment.

6. COMPLETE BLOOD COUNT (CBC)

CBC provides information about the cellular components of the blood, including red blood cells (RBCs), white blood cells (WBCs), and platelets. Abnormalities in the CBC, such as anemia or elevated platelet count, may suggest underlying conditions that can contribute to or result from IHD [32,33].

7. HEMOGLOBIN AND HEMATOCRIT

Hemoglobin, a globin which has a tetrameric structure primarily transport oxygen throughout the body. Hematocrit is a measurement that indicates the proportion of red blood cells in relation to the total volume of blood [34]. Both parameters in the CBC are crucial indicators of anemia a condition where the number of red blood cells or the quantity of hemoglobin in the blood get reduced, leading to a reduced capacity of blood to carry oxygen to tissues and organs throughout the body [35]. Reduce the oxygen-carrying capacity of the blood, cause ischemia in individuals with IHD. Therefore, monitoring hemoglobin levels and the hematocrit is important in IHD. Also, it is relevant in assessing oxygen supply-demand imbalances [32].

8. RED CELL DISTRIBUTION WIDTH (RDW)

RDW is a measure of the variation in size (size heterogeneity) of red blood cells, derived by dividing the standard deviation (SD) of erythrocyte volumes by the mean corpuscular volume (MCV). Elevated RDW has been associated with increased mortality in cardiovascular diseases, including IHD (Normal range 80-100 fL). It can serve as a marker of

underlying systemic inflammation, and oxidative stress [32,33,36,37].

9. PLATELET COUNT AND MEAN PLATELET VOLUME (MPV)

Platelets play a key role in blood clotting, and abnormalities in platelet count or function can contribute to thrombotic events in IHD. Elevated platelet counts or increased platelet reactivity may increase the risk of clot formation in the coronary arteries [32,38]. MPV is a measure of the average size of platelets. Increased MPV has been associated with increased platelet activity and may indicate a prothrombotic state, potentially contributing to the risk of coronary events [38]. Recent studies suggest that larger platelets exhibit increased enzymatic and metabolic activity, contributing to their higher thrombotic potential compared to smaller platelets. Large platelets have a greater surface area relative to their volume, providing more sites for receptor binding and aggregation. This increased surface area facilitates enhanced interactions with various prothrombotic factors, such as von Willebrand factor and fibrinogen, leading to more efficient platelet activation and clot formation. Additionally, larger platelets tend to contain higher concentrations of granules, which store bioactive molecules involved in platelet activation and aggregation, further amplifying their thrombotic ability. Moreover, larger platelets have been shown to express higher levels of glycoprotein receptors, particularly GPIIb/IIIa, which play a crucial role in platelet adhesion and aggregation during thrombus formation [33,39,40].

10. FIBRINOGEN

Fibrinogen is a key factor in blood clot formation. Elevated fibrinogen levels have been associated with increased cardiovascular risk and may contribute to the formation of thrombi in coronary arteries. The elevation of γA/γ′ isoform of fibrinogen in CAD, myocardial infarction, and ischemic stroke was evident [41].

11. D-DIMER

D-dimer is a marker of fibrinolysis and is often elevated in conditions associated with increased blood clot formation and breakdown. Elevated D-dimer levels may indicate ongoing thrombus formation in the coronary arteries [42]. Furthermore, studies have shown that D-dimer level is directly related to the occurrence and recurrence of cardiovascular diseases [42].

12. WHITE BLOOD CELL COUNT (WBC)

White blood cells, which include neutrophils, lymphocytes, monocytes, eosinophils, and basophils, play important functions in the pathogenesis of atherosclerosis. Neutrophils, the most abundant type of WBC, contribute to the initial inflammatory response in atherosclerotic lesions, increasing inflammation and causing tissue damage [33,44]. Lymphocytes, which include B and T cells, contribute to the adaptive immune response during atherosclerosis, altering plaque stability and progression [45]. Monocytes recruited to the arterial wall differentiate into macrophages, which are essential in plaque formation and progression by promoting foam cell formation and producing inflammatory mediators [46]. Although less studied, eosinophils and basophils may contribute to atherosclerosis through their involvement in allergic and inflammatory responses [47]. Inflammatory cytokines and chemokines released by WBCs regulate leukocyte recruitment and activation within plaques, influencing plaque stability and the risk of rupture [48].

13. NEUTROPHILS

Neutrophils, a type of white blood cell, stand as frontline defenders within the immune system, playing a pivotal role in the body's response to infection and inflammation [33,49]. Characterized by a multi-lobed nucleus and a granular cytoplasm, neutrophils are highly mobile and adept at migrating towards sites of infection or tissue damage. Upon arrival at the scene, they engage in phagocytosis, engulfing and digesting pathogens or foreign particles [50]. Neutrophils contain antimicrobial proteins and enzymes stored in their granules, allowing them to neutralize and eradicate invading microorganisms efficiently. While primarily recognized for their role in the innate immune response, recent research has revealed the involvement of neutrophils in various physiological and pathological processes, extending beyond infection control [51].

14. LYMPHOCYTES

Lymphocytes are a type of white blood cell crucial for the adaptive immune system, playing

a pivotal role in recognizing and combating pathogens and foreign substances [52]. They originate from stem cells in the bone marrow and mature into T lymphocytes (T cells), B lymphocytes (B cells), or natural killer (NK) cells. T cells are responsible for cell-mediated immunity, coordinating immune responses and directly attacking infected or abnormal cells. B cells produce antibodies, specialized proteins that target and neutralize specific pathogens or toxins. NK cells are cytotoxic lymphocytes that recognize and eliminate cells that have been infected or transformed, such as cancerous cells. Lymphocytes are essential for maintaining immune surveillance and memory, providing long-term protection against recurrent infections and diseases [33,53-55].

15. MONOCYTES

Monocytes, a vital component of the immune system, are a type of white blood cell with a crucial role in both innate and adaptive immunity. Characterized by a kidney-shaped nucleus and a gray-blue cytoplasm, monocytes circulate in the bloodstream, surveying for signs of infection, inflammation, or tissue damage [56]. Upon encountering a stimulus, such as pathogens or damaged cells, monocytes migrate to the affected site and undergo differentiation into macrophages or dendritic cells [57]. Macrophages, derived from monocytes, are versatile phagocytic cells with a capacity for antigen presentation, contributing to the initiation of specific immune responses. Monocytes also play a significant role in tissue repair and remodeling, contributing to the resolution of inflammation and the maintenance of homeostasis [58].

16. ROLE OF NEUTROPHILS IN IHD

Neutrophils, once viewed solely as frontline defenders against infection, are now recognized as key players in the inflammatory processes underlying IHD. Atherosclerosis, a primary contributor to IHD, involves a complex interplay of inflammatory responses wherein neutrophils assume a pivotal role. These immune cells are recruited to the vascular endothelium in response to inflammatory stimuli, where they adhere and migrate into the subendothelial space, releasing pro-inflammatory cytokines, reactive oxygen species (ROS), and enzymes. This cascade of events contributes to endothelial dysfunction, oxidative stress, and vascular damage [59]. Additionally, neutrophils engage in interactions with platelets, fostering thrombus formation, a critical event in acute coronary syndromes [60,61]. Furthermore, their presence within atherosclerotic plaques can destabilize them, increasing the risk of rupture and subsequent thrombosis leading to myocardial infarction [62]. Moreover, neutrophils release extracellular traps, which exacerbate endothelial dysfunction, plaque destabilization, and thrombosis, further perpetuating IHD progression [63]. Neutrophil-mediated oxidative stress, through the generation of ROS, overwhelms endogenous antioxidant defences, contributing to lipid peroxidation and vascular inflammation characteristic of IHD [64]. Additionally, their secretion of matrix metalloproteinases facilitates plaque destabilization by degrading extracellular matrix components, increasing the risk of rupture and thrombosis [65]. Given the multifaceted involvement of neutrophils in IHD pathophysiology, targeting their recruitment, activation, or effector functions may hold promise for therapeutic intervention, potentially reducing cardiovascular events [66].

17. ROLE OF LYMPHOCYTES IN IHD

In IHD, lymphocytes contribute significantly to the inflammatory response within the arterial walls. T cells are involved in the immune reactions in IHD. Upon activation, T cells migrate to the site of arterial injury, where they release inflammatory cytokines and interact with other immune cells, exacerbating the inflammatory cascade [67]. Additionally, B cells may play a role in IHD by producing antibodies that recognize and bind to antigens present in atherosclerotic plaques, potentially contributing to plaque destabilization and rupture [68]. While the precise mechanisms by which lymphocytes contribute to IHD pathology are still being studied, their role highlights the relationship between the immune system and cardiovascular diseases.

Additionally, a lower lymphocyte count has been identified as a promising prognostic indicator for acute coronary syndrome and stable ischemic heart disease, showing a significant correlation with extended survival among patients with IHD [69,70].

18. ROLE OF MONOCYTES IN IHD

Monocytes play an important role in the pathophysiology of IHD, particularly in the context of atherosclerosis and its complications. Atherosclerosis, a chronic inflammatory condition involving the deposition of lipids and immune cells in arterial walls [71]. Monocytes are central players in the immune response during

atherosclerosis, contributing to the formation and progression of atherosclerotic plaques [72]. Monocytes are recruited to the site of vascular injury or inflammation in response to chemotactic signals. Once at the scene, they adhere to the endothelium and transmigrate into the subendothelial space. Within the vessel wall, monocytes undergo differentiation into macrophages, which become key contributors to plaque formation. Activated macrophages within the arterial wall engulf oxidized low-density lipoproteins, transforming into foam cells. The accumulation of foam cells is a characteristic feature of early atherosclerotic lesions. The lipid-laden foam cells contribute to the formation of fatty streaks, which are precursors to more advanced atherosclerotic plaques. Macrophages and monocytes release pro-inflammatory cytokines and chemokines, fostering a local inflammatory environment within the arterial wall [73]. These inflammatory mediators contribute to the recruitment of additional immune cells and exacerbate the inflammatory response, further promoting atherosclerosis [74,75].

Furthermore, Monocytes and macrophages play a crucial role in the destabilization of atherosclerotic plaques. Their presence contributes to the thinning of the fibrous cap covering the plaque, making it more susceptible to rupture. Plaque rupture exposes thrombogenic material, triggering platelet aggregation and thrombus formation, which can lead to acute cardiovascular events such as myocardial infarction [76].

19. FUTURE DIRECTIONS

The investigation of neutrophils, lymphocytes, and monocytes in IHD represents a dynamic research area where future directions hold great promise for improving our understanding and therapeutic approaches. Examining the complex roles played by these immune cells in various IHD subtypes, such as acute myocardial infarction, unstable angina, and stable angina, may provide an understanding on how these cells change as atherosclerosis develops. Furthermore, studies examining the ways in which common comorbidities such as diabetes, hypertension, and obesity influence neutrophil, lymphocyte, and monocyte behaviors in the context of IHD represent essential research directions. We may be able to identify new therapeutic targets and approaches for addressing the complicated relationship between these factors and IHD.

20. CONCLUSION

In conclusion, the important role of neutrophils, lymphocytes and monocytes in IHD reveals a complex narrative where these immune cells, traditionally considered defenders of the body, can manifest as both friends and foes. While these cells are crucial in the immune response against pathogens, their involvement in the inflammatory processes of atherosclerosis and subsequent plaque destabilization poses significant challenges in the context of cardiovascular health. The delicate balance between protective and harmful effects of neutrophils, lymphocytes and monocytes in IHD shows the need for a better understanding of their roles. This review has attempted to explain the comprehensive contributions of these white blood cells in various stages of IHD, from the initiation of atherosclerotic lesions to the critical events leading to acute cardiovascular events.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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