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Contemporary Strategies for Comorbid Obesity, Hypertension, and Chronic Heart Failure in Primary Care: An Evidence-Based Perspective

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Abstract

Background: The growing prevalence of comorbid obesity, hypertension, and chronic heart failure (CHF) represents a significant public health challenge, particularly in primary care. These conditions create a complex clinical triad that exacerbates cardiovascular risk, worsens prognosis, and increases healthcare burdens. Understanding the multifaceted pathophysiology and adopting evidence-based strategies is essential for improving patient outcomes.

Methods and Materials: This study synthesized data from clinical guidelines, systematic reviews, meta-analyses, and peer-reviewed journal articles, focusing on evidence-based management of obesity, hypertension, and CHF. Sources included PubMed, Cochrane Library, NICE guidelines, and studies on advanced diagnostics, pathophysiology, and emerging therapeutic approaches such as SGLT2 inhibitors and GLP-1 receptor agonists.

Results: The findings highlight the critical role of neurohormonal dysregulation, inflammation, and metabolic derangements in the development of comorbidities. Pharmacological interventions like SGLT2 inhibitors and GLP-1 receptor agonists demonstrated significant cardiovascular and renal benefits, while personalized lifestyle modifications, including diet and tailored exercise regimens, improved outcomes. Furthermore, novel biomarkers and genetic insights enable precision risk stratification and early intervention strategies in primary care.

Conclusion: Integrated, multidisciplinary approaches are essential for managing comorbid obesity, hypertension, and CHF. Combining personalized pharmacotherapy with innovative diagnostics and lifestyle interventions optimizes clinical outcomes, reduces disease progression, and enhances quality of life. Addressing barriers in primary care will further refine the management of these high-risk patients.

Keywords: Comorbid Obesity, Chronic Heart Failure, Hypertension Management, Multidisciplinary Approach, Precision Medicine

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List of abbreviations

CHF – Chronic heart failure

CVD – Cardiovascular disease

AT – Adipose tissue

ROS – Reactive oxygen species

ED – Endothelial dysfunction

VAT – Visceral adipose tissue

PVAT – Perivascular adipose tissue

TNF-α – Tumour Necrosis Factor-alpha

EC – Endothelial cell

EAT – Epicardial adipose tissue

SNS – Sympathetic nervous system

BP- Blood pressure

RAAS – Renin-Angiotensin-Aldosterone System

AGT – Adipocyte angiotensinogen

BMI – Body Mass Index

AT1 – Angiotensin II receptor type 1

AT2 – Angiotensin II receptor type 2

ENac – Endothelial Na^+ channel

eNOC – Endothelial nitric oxide synthase

IL-6 – Interleukin 6

NF-κB – Nuclear factor kappa B

JAK-STAT – Janus kinase/signal transducers and activators of transcription

LVH – Left ventricular hypertrophy

Gal-3 – Galectin-3

AGE – Advanced glycation end-product

CAD – Coronary artery disease

CML – Carboxymethyl

RAGE – Receptor for advanced glycation end products

sRAGE – Soluble receptor for advanced glycation end products

PRA – Plasma renin activity

ADMA – Asymmetric dimethylarginine

ET-1 – Endothelin-1

CRP – C- reactive protein

DXA – Dual-energy X-ray absorptiometry

MRI – Magnetic resonance imaging

FTO – Fat mass and obesity-associated gene

MC4R – Melanocortin 4 Receptor

LEP – Leptin

POMC – Proopiomelanocortin

AGRP – Agouti-related peptide

ADRA2A – Adrenoceptor Alpha 2A

MYH7 - Myosin heavy chain 7

LMNA – Lamin A/C gene

TNNT2 - Troponin T2

PPARG – Peroxisome Proliferator-Activated Receptor Alpha

TGFβ-1 – Transforming Growth Factor Beta-1

CTCF – CCCTC-binding factor

DASH – Dietary approaches to stop hypertension

SG2T2 – Sodium-glucose cotransporter 2

HFrEF – Heart failure with reduced ejection fraction.

CKD – Chronic kidney disease.

GLP-1 – Glucagon-like peptide 1

QOL – Quality of life

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Introduction

Relevance of the topic

The comprehensive preponderance of comorbid obesity, arterial hypertension, and chronic heart failure (CHF) depicts an expanding public health concern with significant implications for patient outcomes and primary healthcare systems globally. Comorbid obesity and arterial hypertension are ingrained risk factors for the progression and advancement of cardiovascular diseases, especially heart failure. The co-occurrence of these susceptibilities offsets a multiplex clinical condition that involves an integrated and multifaceted strategy for treatment.

Moreover, the significant prevalence of obesity, heightened by the aging population, is promoting the surge in chronic heart failure, devoting the clinical triad of obesity, arterial hypertension, and cardiovascular diseases a crucial space for primary care interventions. Such interfacing circumstances offer a glimpse into diagnostics and therapeutic significance as they not only need diligent coordination of strategies in primary care but also comprise risks for advanced morbidity, curtailed life quality, and raised the cost of healthcare.

A comprehensive review of current studies indicates that integrated and contemporary modes of approaches are required to tackle these comorbidities in the practice of general practitioners. These approaches promote the scope for ameliorated clinical outcomes using pre-emptive strategies and the paradigm of comprehensive care. The integrative assessment suggests that optimizing the management framework of comorbid obesity and arterial hypertension in patients with chronic heart failure may interfere with the disease progression, hospital stays, and mortality rates [1,2].

Aim of the Study

To evaluate contemporary strategies for comorbid obesity, hypertension, and chronic heart failure in primary care settings, emphasizing evidence-based approaches in the practice of general practitioners.

Objective of the Study

To explore effective modalities of contemporary approaches and comprehensive management strategies of the clinical triad of comorbid obesity, arterial hypertension, and

chronic heart failure. It aims to ensure that the key elements influencing patient outcomes are lifestyle alterations, pharmaceutical interventions, and multidimensional care coordination. The study also intends to explore the obstacles to multifaceted care and suggest pragmatic approaches for enhancing clinical outcomes. Besides, it will assess the influence of primary care interventions on decreasing the incumbrance of these comorbidities on the primary health care system.

Material and Method of the Study

The study is made with the help of a combination of scientific articles, authorized clinical guidelines, clinical trials, meta-analyses based on peer-reviewed journals, and systematic reviews. Approved sources include the European Society of Cardiology (ESC), American Heart Association Journal (AHA/ASA), PubMed, National Institute for Health and Care Excellence (NICE) Guidelines, Google Scholar, Cochrane Library, and ClinicalKey. Data are collected from studies concentrating on mechanisms and multidimensional pathophysiology of obesity, arterial hypertension, and CHF. In addition to advanced diagnostics and precision risk stratification, the study views integrated, multidisciplinary management approaches. Furthermore, the study analyses the controversies, challenges, and clinical dilemmas and explores the emerging therapeutic frontiers.

Practical Significance

The importance of this study localizes in its capacity to address a critical issue within the primary care setting from the practice of general practitioners: the complex interactions between obesity, hypertension, and CHF. These diseases are predominant among the aging population and result in novel challenges in diagnostic and therapeutic strategies. The increased prevalence of comorbid obesity exacerbates the imposition of arterial hypertension and heart failure, poor prognosis, and premature mortality. Thus, distinguishing and executing contemporary strategies towards these comorbidities in primary care modalities could improve the clinical outcome of the patient, slow disease progressions, and prevent complications.

Despite proliferating awareness of the demand for adequate care, numerous primary health care providers, in particular general practitioners, still strive to effectively handle the clinical triad of comorbid obesity due to a lack of a framework of clinical strategies or insufficient access to specialized assimilation. In primary care, where many of these patients are managed,

lead-time constraints, inadequate practice, and intervals in multidimensional association show significant obstacles to optimal healthcare.

The resolution to concentrate on this topic is determined by the importance of enhancing the strategies and developing pragmatic solutions for primary care providers. With the increasing prevalence of comorbidities and their extreme influence on patient well-being, this study aims to provide an understanding of the field. By identifying key elements that integrate polypharmacy in comorbid patients, navigate drug interactions, and optimize therapeutic outcomes, the study can inform primary care providers and shape healthcare policies aimed at improving care for this high-risk population.

Chapter 1: Mechanisms and Multidimensional Pathophysiology

1.1 The Adipocyte-Endothelial Axis: Insights into Obesity-Induced Cardiovascular Remodelling

Obesity is stratified as one of the risk factors for metabolic and cardiovascular diseases. Globally, 1.9 billion people are expected to be obese. Comorbid obesity significantly impacts multidimensional pathways by affecting both structural and functional aspects of cardiovascular remodeling [2]. The overabundance of adiposity deceives the function of normal adipose tissue. It triggers the synthesis of microvesicles, adipokines, and reactive oxygen species (ROS), which play a central role in vascular dysfunction. Especially in AT, dysfunction liberates pro-inflammatory cytokines and creates insulin resistance, advancing cardiovascular remodeling and complications such as CHF. Obesity-induced cardiovascular remodeling manifested by endothelial dysfunction (ED), which is characterized by vitiated vasodilation due to vascular inflammation, often antedates CVD. Furthermore, obesity-related endothelial damage is linked with a modified act of nitric oxide (NO), leading to endothelial dysfunction, a platform for atherosclerosis and CVD [3].

AT is the largest endocrine organ in an organism and plays a crucial role in lipid management and homeostasis of glucose, but these functions are inhibited by comorbid obesity. The inverse function of AT is persuaded by its cellular structure, secretome, and anatomical peculiarities. In comorbid obesity, adipocytes become enlarged and contribute to vascular inflammation and insulin resistance, resulting in dyslipidemia and metabolic disturbances.

Visceral AT (VAT) and perivascular AT are key elements in modulating vascular biology by secreting inflammatory mediators such as tumor necrosis factor-alpha (TNF-α), microRNAs, and interleukins. The contribution of bioactive molecules leads to endothelial dysfunction, a state of pro-atherogenic and pro-inflammatory, heightening the risk of CVD. Moreover, dysfunctional AT increases the production of angiotensinogen and ROS, leading to endothelial injury, pro-atherogenic, and increased risk of thrombosis.

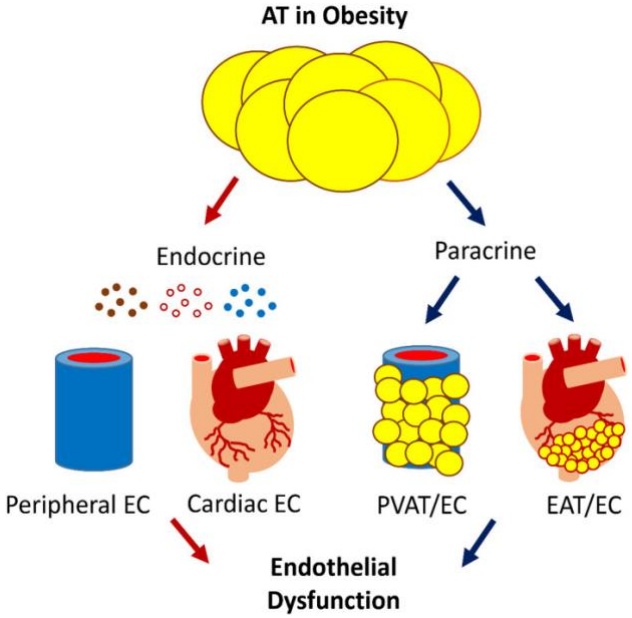

Figure 1. The design of AT – EC in obesity-induced ED. Adapted from Li, M., Qian, M., Kyler, K., & Xu, J. (2021) by Frontiers in cardiovascular medicine, 8, 681581. https://doi.org/10.3389/fcvm.2021.681581

Figure 1, mentioned above, shows the interplay between AT and EC in ED. In obesity-induced ED, the interaction between AT – EC appears through endocrine and paracrine forms. Cytokine and adipokines are secreted into the bloodstream by AT in endocrine form, and the systemic circulation of these components promotes vascular volatility and inflammation. While in paracrine form, AT secretes adipokines, and microRNAs affect the adjacent vascular cells, hindering vascular tone and endothelial dysfunction. PVAT is the main component of vascular health due to its juxtaposition to blood vessels, and its dysfunctionality in comorbid obesity leads to insulin resistance and cardiovascular remodeling. The epicardial AT (EAT) around the coronary arteries also triggers pro-inflammatory cytokine secretion, resulting in coronary

artery disease. Comprehending the interplay between AT-EC indicates contemporary and target therapeutic strategies for obesity cardiovascular modeling in primary care settings [4,5].

1.2 Neurohormonal Dysregulation: Sympathetic Activation in Obesity, Hypertension, Chronic Heart Failure.

The role of the sympathetic nervous system (SNS) in obesity-induced arterial hypertension is inevitable. The direct implications of SNS in the balance of sodium and vascular tone may be overestimated. Acute sympathetic barricade in obesity-induced hypertension results in a considerable decline in blood pressure (BP) and systemic vascular resistance prior to the occurrence of sodium balance. This implies mechanisms such as invigoration of the renin-angiotensin-aldosterone system (RAAS). The SNS activates RAAS swiftly, releasing β-adrenoceptor-mediated renin and gradually through the synthesis of adipocyte angiotensinogen (AGT) upregulation. The stimulation of white AT's SNS activity and rising expression of AGT due to dietary carbohydrates can be intervened by sympathectomy. Activation of RAAS in the systemic circulation of obese patients, which leads to arterial hypertension, can be tackled by weight loss and reducing the activation of this component [6].

Leptin is increased in obese individuals due to the high mass of adipose tissue, which leads to obesity-induced hypertension by increasing the activity of SNS. Regardless of leptin resistance in obesity, the association of hyperleptinemia is evident in heightened sympathetic efflux and BP. An epidemiology study across various populations, such as Hispanics, Europeans, and Japanese, shows a definite correlation between the level of leptin and BP, adiposity significance, and body weight. The regulation of BP may be affected by leptin and its function of inhibiting appetite [7].

Leptin plays a crucial role in comorbid obesity and CHF through its ongoing activity on peripheral tissues involving the heart. In an autocrine manner, the cardiomyocytes express and secrete leptin by leptin receptors. Individuals with leptin-related gene mutations are at risk of developing obesity and CVD, and hyperleptinemia is a predisposed risk factor for heart failure in aging populations.

In patients with CHF, leptin and leptin soluble receptors are increased, and these elevations relate to clinical severity, inhibited physical endurance, clinical uncertainty, and poor clinical

outcomes. Primarily, the leptin level is increased individually by BMI in CHF, recommending obesity and cardiovascular dysfunction lead to increased leptin levels in these individuals.

However, in some CHF patients with cardiac cachexia, a low level of leptin is noticeable. Appropriate management will be able to reverse the cardiac cachexia by increasing leptin levels as AT mass is rehabilitated. This emphasizes the interlinked correlation between leptin levels and CHF, where hyperleptinemia in cardiac cachexia conflicts with hyperleptinemia in obesity-induced CHF.

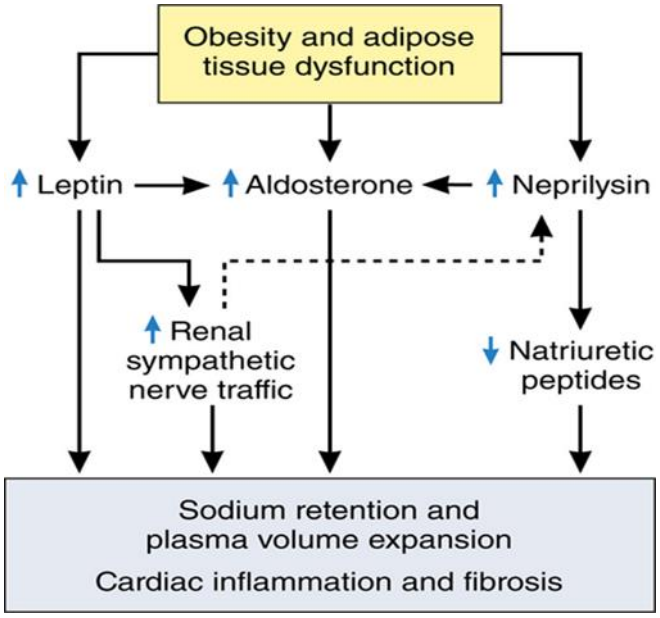

Figure 2. Mechanisms by which activation of the leptin-aldosterone-neprilysin axis may exacerbate the pathophysiological abnormalities of heart failure. Adapted from Packer, M. (2018). Leptin-Aldosterone-Neprilysin axis. Circulation, 137(15), 1614–1631. https://doi.org/10.1161/circulationaha.117.032474

In obesity-induced CHF, hyperleptinemia leads to the development and progression of CHF, but the clinical significance may differ based on the concomitant phenotype, as mentioned in Figure 2. A recent study shows that several clinical pathways, especially the renal and heart, help understand how heightened leptin receptor signaling might result in multiple forms of CHF. These outcomes highlight the demand for deeper insight into the role of leptin in obesity-induced CHF to improve the guidance of treatment strategies [8].

1.3 Obesity and the Renin-Angiotensin-Aldosterone System (RAAS): A Central Player in Disease Progression

The RAAS is a key element of BP and osmotic balance; its deregulation in obese patients results in arterial hypertension and CHF. The activation of RAAS in obese patients is impelled by complex factors involving raised adiposity measures, increased SNS activity, and hyperleptinemia. Adipocytes release angiotensinogen and precursors of angiotensin II. Furthermore, adipocytes contribute to heightened RAAS activity [9].

The key regulator of RAAS is angiotensin II, which acts via AT1 and AT2 to raise the BP through vasoconstriction and activation of aldosterone secretion, which influences the sodium and fluid retention in the renal system. In obese individuals, the long-term stimulation of RAAS influences vascular tone, volume expansion, and sodium retention, promoting BP elevation. Moreover, the abundant RAAS activation leads to cardiovascular remodeling, fibrosis, increased arterial stiffness, and endothelial dysfunction, increasing atherosclerosis and CHF's pace [10].

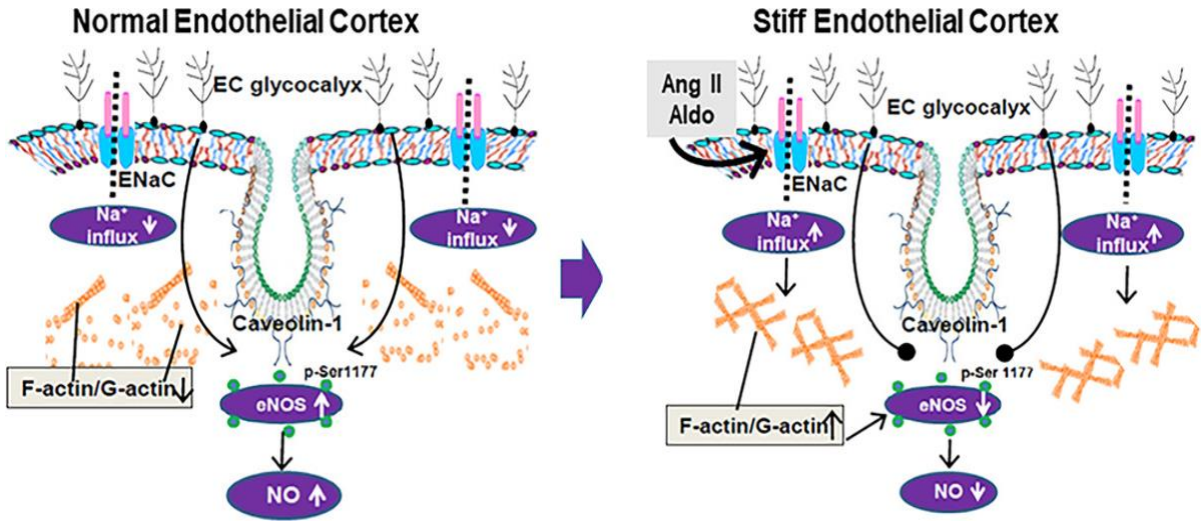

Figure 3. Interlink between endothelial cell (EC) glycocalyx, EnNac, and Enos causes endothelial stiffness and BP. ECs are covered by well-structured glycocalyx that limits the entrance of Na+ into endothelial cells and preserves a respective status of vasodilation. The abundance of the EnNac membrane is raised by angiotensin II and aldosterone, which allow Na+ to enter the endothelial cells and stimulate the synthesis of G-actin and F-actin polymerization, causing mitigation of eNOS and NO secretion and a consecutive increase in arterial stiffness and arterial pressure [11].

1.4 Molecular Mechanisms Linking Obesity to Heart Failure: The Role of Inflammation, Oxidative Stress, and Metabolic Derangement

The multidimensional pathophysiology of obesity and heart failure is complex; it involves multiple interconnected molecular mechanisms involving inflammation, oxidative stress, and metabolic derangements. Adipose tissues produce pro-inflammatory cytokines such as TNF-α, interleukin-6 (IL-6), and C-reactive protein (CRP), resulting in chronic low-grade systemic inflammation, a trademark of obesity. The pro-inflammatory cytokines progress into systemic inflammation and damage the endothelial cells, causing myocardial dysfunction and fibrosis.

Oxidative stress due to obesity is an additional key factor in the development of CHF. VAT is a vast promoter of ROS, which interferes with mitochondrial function, modifies the cellular components' signaling pathways, and causes cardiomyocyte apoptosis. Thus, the violation of mitochondrial function leads to depletion of energy production, and the progression of CHF is evident.

Obesity-induced metabolic derangements such as dyslipidemia, inhibition of fatty acid metabolism, and insulin resistance contribute to the exacerbation of CHF. Free fatty acids accumulate in the bloodstream due to insulin resistance, which creates a toxic environment for cardiomyocytes and leads to lipotoxicity. Moreover, modifying substratum utilization in cardiomyocytes, with a shift against immoderate oxidation of fatty acids with the loss of glucose metabolism, reduces myocardial efficacy and heightens susceptibility to CHF.

A recent study shows that inflammation and oxidative stress in obesity are able to trigger many molecular pathways, such as the NF-κB and JAK-STAT pathways, which induce myocardial remodeling and CHF progression [12].

1.5 Cardiovascular Adaptation or Maladaptation? The Impact of Obesity on Cardiac Function

Comorbid obesity contributes to adaptive and maladaptive modifications in cardiac function. As a compensatory mechanism, the metabolic demand of the heart is increased by enlargement of its volume and increased contractility in the initial stage of obesity. This compensation leads to left ventricular hypertrophy (LVH) due to increased mass of the left ventricular, which is an initial adaptive phenomenon. Nevertheless, persistent obesity-induced

cardiac stress results in maladaptive phenomena in cardiovascular remodeling, such as fibrosis of the myocardium, diastolic dysfunction, and CHF.

One of the major components of the maladaptive phenomenon is heightened cardiac workload due to obesity-induced arterial hypertension and modified metabolic substrates. Eventually, the cardiac incompetency is revealed by decreasing contractility, leading to reduced cardiac output and a clinical picture of CHF. The underlying diseases, such as diabetes mellitus type II and arterial hypertension, speed up this process. Furthermore, obesity-related inflammation and oxidative stress play a crucial role in converting adaptive to maladaptive cardiovascular remodeling.

In addition, obesity leads to multidimensional and complex cardiovascular maladaptation over the amalgamation of structural, molecular, and neurohormonal modifications. These phenomena raise the risk of arterial hypertension, atherosclerosis, and CHF. The molecular mechanisms responsible for these phenomena provide a prospective therapeutic approach for reducing the cardiovascular burden of obesity [13].

Chapter 2: Advanced Diagnostics and Precision Risk Stratification

2.1 Next-Generation Biomarkers in Heart Failure and Hypertension: Beyond the Traditional Models

Traditionally, B-type natriuretic peptides (BNP) and troponins are used in the diagnosis and prognosis of CVD. The downsides of these biomarkers are the inability to detect the disease in its early stages, stratification of risk factors, and prognostic estimation in CVD. The emergence of next-generation biomarkers contracts to enhance the accuracy of risk stratification, assist in a personalized treatment regimen, and conduct early intervention.

The element of the lectin family, Gal-3, promotes vascular inflammation, cardiac fibrosis, and remodeling. Increased Gal-3 is linked to poor prognosis of heart failure, with recent studies showing its advent prediction in morbidity and mortality. The value of Gal-3 in the prognosis of stroke in arterial hypertension patients has also been established in recent years. Increased Gal-3 serum was associated with a heightened risk of mortality and profound disability in ischemic stroke in the course of 3-month follow-up. The increased level of serum Gal-3 is linked to poor clinical outcomes and repetitiveness of ischemic stroke in patients with hyperglycemia [14].

Advanced glycation end-product contributes to the development and advancing of CHF and metabolic diseases. Accumulation of AGEs, in the long run, has been linked to the development and concatenation of coronary artery disease. Current studies suggest increased levels of AGEs, especially CML and pentosidine, in CAD patients. Elevated levels of AGE are linked to major CAD severity, including the acceleration of the pro-atherogenic mechanism. AGE can attach to the surface of the RAGE receptor, promoting pro-inflammatory and pro-atherogenic pathways. Decreased levels of soluble RAGE (sRAGE), which imitate the confederate receptors of AGE, have been related to the increased severity of CAD [15].

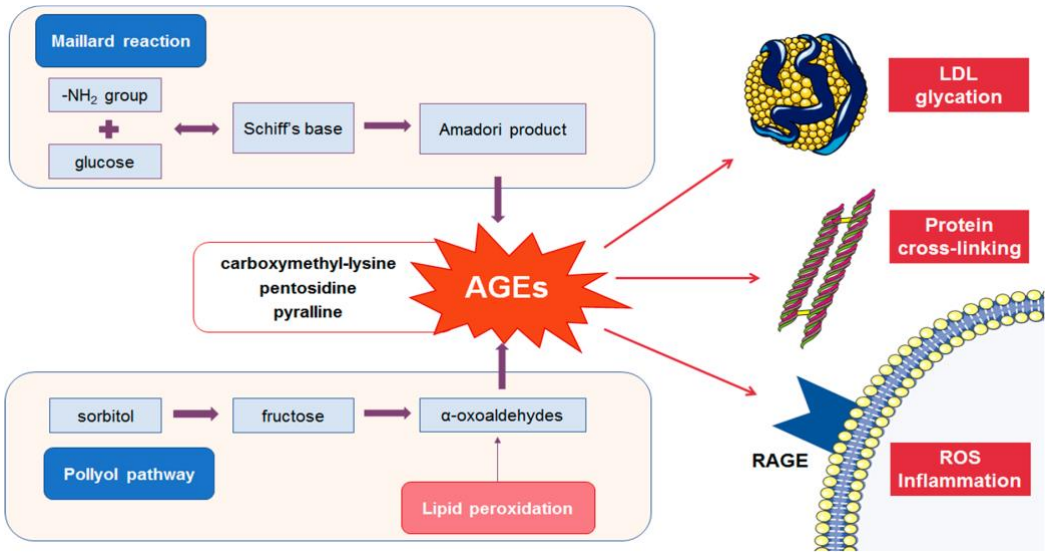

Figure 4. The scheme of formation of AGE and their pathological effect. Adapted from: Vekic, J., Vujcic, S., Bufan, B., Bojanin, D., Al-Hashmi, K., Al-Rasadi, K., Stoian, A. P., Zeljkovic, A., & Rizzo, M. (2023). The role of advanced glycation end products on dyslipidemia. Metabolites, 13(1), 77. https://doi.org/10.3390/metabo13010077

The scheme shown in Figure 4 illustrates the Maillard process, which is initiated by protein lysine residue from a non-enzymatic reaction. Protein lysine residues are most commonly glycated, and a water molecule's subsequent loss produces glucose. This reversible reaction initiates the formation of Schiff base, which is an unstable compound. These compounds undergo some molecular reshuffle and become stable compounds known as Amadori products. Over some period, the Amadori product transforms into AGE through oxidation. Denaturation and browning of the AGEs become irreversible [16].

Identifying the latest biomarkers in arterial hypertension provides an understanding of early vascular impairment and better estimates of the long-term stratification of cardiovascular risk. Markers of RAAS stimulation involving PRA and aldosterone levels have been linked to the development of arterial hypertension and CVD. Moreover, specific microRNAs (miRNAs) such as miR-21 and miR-155 have been associated with vascular inflammation and ED mechanisms, a key element in arterial hypertension. In addition, markers of ED, such as ADMA, which promotes the inhibition of NO synthase, and ET-1, which causes vasoconstriction, are the indicators of ED in hypertensive individuals [17].

The implications of next-generation biomarkers improve the diagnostic and therapeutic approach, refinement of patient stratification, and cultivation of treatment protocols. For example, the inclusion of next-generation biomarkers allows general practitioners to distinguish high-risk populations earlier, individualize pharmacological interventions, and monitor the efficacy of the treatment in the long run.

2.2 Phenotyping Obesity: More Than Just BMI – Implications for Cardiovascular Risk

Obesity, claimed by a BMI ≥30 kg/m2, was for a long time considered a significant risk factor for CVD. Anyhow, BMI alone neglects to seize the diversity of obesity and its heterogenous cardiovascular implications. It is now recognized that phenotypic features such as metabolic dysfunction, inflammatory status, and fat distribution are crucial to comprehending obesity-related CVD risk.

The distribution of fat in central obesity, also known as visceral adiposity, is described by extensive fat deposition in the abdomen region and is more firmly related to unfavorable outcomes in CVD than in general obesity. The visceral adiposity is responsible for triggering pro-inflammatory cytokines such as TNF-α and IL-6 due to its dynamic metabolic activity. This circumstance promotes insulin resistance, elevated arterial stiffness, and ED [18].

In some obese individuals, traditional metabolic abnormalities such as dyslipidemia, arterial hypertension, and insulin resistance are not evident. This phenomenon is described as metabolically healthy obesity, which shows a decreased risk of CVD contrasted with metabolically unhealthy obesity. Metabolically unhealthy obesity presents with major insulin resistance and racks up lipid profiles [19].

Ectopic fat deposition, the accumulation of ectopic fats in non-adipose tissues involving the heart, skeletal muscles, and liver, has been recognized as a significant factor of obesity-related CVD. For example, hepatic fat accumulation is associated with the development of non-alcoholic fatty hepatic disease, which heightens the risk for the development of atherosclerosis [20].

Furthermore, chronic low-grade inflammation is a trademark of obesity and is reviewed as a key element of progression to CVD. Elevated levels of CRP and markers of inflammation are regularly seen in obese individuals, promoting ED and atherosclerosis. Moreover, the regulators of energy balance and inflammation, such as adipokine, leptin, and adiponectin, have been entangled in obesity-induced CVD [21].

Obesity phenotyping permits more refined strategies for cardiovascular risk stratification. Diagnostic tools such as DXA and MRI are progressively being used to examine the accumulation of visceral fat, whereas biomarkers such as CRP, leptin, and adiponectin provide an understanding of the inflammatory and metabolic derangements in obese patients.

2.3 Genomic and Epigenetic Considerations: How Genetics Influence Comorbid Obesity, Hypertension, and Heart Failure

The interlink between genetics and environment plays a critical role in the advancement of obesity, arterial hypertension, and CHF. The emerging genomic and epigenetic applications have allowed a profound understanding of the hereditary patterns and modifiable factors contributing to these diseases. At the same time, the determination of genetic predispositions has provided direction towards targeted therapeutic and diagnostic approaches by epigenetic modification, influences of gene expressions, and progression of diseases.

The genomic factors that contribute to obesity are variants of gene expression involving regulation of appetite control, balance of energy, and fat storage. The FTO gene is one of the most established genes correlated with the risk of obesity through specific variants causing increased susceptibility to elevated BMI and accumulation of fat. Additionally, MC4R and LEP manage hunger and satiety signals and have been included in the pathogenesis of obesity.

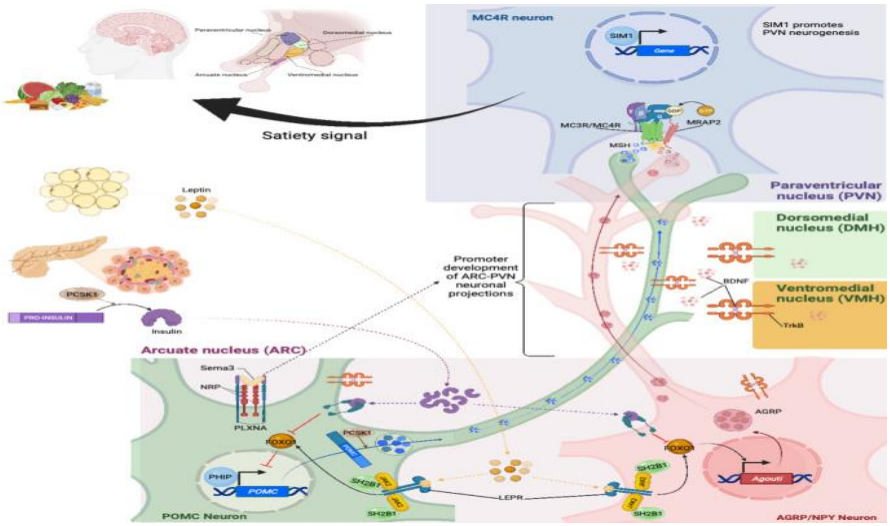

Figure 4

Figure 4. Illustration of leptin mineralocorticoid pathway.

Leptin is considered an anorexigenic hormone synthesis of white AT across its levels impelled by fat mass and affects food consumption and energy balance. When the circulation of leptin decreases during the fasting period and increases during the feeding period, leptin regulates appetite through the hypothalamus. The arcuate is the leptin receptor's main isoform and inhabits two neuron variants. Leptin triggers POMC neurons, which are responsible for processing different melanocortin peptides. The POMC neurons communicate with MC4R neurons situated in PVN, where these melanocortin peptides cause the mitigation of food intake. At the same time, the antagonist of MC4R is AGRP, which inhibits the mitigation of food intake and promotes appetite, as shown in Figure 5 [22].

Additionally, several gene expression variants have been associated with regulating blood pressure. The angiotensin-converting enzyme encoded by ACE genes plays a main role in the RAAS and has been related to the development of arterial hypertension. Polymorphism in AGT and ADRA2A also increases the susceptibility to arterial hypertension. Genetic predisposition to heart failure is due to mutations in structural proteins of the heart such as MYH7 and LMNA; sarcomere proteins such as TNNT2 have been recognized in primary familial hypertrophic and dilated cardiomyopathies and progressed into heart failure [23].

Epigenetic remodeling involving DNA methylation, histone modifications, and microRNA regulation can modify gene expression without transforming the primary sequence of DNA. These modifications are caused by environmental factors such as diet, physical activity, and

stress, which contribute to the multidimensional pathophysiology of comorbid obesity, arterial hypertension, and CHF. Transformation in DNA methylation activity in genes included in fat metabolism, such as PPARG and FTO, is associated with developmental obesity. Infancy exposure involving gestational and nutritional factors during prognosis also results in epigenetic modification, which heightens the risk of obesity in newborns [24].

Furthermore, the development of hypertension is due to epigenetic modification in RAAS genes and vascular tone regulating genes (eNOS) responsible for persistent hypertension in obese individuals regardless of environmental or lifestyle modifications. Meanwhile, epigenetic modification in heart failure is caused by TGF-β1 and CTGF genes influencing cardiac remodeling, inflammation, fibrosis, and arterial stiffness [25].

Chapter 3: Integrated, Multidisciplinary Management Approaches

3.1 Lifestyle Medicine 2.0: Innovative Diet and Exercise Regimens Tailored for the Comorbid Patient

Lifestyle medicine 2.0 is a contemporary approach in the primary care setting that views personalized patient care, genomic and epigenetic approaches, and the presence of concomitant diseases such as comorbid obesity, arterial hypertension, and CHF. Unlike the retrospective approach to lifestyle modifications, this contemporary approach accentuates individualized patient care and evidence-based strategies incorporating nutrition, physical activity, and behavior modifications personalized to the patient's genetic peculiarity and metabolic outlines. The target is to enhance clinical outcomes of various comorbidities concurrently, improving the well-being of patients. Recent studies show that lifestyle modification, especially those aiming for diet and physical exercise, can substantially affect the clinical outcomes in patients with multiple comorbidities [26].

Diet plays a main role in Lifestyle Medicine 2.0. A plant-based diet, DASH, and a Mediterranean diet are recommended to decrease BP, increase cardiovascular health, and prevent cardiac complications. These diets contain high levels of fiber, antioxidants, and healthy fats and are rich in whole foods, which leads to decreased systemic inflammation and elevated metabolic function. Furthermore, current innovation of personalized nutrition, where strategies are centered on the patient's genetic constitution and composition of the microbiome,

indicates positive outcomes in managing comorbid obesity, diabetes, arterial hypertension, and CHF.

Physical exercise is another keystone in Lifestyle Medicine 2.0. Aerobic and resistance training exercises show a decrease in the occurrence of cardiovascular diseases, an increase in cardiovascular function, and mitigation of the severity of the clinical picture in arterial hypertension and CHF. Recent studies emphasize the significance of personalized physical exercise regimens that are modified to the patient's physical endurance and overall well-being. Aerobic physical exercise such as cycling, swimming, jogging, and walking is advantageous for enhancing cardiac fitness, decreasing BP, and improving endothelial function. Exercises must be planned for patients with concomitant diseases with careful consideration of the limitations and abilities of patients [27].

3.2 SGLT2 Inhibitors: A Game-Changer in Heart Failure and Hypertension Management

SGLT2, primarily used in the treatment of diabetes mellitus type II, has appeared as a central class of drug in the treatment of heart failure and arterial hypertension. The mechanism of the drug is inhibiting the SGLT2 protein, which is responsible for glucose resorption in the kidneys. This medication reduces glucose and encourages natriuresis, resulting in decreased water retention and reduced BP. The effect of diuresis is beneficial in CHF, where fluid retention causes cardiac edema and dyspnea. Recent clinical studies revealed that SGLT2, including dapagliflozin and empagliflozin, promotes substantial improvement in the outcome of CHF patients with HFrEF [28].

The advantages of SGLT2 in the cardiovascular system are greater than those of CFH. In hypertensive and hyperglycaemic patients, these medications decrease the prevalence of cardiovascular events involving hospitalization and mortality rates. The EMPEROR-Reduced trial shows that SGLT2 decreases the incidence of mortality and hospitalization due to CHF, keeping them a keystone in the treatment of these patients. Markedly, the advantage of SGLT2 ranges to patients without diabetes mellitus type II, contributing to a wider range of therapeutic approaches in CHF and arterial hypertension [29].

In addition, SGLT2 also provides nephroprotection, especially in arterial hypertension and hypoglycemic patients at risk of CKD. These medications decrease albuminuria and slow the

advancement of kidney failure. Recent studies show canagliflozin is a promising option in patients with mitigating renal-related complications involving terminal states of renal failure and complicated comorbidities such as CHF, diabetes mellitus type II, and arterial hypertension [30].

The common side effects of SGLT2 are genital mycotic infections and urinary tract infections; despite these being commonly mild and easy, they could be managed. Diabetic ketoacidosis has been noticed, but it's a rare but serious adverse effect. Physicians should be vigilant in considering patient risk factors and monitoring the prospective complications. Nevertheless, the general safety profile and broad advantages of SGLT2 make them a main component of contemporary CHF management.

3.3 GLP-1 Receptor Agonists in Obesity and Cardiovascular Disease: A Dual Approach to Weight Loss and Heart Protection

GLP-1 receptor agonists are a new group of drugs that demonstrate exceptional results in the management of obesity and CHF. Semaglutide, exenatide, and liraglutide imitate the impact of the natural hormone GLP-1, which plays a central role in glucose metabolism and the regulation of hunger, by increasing secretion of insulin, glucagon release suppression, and deceleration of gastric emptying. GLP-1 agonists assist in weight loss and increase glucose control, which are essential in managing obesity-related CHF. Recent studies show that GLP-1 agonists substantially decrease the risk of serious cardiovascular events in diabetic and CHF patients.

The advantage of the GLP-1 agonist range over glucose control and weight loss is that these medications also increase endothelial function and decrease BP and vascular inflammation, which are cornerstones in the pathophysiology of CHF. Clinical trials show semaglutide decreases the risk of stroke, ischemic heart diseases, and mortality due to CHF. In addition, GLP-1 agonists are related to mitigation in atherogenic markers, improved lipid profiles, and prevention of cardiac complications. One of the most persuasive points of GLP-1 agonists is their capability to offer persistent weight loss. In essence, studies show that the risk of CHF is reduced significantly for every 5% of weight loss. This establishes the key value of GLP-1 agonists in contemporary strategies for managing comorbid obesity and CHF [31].

3.4 The 'Obesity Paradox': Revisiting Outcomes in Overweight and Obese Patients with Heart Failure

The theory of the obesity paradox is a captivating field of study in the CHF. Despite entrenched antagonistic correlations between comorbid obesity and CVD, certain studies suggest that CHF in obese or overweight individuals has a better chance of survival compared to healthy individuals with CHF. The obesity paradox opposes the retrospective clinical conjecture and elevates the significant queries regarding the complexity between BMI and CHF outcomes. A study suggests that CHF in class I obese and overweight individuals show decreased mortality rates compared to CHF in normal BMI individuals, which formulates a new discussion about how an increase in body mass may increase the body's compensatory and protection mechanisms via the reservation of energy through increased muscle mass.

The possible advantage of increased BMI in CHF is considered multivariable. For example, an increase in tissue adiposity may influence the energy reservation in CHF, especially in cardiac cachexia. Furthermore, heightened fat deposition could reduce the negative impact of systemic inflammation and alleviate the tolerance in CHF. On the other hand, it is necessary to draw attention to this compensatory mechanism, which promotes the advancement of comorbid obesity and arterial hypertension, which is responsible for the exacerbation of concomitant CHF [32].

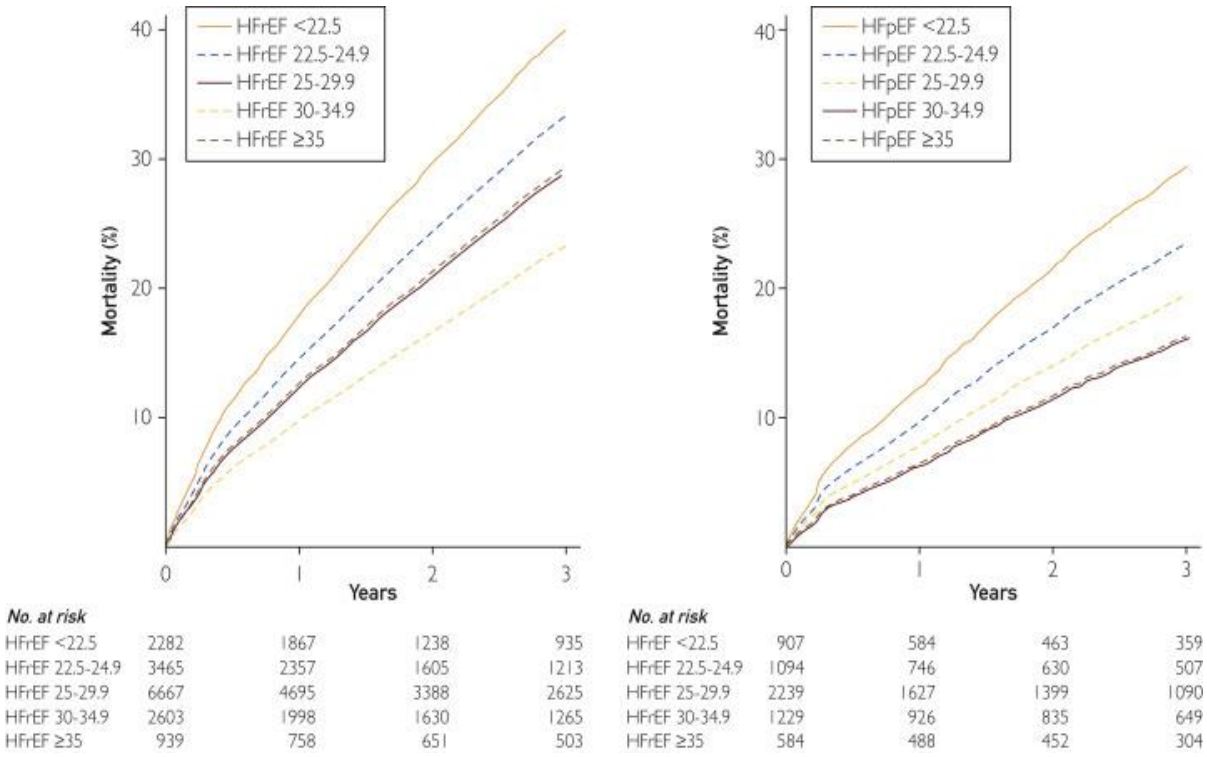

Figure 5

Figure 3. Total mortality rate classified by body BMI and CHF. Patients with CHF and increased BMI had a decreased mortality rate than those with a lower BMI. CHF is categorized as CHF with reduced ejection fraction (HFrEF) or HF with preserved ejection fraction (HFpEF). Adapted from: Obesity and Heart Failure: Focus on the Obesity Paradox Carbone, Salvatore et al. Mayo Clinic Proceedings, Volume 92, Issue 2, 266 - 279

The studies suggest that the obesity paradox interfered in patients with CHF due to decreased CRF, which is demonstrated in Figure 5 by heights of VO_2 of 14 $mL \cdot kg^{-1} \cdot min^{-1}$ or higher. When a patient is classified by CRF using the height of VO_2 ceases 14 mL·kg−1·min−1, the compensatory mechanism of increased BMI is diminished, outlining the more critical role of CRF, compared to BMI, in describing the prognosis of CHF. VO2, increased lean mass, and CRF can improve the clinical course despite BMI. Similar studies showed that metabolically healthy obese individuals demonstrated obesity according to BMI but the absence of metabolic derangements such as diabetes mellitus [32].

Conclusion

The rising perplexity of strategies for comorbid obesity, arterial hypertension, and CHF necessitates a multidisciplinary approach that forms contemporary diagnostic and therapeutic approaches. The profound understanding of multidimensional pathophysiologies in comorbid obesity, such as neurohormonal dysregulation such as activation of SNS, selective leptin resistance, and activation of RAAS, and the mechanism of advanced glycation end-product outlines the requirements of specific target therapy in the identification of main causes of these conditions. In addition, the genomic, epigenetic, and microbiome studies of comorbid obesity aid in early intervention and contribute to more appropriate treatment strategies such as personalized treatment regimens.

Meanwhile, the new pharmacotherapy, including SGLT2 and GLP-1, improves clinical outcomes in chronic heart failure and management of metabolic derangements. Moreover, the obesity paradox and diverse individual reactions to management highlight the significance of a refined therapeutic and diagnostic approach that counterbalances radical intervention with QOL. In addition, lifestyle modification, including personalized diet, exercise, and treatment, is essential in comprehending the appropriate management, clinical outcomes, prevention of progression, and complications.

In conclusion, the prospective approach toward diagnosis and treatment of comorbid obesity, arterial hypertension, and CHF includes a personalized treatment regimen incorporating a multidisciplinary specialist that improves the patient's clinical outcome and increases the QOL.

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