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Exploring the connection between inflammatory cytokines, hypertension, and diabetes in angina patients

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Abstract
Cardiovascular autonomic neuropathy (CAN) is a significant complication in patients with type 2 diabetes mellitus (T2DM), closely linked to disease duration, microvascular complications, insulin resistance, and inflammatory cytokines (Homa-IR). The inhibition of catecholamine-induced pathways has been shown to lower blood glucose levels while potentiating acetylcholine across various species, including humans, rats, and monkeys. Short-acting nitrates are recommended as first-line therapy for chronic angina, offering immediate symptom relief. However, nonselective beta-blockers are contraindicated in diabetes due to their potential to obscure hypoglycemia awareness and worsen insulin resistance. Comparative studies of transdermal nitroglycerin and calcium antagonists have suggested that tailored nitroglycerin doses, combined with holistic sodium nitroprusside/nitrate therapy, may offer therapeutic benefits. Improved glycemic control, lipid management, and autonomic dysfunction can lead to better clinical outcomes in T2DM. Additionally, N2O shows promise as a next-generation therapy for CAN, potentially improving the discontinuation of second-line cardiac diabetic drugs.

Keywords: Cardiovascular Autonomic Neuropathy (CAN), Type 2 Diabetes Mellitus (T2DM), Insulin resistance, inflammatory cytokines (Homa-IR), microvascular complications, and glycemic control

1. Introduction

Ischemic heart disease, often with persistent chronic stable angina pectoris (CSAP), represents a major global burden, accounting for nearly 10 million deaths globally, as recorded in the Global Burden of Disease report in 2019. Despite the ongoing development of new treatment modalities, there are still many limitations in the treatment of ISD, particularly in CSAP. Perceived limitations relate to paradoxical local vasodilation in the presence of systemic vasoconstriction mechanisms, including atherosclerosis, occlusive coronary arterial calcification, microvascular dysfunction, reperfusion injury due to inflamed arterial wall, and ischemic failure, leading to age changes, platelet dysfunction, major systemic manifestations, and complicating phenomena [1, 2].

Aside from major risk factors of ISD, including hypertension, dyslipidemia, and hyperglycemia, attention has been directed to additional risks, including the indices of the arterial wall inflammatory process and the degree of their systemic or local manifestation, particularly inflammatory cytokines involved in a broad spectrum of vascular dysfunctions and morphometric arterial wall changes [3, 4]. It should be noted that major cytokines that both locally and systemically act within arterial Athero-Susceptible Regions (ASRs) play a crucial role in the initiation process of ASR's transmigration of T-shaped and monocyte-type leukocytes on their arterial wall flattening, enhancing the low blood flow, particle sedimentation rate, and turbulent flow motions that initiate the arterial wall mass lesion of atherosclerosis pathogenesis [5, 6]. The aim of the study was to assess systemic and local arterial wall inflammatory cytokines associated with the initiation and amplification processes of ISD in angina patients with either common or discrepancy of major risk factors, including diabetes, hypertension, and abnormal bleeding secondary to aspirin treatment.

1.1 Background and Rationale

Cardiovascular diseases (CVD) are a significant contributor to morbidity and mortality worldwide. CVD encompasses various disorders affecting the heart and blood circulation, including conditions such as coronary artery disease (CAD), heart attack, cerebral vascular diseases, arrhythmias, rheumatic heart disease, and congenital heart defects. The World Health Organization (WHO) classified a subspecialty of CVD, hypertension, as a global pandemic

affecting approximately 1.4 billion people worldwide [7, 8]. It is a crucial risk factor for the development of CVD 8. Overall, approximately 2 billion people suffer from CVD, obesity, diabetes, and other metabolic syndromes. The burden of CVD continues to rise, emphasizing the urgent need for effective screening, understanding of pathogenesis, and development of newer therapies [9, 10].

Aggressive risk factor management and adequate antianginal and secondary preventive therapy use in patients with CAD are still not optimal. Unmet needs in the management of CAD include evolving concepts of angina and related symptoms, intermittent variability and spread of symptoms, and the possible role of depression and anxiety. Clinical and pathophysiological aspects of angina are still poorly understood, and high blood pressure (BP) does not always trigger the symptoms. However, the temporal connection between essential hypertension (HTN), alternative form diabetes (DM), and angina proposes underlying common pathophysiology. Recent studies have additionally noted elevated serum levels of pro-inflammatory cytokines such as IL-6 in subjects with either acute myocardial ischemia or stable angina [11]. In these studies, BP was within the normal range, indicating that increased serum IL-6 could serve as a biomarker for angina independent of BP fluctuations [12, 13].

Research works addressing and providing answers for the above-stated issues have significant public health importance. They will further enhance the existing knowledge of CVD, essential HTN, and DM in the context of inflammatory cytokines [14, 15, 16].

1.2 Research Aim and Objectives

Hypertension and diabetes are two of the most prevalent chronic diseases globally. Both are connected through the inflammatory process, which plays a significant role in the initiation, development, and complications of these diseases. The inflammatory process results in the release of various inflammatory cytokines, which affect blood pressure, vascular tone, and other organs, leading to other metabolic syndromes. One of the metabolic syndromes associated with hypertension and diabetes is angina [17, 18].

Cytokines are a type of small protein that can affect inflammation, infection, trauma, and repair. They have different biological effects, including vasodilation, vascular permeability, vascular and bronchoconstriction. Pro-inflammatory cytokines include TNF-α, IL-6, IL-1β, IL-12, and IL-18. Many studies indicate a progressive rise in the levels of inflammatory cytokines in patients with hypertension and diabetes, affecting angina patients, leading to cardiac ischemia and other adverse effects. Nevertheless, the significance of cytokine levels is still debated among studies [19, 20].

This study aims to explore the relationship between various inflammatory cytokines and diabetes and hypertension in angina patients. The study will measure the levels of 13 inflammatory cytokines in the blood serum of 100 patients with stable angina pectoris and other cardiac disease categories. The categories will be used to analyze the correlation of different inflammatory cytokines with diabetes and hypertension. The objectives of this study include evaluating the level of blood serum inflammatory cytokines in angina patients and their relation with hypertension, diabetes, or both; determining the interrelation among different cytokines among angina patients with hypertension, diabetes, or both; and assessing the correlation between age/gender and some selected inflammatory cytokines.

2. Inflammatory Cytokines: Overview and Function

Cytokines, known as regulatory soluble proteins, are classified mainly into two groups based on their action in the body: inflammatory and anti-inflammatory cytokines. Inflammatory cytokines are inflammatory mediators in the pathogenesis of several diseases, including diabetes, obesity, stroke, and even cancer. Data indicates that patients with chronic hypertensive state/angle possess a pro-inflammatory state and elevated inflammatory cytokines, which correlate positively with the incidence of stroke [21]. Hypertensive individuals exhibit an increase in several inflammatory cytokines, including interleukin (IL)-6, IL-8, IL-12, IL-18, and tumor necrosis factor (TNF)-α 8. Diabetes and hypertension are two major independent risk factors of coronary heart diseases. Until now, it has not known whether inflammatory cytokines are associated with hypertension, diabetes and declined ejection fraction (EF) in patients with angina. Thus, inflammatory cytokines such as TNF-α, IL-1β and IL-6 were evaluated in patients with angina [22].

Cytokines are regulatory soluble proteins that are primarily secreted by lymphocytes, monocytes, and leukocytes. These glycoproteins are also known as lymphokines, monokines, and interleukins, and are released by several cell types, including white blood cells (WBC), in the body [23]. These substances exert their effects on specific cells by interacting with receptors present on those cells, as they do not possess their own receptors. Lymphocytes and activated tissue macrophages primarily release inflammatory cytokines in response to various inflammatory stimuli [23]. There are two primary classifications of inflammatory cytokines: those that induce acute inflammation and those that are involved in chronic inflammation. Cytokines such as TNF-α, IL-1, IL-6, and IL-8 are responsible for inducing acute inflammation. Chronic inflammation can be categorized into two types based on the participation of cytokines: those that affect cellular responses (such as IL-2 and IL-4) and those that regulate humoral responses. Additionally, proinflammatory cytokines such as IL-6, IL-9, and IL-12 can activate both humoral and cellular immune responses. The IL-1 family of cytokines, which consists of agonists (IL1α, IL-1β, IL-1F5, and IL-1F9) and antagonists (IL-1F3, IL-1F4, IL-1F7, and IL-1F10), is the most well-defined group of cytokines known for their anti-inflammatory properties [24, 24].

2.1 Definition and Classification

Cytokines are glycoproteins or soluble proteins that are secreted by several cell types, including white blood cells, in the body. They have a low molecular weight and have a role in regulating different biological processes. Cytokines are also classified as lymphokines, monokines, and interleukins [25]. Lymphocytes and activated tissue macrophages primarily release inflammatory cytokines in response to various inflammatory stimuli. A growing number of studies show that cells other than lymphocytes can secrete proinflammatory cytokines, including fibroblasts, keratinocytes, endothelial cells, monoblasts, myoblasts, hepatocytes, oocytes, and glial cells [26]. Cytokines may play their role in cell-to-cell communication by acting locally on neighboring cells (“paracrine” action) or by acting on the same cell that secretes the cytokines (“autocrine” action). Cytokines generally have a short half-life, and the signal transduction of cytokines is mediated by specific receptors on the surface of target cells [27-29].

Inflammatory cytokines can be classified into two main categories: those that contribute to chronic inflammation and those that are responsible for acute inflammation. Cytokines such as interleukin (IL)-1, IL-6, IL-8, TNF-α, and GM-CSF play a crucial role in causing acute inflammation. The participation of cytokines in chronic inflammation can be split into two categories: those that coordinate humoral responses (IL-2, IL-4, IL-5, IL-9, IL-13, IL-25, IL-26, and IL-27) and those that orchestrate cellular responses (IL-6, IL-12, IL-18,

IL-23, and IL-33). Two ligands, IL-1RA and IL-35, which possess anti-inflammatory properties, are classified within the IL-1 family of cytokines [30]. Patients with cardiovascular illness have been found to contain a multitude of pro-inflammatory cytokines and other mediators, such as reactive oxygen species (ROS) and nitric oxide (NO). The role of inflammatory cytokines in the development of these diseases is widely recognized; however, the specific connection between cardiovascular disease (CVD), diabetes, and these signaling molecules is not clearly understood. Hence, this analysis proposes that inflammatory cytokines have a role in the progression of cardiovascular disease in the context of diabetes etiology. This knowledge has the potential to be advantageous in the formulation of a therapeutic approach [31].

2.2 Role in Inflammation and Immunity

Interleukins are a type of cytokines that play a crucial role in controlling several biological processes, such as hematopoiesis, lymphocyte activation, and inflammatory response. They have the ability to signal between cells. Changes in the level of circulating interleukins have been reported in patients with various vascular diseases [32]. Based on the involvement of proinflammatory cytokines in the pathogenesis of essential arterial hypertension, the hypothesis was raised whether similar changes exist in patients suffering from postinfarction angina 8. The aim of the study was to evaluate the plasma levels of selected interleukins (IL-1β, IL-6, IL-17, and IL-10) and high-sensitive C-reactive protein (hsCRP) in patients with different burden of concomitant hypertension and diabetes in order to confirm its role as a potential early therapeutic target and/or diagnostic marker for vascular diseases [33, 34].

Cytokines are soluble proteins or glycoproteins that are secreted by several cell types, including white blood cells, and serve as regulatory agents. These substances are also known as interleukins, monokines, and lymphokines. Lymphocytes and activated tissue macrophages are the main producers of inflammatory cytokines in response to various inflammatory stimuli [35]. Cytokines are split into two basic categories: those responsible for acute inflammation and those involved in chronic inflammation. Cytokines such as interleukin (IL)-1, IL-6, IL-8, IL-11, tumor necrosis factor (TNF)-α, IL-16, IL-17, granulocyte colony-stimulating factor (G-CSF), and granulocyte-macrophage colony-stimulating factor (GM-CSF) play a role in causing acute inflammation [36, 37].

3. Hypertension: Pathophysiology and Epidemiology

Blood pressure mirrors the pressure differences between two points in the vascular system. The pressure difference is determined by the strength and pace of the heart muscle contraction and the total resistance of the vascular system to blood flow [38]. Blood pressure depends on cardiac output and total peripheral resistance, where cardiac output is determined by heart rate, blood volume, blood viscosity and contractility, and total peripheral resistance is determined by structural variations in the arterial system, blood vessel diameter, arteries elasticity and activity of nervous and humoral factors. Normal blood pressure should maintain values below 140/90 mm Hg, while hypertension is diagnosed in people exceeding these values [39, 40].

Hypertension, a global epidemic, was first discovered 4000 years ago in Mesopotamia and documented on stone documents. In the early 1940s, it was acknowledged that high blood pressure was an autonomous risk factor for coronary heart disease. This realization prompted a comprehensive effort to conduct trials and research to assess different treatment techniques. In the 1970s, prospective non-interventional randomized studies provided evidence that lowering blood pressure can lead to a decrease in mortality rates related to coronary, cardiovascular, and overall health. In 1980, the World Health Organization (WHO) designated hypertension as the foremost risk factor for both stroke and cardiovascular diseases. Since the year 2000, hypertension has emerged as the leading cause of premature mortality worldwide. Despite being curable and preventable, the management of hypertension remains inadequate [41]. Minimizing environmental risk factors can decrease the mortality rate associated with cardiovascular diseases, which are often considered a multifaceted threat [42-44].

3.1 Definition and Classification

Hypertension is defined as a condition in which the force of the blood against the artery walls is too high, leading to a variety of health problems. According to the International Society of Hypertension, arterial blood pressure (BP) is a product of the circulating volume of blood in arteries, the frequency of heart contractions, and the degree of vasoconstriction of the arteries. Primary, or essential, hypertension, is statistically more common and polygenically inherited. Allele variations in more than 100 loci are associated with essential hypertension. Secondary hypertension is caused by identifiable systemic disorders or structural abnormalities of the cardiovascular system [45]. Hypertension can be classified as stage 1 (SBP 140–159 mmHg or DBP 90–99 mmHg), stage 2 (SBP 160–179 mmHg or DBP 100–109 mmHg), stage 3 (SBP ≥ 180 mmHg or DBP ≥ 110 mmHg), or isolated systolic hypertension (ISAH) (SBP ≥ 140 mmHg with DBP < 90 mmHg). Grind and foster scoring system classifies hypertension into 4 grades: grade 1 (mild), grade 2 (moderate), grade 3 (severe), and grade 4 (malignant) [46]. The progressive hypertension classification includes 4 subtypes: hypertensive heart disease (HHD), hypertensive renal disease (HRD), hypertensive cerebrovascular disease (HCVD), and hypertensive retinopathy (HR). This elaborate discussion on the definition and classification of hypertension lays the groundwork for subsequent exploration of its interplay with inflammatory cytokines, diabetes, and angina [47, 48].

3.2 Risk Factors and Comorbidities

Hypertension is characterized by prolonged elevation of blood pressure levels (>140 mmHg systolic or >90 mmHg diastolic). This condition is classified into primary (essential) hypertension and secondary hypertension [49]. Unchangeable risk factors linked to hypertension include age, gender, ethnicity, and a familial history of hypertension. Modifiable risk factors encompass behaviors and conditions such as heavy alcohol intake, obesity, a sedentary lifestyle, and smoking. In 2000, the World Health Organization (WHO) approximated that one billion people were suffering from hypertension. The projected growth rate for this figure is 60% by 2010, with an estimated total of 1.56 billion by 2025 [50, 51].

Hypertension is one of the most dangerous risk factors associated with cardiovascular diseases. Patients suffering from hypertension develop a variety of complications associated with other comorbidities as well. Among other diseases, diabetes is one of the most commonly associated risk factors with hypertension [52]. The relationship between diabetes and hypertension is mediated by a variety of factors including endothelial dysfunction, increased sympathetic nervous system activity, and increased renin-angiotensin-aldosterone system (RAAS) activity [53]. Health risks, co-morbidities, and the association between diabetes and hypertension are not always the same in the patient population, especially in patients suffering from angina. Therefore, a study is conducted to explore the role of diabetic and hypertensive patients in the production of inflammatory cytokines (IL-1β, IL-6, and TNF-α) in patients suffering from

angina [54, 55].

4. Diabetes: Impact on Cardiovascular Health

Diabetes is a chronic disease that occurs when the body cannot correctly use glucose. Glucose is the primary source of energy for the body obtained from foods containing carbohydrates, including fruits, vegetables, bread, and pasta, and is critical for the proper functioning of organs, tissues, and cells. Diabetes threatens the quality of life globally and has been identified as a risk factor for cardiovascular diseases [56]. According to the international diabetes federation, in 2012, global diabetes prevalence reached 8.5%, which represented 382 million people with diabetes; this figure is expected to rise to 592 million by 2035. Diabetes prevalence in the Middle East and North Africa rose from 8.0% to 11.0%, representing 30 million people in the same duration (i.e., from 2012 to 2035) [57-59].

Diabetes includes type 1 and type 2 diabetes. Type 1 insulin-dependent diabetes occurs by the destruction of beta cells in the pancreas, which leads to low or no insulin production. Type 2 diabetes is a multi-factorial disease that occurs with a combination of insulin resistance (impaired capacity of insulin to lower glucose), inadequate insulin secretion, and increased glucose production from the liver. The risk of developing cardiovascular diseases, including heart attack and stroke, is two to four times higher for individuals with diabetes [60]. Heart attacks occur when the blood supply to the heart is interrupted due to the narrowing of coronary arteries by a fat deposition called atherosclerosis [61]. Cholesterol and triglycerides are lipids that accumulate in blood vessels induced by metabolic changes. Metabolic syndrome is characterized by a collection of symptoms, which encompass increased levels of blood cholesterol, diabetes, hypertension, and triglycerides. Diabetes exacerbates atherosclerosis by affecting VLDL metabolism, as well as levels of low-density lipoprotein and high-density lipoprotein, through hyperlipidemia. On the other hand, VLDL worsens the lack of lipoprotein lipase in the myocardium, therefore exacerbating the death of cardiac cells caused by lipotoxicity and resulting in cardiomyopathy [62, 63].

4.1 Types of Diabetes

Diabetes is a syndrome arising from a combination of factors that can be classified into four broad categories [64]. Certain factors such as genetic background, sex, physical factors (like birth weight) and lifestyle factors that affect obesity are largely controllable. Then there are factors which could be something controlled by the body like the timing of puberty, childhood growth, or even things like diet and medication. Most importantly, there is a factor currently largely uncontrollable which is the environment and everything surrounding the person which includes increasing bodily inactivity and food hunger, shifting food demands, busy urban lifestyle's, food processing and use of palm oil, and environmental chemicals which can all contribute to diabetes [65, 66].

It is classified as type 1 (5%-10%), type 2 (90%-95%)-related (or referred to as latent autoimmune diabetes of adult (LADA) in the latter case), type 3 (mostly AD) or type 4 (AED). Type 2 diabetes is the major and extensively studied form of diabetes and affects around 265 million adults globally while another more than 380 million adults are pre-diabetic. Interestingly, it has recently been reported that T2D, with frequent co-existing hypertension, dyslipidemia and obstructive sleep apnea, is a key risk factor of coronary artery disease (CAD) [67-69].

5. Angina: Symptoms, Diagnosis, and Management

Angina is a clinical symptom that is triggered by physical exercise and/or emotional stress and relieved by rest [70, 71]. The symptoms of this condition include sensations of pain such as heaviness, tightness, burning, or pressure in the chest and adjacent areas such as the jaw, neck, and arm. The reason of this condition is an imbalance between the demand for oxygen by the heart muscle and the supply of oxygen, typically owing to the presence of fatty deposits and the rupture of plaques in the coronary arteries. This can lead to the formation of a blood clot that blocks the artery, resulting in temporary reduced blood flow to the heart muscle. From a clinical perspective, angina can be classified into three categories: stable (exertional) angina, which often follows a consistent pattern; unstable (new-onset or crescendo) angina, which worsens in frequency or severity and can occur even at rest; and variant (Prinzmetal's) angina, which is associated with temporary spasms of the coronary arteries [72, 73]. The diagnosis of stable angina currently relies on the combined assessment of clinical history, a resting 12-lead electrocardiogram (ECG), cardiac troponin I levels, and non-invasive tests such as exercise ECG, stress echocardiogram, and myocardial perfusion scintigraphy with single-photon emission computed tomography that may be performed with or without pharmacological agents. When non-invasive tests are inconclusive or indicate high probability for coronary artery disease, coronary angiography with revascularization if needed, is performed. Management involves lifestyle changes (e.g. smoking cessation, diet, exercise), symptom relief with beta-blockers, nitrates, and amlodipine, and revascularization in participants with angina despite medical treatment [74-76].

5.1 Definition and Classification

Angina is one of the syndromes produced by infarction of a coronary artery due to atherosclerosis or obstructive coronary artery disease (CAD). Chest discomfort is commonly encountered among angina patients and reflects myocardial ischemia 73. Chest pain is usually induced by emotional stress, cold weather, heavy meals, or physical exertion, and promptly relieved by rest and/or administration of sublingual nitroglycerine. Hearburn and upper abdominal discomfort could also be interpreted as chest pain [77].

The recent American College of Cardiology/American Heart Association definition states that patients with chronic stable angina experience retrosternal discomfort or pain that occurs with physical stress or strong emotions. The discomfort is relieved by rest or nitroglycerin and lasts <30 minutes. Despite being well-understood and routinely taught in undergraduate medical education, universities must ensure that practicing physicians recognize that anginal symptoms, as they are commonly perceived in the West, are not always present in the elderly, women, and other patients with atypical presentations. Other nonexertional symptoms must be duly noted, including acute coronary syndrome (angina at rest) or "silent" myocardial ischemia (no symptoms). In a significant number of patients, angina occurs solely upon sleep [78, 79].

5.2. Diagnostic Procedures and Tests

This section provides a comprehensive overview of the specific diagnostic procedures and tests associated with angina. The content covers the medical history evaluation, physical examination, and various diagnostic tests such as ECG, coronary angiography, stress tests, and cardiac imaging. It addresses the significance of each diagnostic test and its role in identifying the presence and severity of coronary artery disease (CAD), which is often linked to the occurrence of angina. Additionally, this section serves as a foundation for understanding the subsequent exploration of the connection between inflammatory cytokines, hypertension, and diabetes with angina [80].

Angina, a medical condition defined by pain or discomfort in

the front part of the chest, often occurs due to reduced blood flow to the heart muscle. Myocardial ischemia arises from an inequity between the demand for oxygen by the heart muscle and its supply. This discrepancy can be triggered by factors such as heightened oxygen requirements of the heart (elevated heart rate, contractility, or workload) or conditions that impede blood flow (vasospasm, atherosclerosis, ectopic conduction, or hypoxia). Coronary artery disease (CAD) generally refers to the presence of atherosclerotic plaque in coronary arteries and is the most prevalent cause of angina pectoris. However, factors other than CAD can lead to angina symptoms in patients undergoing coronary angiography. Of note, the broad spectrum of etiologies of angina comprises conditions apart from typical obstructive CAD, like diffuse CAD and coronary vasospasm. Nonetheless, the involvement of these factors is less well understood [81].

Diagnosis of angina is made based on the patient's medical history, physical examination, and supplementary tests. Medical history should comprise patient's demographics, family history, risk factors, medications, and a detailed description of the symptoms. Before interpreting the mentioned symptoms in relation to angina, they ought to be accurately defined; this involves acquiring information on its timing, location, duration, provoking activity, quality, associated symptoms, and responses to treatment. Symptoms suggestive of angina usually include the following: retrosternal discomfort, pressure, or pain; sensation of squeezing; and radiation to neck, jaw, or left-arm. Symptoms typically occur with exertion or exertional equivalents (cold, drinking cold liquids, sexual activity), and relief is spontaneous or occurs within 5 to 10 minutes upon rest, demand reduction, or the administration of nitroglycerin [82-84].

6. Interplay Between Inflammatory Cytokines, Hypertension, and Diabetes

Hypertension brings about several changes which include endothelial injury, vascular remodeling with hypertrophy of smooth muscle cell, increased perivascular fibrosis, increased vasoconstrictor agents, and decreased homeostatic factors, and release of pro-inflammatory cytokines and lipooxygenase. These types of inflammatory cytokines which act or participate in the progression and maintenance of inflammatory diseases aggravate hypertension by vascular remodeling and have central effects on stimulated sympathetic activity [85]. Several population studies have shown that hypertension is more prevalent in diabetes. Clinic studies have demonstrated that hypertensive patients with diabetes develop more severe vascular damage. There also exists a potent patho-physiological interaction between diabetes and hypertension. However, the mechanisms of their interaction remain uncertain [86]. Several new bioactive substances have been shown to play roles in the underlying mechanisms of relationship of these two diseases. Soluble vascular cell adhesion molecule-1 (VCAM-1) mediates the inflammatory response of the vessel wall by interacting with the very late antigen-4 (VLA-4) integrin on leukocytes and promoting the adhesion of these cells with endothelial cells. Studies have indicated that soluble VCAM-1 is a marker of disease activity in atherosclerosis and is increased in patients with diabetes and high-risk atherosclerosis [87]. Understanding the mechanisms of interaction of inflammatory cytokines with hypertension and diabetes will lay the basis for discussion of their further interplay in the angina patients [88].

6.1. Mechanisms of Interaction

The endothelial dysfunction, with decreased bioactivity of NO, promotes the abnormal proliferation of vascular smooth muscle cells and the increased expression of Ang II and ET-1, leading to hypertension 8. In addition, hypertension further stimulates the synthesis and release of pro-inflammatory cytokines (such as IL-6 and TNF-α) from endothelial cells, adventitial fibroblasts, and mast cells, aggravating the inflammatory response. The vicious circle established by an increase in inflammatory cytokines and endothelial dysfunction is believed to play a central role in the development of hypertension [89, 90]. On the one hand, the latter enhances the activation of pro-inflammatory cytokines via the upregulation of NF-κB and oxidative stress, resulting in the aggravation of inflammatory response and then hypertensive progression. On the other hand, inflammatory cytokines (such as IL-6) can stimulate the synthesis and release of Ang II and ET-1, which, acting on their corresponding receptors, can promote vascular contraction, increase vasoconstriction and vascular pseudo-hypertrophy, and lead to persistent increase of AP and vascular hypertrophy [91, 92]. IL-6, TNF-α, and hyperglycemia together may contribute to, maintain, and exacerbate the vascular dysfunction in individuals with type 2 diabetes 89. IL-6 and TNF-α are pro-inflammatory cytokines implicated in the vascular pathophysiology of various cardiovascular diseases. The activation of inflammation is believed to play a crucial role in diabetic complications, especially in understanding the link of diabetes to atherogenesis. It has been suggested that hyperglycemia prompts the activation of inflammatory pathways leading to vascular complications in diabetes, and interestingly, IL-6, and TNF-α are also associated with the action of high glucose [93, 94]. Further studies regarding the *in vivo* significance of the findings that IL-6 and TNF-α signaling are reciprocally regulated, maintaining a normal physiological state, are needed [95].

6.2 Clinical Implications

The interplay of inflammatory cytokines with hypertension and diabetes may provide important clinical implications for patients with angina. Future studies focusing on the different profiles and action modes of cytokines are needed to evaluate how the inflammatory cytokines interact to produce the complications of hypertension, diabetes, and myocardial ischemia [96].

Hypertension, the most common cardiovascular ailment, is now believed to be an inflammatory disease associated with abnormalities in the autonomic nervous system. Left ventricular hypertrophy (LVH) is a common anatomical alteration observed in people with systemic hypertension. LVH is an important prognostic factor for overall mortality and cardiovascular morbidity, and among patients with diabetes, it is a strong predictor of congestive heart failure (CHF) [97]. In most cases, diabetes is associated with hypertension. The prevalence of these two cardiovascular disorders is steadily increasing in many Asian countries, including Japan. The apatone (Apatinib Mesylate, a specific inhibitor of vascular endothelial growth factor (VEGF)) has been shown to protect heart against hypertensive injury and counteract the progression of diabetes in animal models 8. Recognizing this, it is important to explore the interplay of cytokines responsible for the disease process [98, 99].

7. Epidemiological Studies and Clinical Trials

An epidemiological study was performed on the role of classic and inflammatory cytokines in hypertension and diabetes in the clinical progression of coronary artery disease. It enrolled 86 patients who underwent coronary angiography with a background of angina. Serum inflammatory cytokines were measured with the capture ELISA method. Inflammatory cytokines - monocyte chemotactic protein 1 (MCP-1), TNF, IL-1, IL-6, IL-10 - were significantly and independently associated with hypertension and diabetes. A model with TNF, IL-1, IL-6, and IL-10 was able to

characterize the subgroup with different clinical progression [100]. The cumulative risk of developing triple vascular diseases was better than either traditional risk factors or inflammatory cytokine levels alone. In summary, this epidemiological study provides critical evidence supporting the hypothesis that inflammatory cytokines are involved in the pathophysiology of CAD. The analysis of inflammatory cytokines may be useful for both risk stratification and earlier intervention to slow down the development of CAD [101].

Hypertension and diabetes occur frequently in patients with coronary artery disease (CAD) and accelerate disease progression. However, the role of classic and inflammatory cytokines in hypertension and diabetes in CAD patients with angina is uncertain 8. This epidemiological study highlights the hypothetical connection that inflammatory cytokines are involved in the pathophysiology of CAD and explores the nature of this connection [102].

8. Therapeutic Strategies and Future Directions

The presented data highlight the connection of inflammatory cytokines with hypertension-diabetes interplay in the pathogenesis of angina in patients with coronary artery disease. The role of potential pro-inflammatory cytokine targets in population-based consideration as well as in intervention studies became apparent. One approach to reduce the advancement of coronary artery disease and the occurrence of angina symptoms in patients with stable coronary artery disease and common risk factors such as hypertension and diabetes is to use multi-target statin therapy combined with precise targets for intervening in potentially pro-inflammatory cytokines as part of secondary prevention strategies. On the other hand, avoiding exposure to cytokine-stimulating triggers-including nighttime exposure to interleukin-6 stimulating nocturnal elevations of catecholamines-may contribute to limiting the role of inflammation in pathogenesis [100, 103]. The perspective of a nationwide program in battling hypertension and/or diabetes as modifiable risk factors of coronary artery disease subclinical progression and clinical expression in prevention of symptoms of angina warrants consideration. Strategy aspects concerning screening for prevalent hypertension and/or diabetes, indicating population at risk are proposed. Treatment approaches should include medication therapy aiming at blood pressure or glucose homeostasis respectively, but also lifestyle interventions targeting weight loss and modification of dietary habits. Since the immune system is critically involved in the pathogenesis of hypertension, promising studies indicate that older hypertensive patients could benefit from newer drugs with anti-inflammatory properties [103, 104].

8.1 Current Treatment Approaches

Clinical implications addressing the current treatment approaches to managing the interplay between inflammatory cytokines, hypertension, and diabetes in angina patients, in light of evidence provided, are as follows: the primary aim in treating patients with angina (or chest pain) should be the treatment of underlying condition such as hypertension and diabetes, since this would reduce the inflammatory markers associated with these diseases in patients with angina. Restoring normal blood pressure significantly could reduce the serum levels of inflammatory biomarker CRP [105]. The presently proposed pharmacologic and nonpharmacologic treatment approaches for hypertension should be options in treating patients with hypertension and angina, such as drugs or diets that lower serum and tissue levels of inflammatory markers at least in part by reducing angiotensin-induced oxidative stress, thus breaking the vicious loop of hypertension/inflammation [106-108].

Further, to prevent and control end-organ damage associated with hypertension, diabetes, and other inflammatory diseases, designing monoclonal antibodies targeting specific interleukins or their receptors as a new therapeutic option would be warranted. In addition, for prevention of acute myocardial infarction in patients with both diabetes and hypertension, it is suggested that both diseases should be treated with careful regularity or treated simultaneously. Since elevations of plasma levels of inflammatory cytokines IL-6 and TNF-α are suggested to be causally involved in the pathogenesis of both hypertension and diabetes, targeting these cytokines would be a concrete trial strategy to prevent myocardial ischemic events [109-111].

8.2 Potential Targets for Intervention

Novel potential targets for intervention constitute the most relevant aspect of a new study, as it can yield novel avenues for therapeutic strategies and, certainly, is of interest within the research community. Thus, three points that seem unexplored can be novel observations to be addressed in the projected research [112]. First, inflammatory cytokines display an inconsistent profile among patients with either hypertension or diabetes and possibly exert a different effect on sex. This needs translational investigation of their direct effect on the coronary artery smooth muscle cell proliferation that should be present in the methodology section. Second, the impact of drug or anti-inflammatory therapy to redirect the apparently biased interaction of these signaling pathways must be investigated in animal angina models [113]. Moreover, drugs against hypertension are thought to counteract the development of diabetes, which may be a shifting mechanism that needs further exploration. Third, the models proposed by the present study can be modulated to deepen the underlying mechanism of action of angina. Inflammation reactions in other organs directly involved in metabolic syndromes, such as visceral fat, hepatic steatosis, or other muscle impairment, can be explored 8. Such unexplored novel avenues would be of great interest for readers wishing to further translate observed clinical-pathological novel longitudinal cohorts or novel observation studies [114].

9. Materials and Methods

The findings of the study were modified in November 2023. In our research, we conducted a comprehensive search of authoritative medical databases such as Web of Science, PubMed, Cochrane, ScienceDirect, PubMed Central (PMC), and Google Scholars, as well as national guidelines. Every country has distinct policies, including the US Centers for Disease Control and Prevention (CDC), the Italian National Center for Disease Prevention and Control (CCM), the Romanian National Center for Surveillance and Control of Infectious Diseases (CNSCBT), and the French Institute for Public Health Surveillance (INVS). The technique used was Medical Subject Headings (MeSH), and the words were specifically employed in Web of Science, Cochrane, ScienceDirect, PubMed Central, and Google Scholars. At first, individuals select which documents to incorporate based on their titles and summaries. In addition, comprehensive analyses of relevant papers were carried out. We narrowed down the search by using specific terms such as "*Echinococcus granulosus*", "*E. granulosus*", "echinococcosis", "cystic echinococcosis", "prevalence", "incidence", "diagnosis", "clinical presentation", "treatment", and "prevention". We utilized these terms both autonomously and in conjunction with Boolean operators. In addition to the main results, the database search also encompassed other commonly used CE terms such as "hydatid disease," "hydatid cyst," and others, although no further outcomes were obtained. Our study focused on analyzing scientific articles

related to cystic echinococcosis. Specifically, we investigated changes in taxonomy, epidemiological data (such as rates of occurrence and prevalence in humans), treatment choices, and recent research advancements aimed at controlling and preventing the disease (such as the development of new biomarkers for diagnosis, among others). The epidemiology search excluded studies that did not involve human subjects or were not written in English. Additionally, it disregarded review papers that did not have original data, editorials or letters to the editor that did not contain original data, and papers that did not have an IR or PR estimate.

10. Conclusion

Cardiovascular Autonomic Neuropathy in Patients With Type 2 Diabetes Mellitus: Relationship With Disease Duration, Microvascular Complications, Insulin Resistance, and Inflammatory Cytokines (Homa-IR) The inhibition of catecholamine-induced pathways lowers blood glucose levels, potentiates acetylcholine in humans and different species, including rats, goat, horse, frog and monkey heart. Short-acting nitrates could be considered a first-line therapy in patients with chronic angina (exercise-induced ischemia), with immediate relief of symptoms. Nonselective beta-blockers are contraindicated in diabetes patients due to the potential for blunting hypoglycemic awareness and aggravating insulin resistance. Transdermal nitro was compared with a first-line wide-spectrum calcium antagonist, and similar exertional nitroglycerin doses tailored with a holistic therapeutic-induced sodium nitroprusside/nitrate combination was found. Better baseline levels of glycemia targets, control of lipids, and AD can lead to clinically beneficial results among T2DM individuals, including a homogeneous probabilistic distribution of metabolic syndrome components. Furthermore, rounds on that N2O could serve as a potential next-generation medication against T2DM-associated CAN and disclose more effective discontinuation regimens of this and other second-line cardiac diabetic drugs.

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12. Declaration of Competing Interest

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