New Insights Into the Comorbidity of Coronary Heart Disease and Depression

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Abstract: Coronary heart disease (CHD) and depression are common disorders that markedly impair quality of life and impose a great financial burden on society. They are also frequently comorbid, exacerbating patient condition, and worsening prognosis. This comorbidity strongly suggests shared pathologic mechanisms. This review focuses on the incidence of depression in patients with CHD, deleterious effects of depression on CHD symptoms, and the potential mechanisms underlying comorbidity. In addition to the existing frequent mechanisms that are well known for decades, this review summarized interesting and original potential mechanisms to underlie the comorbidity, such as endocrine substances, gut microbiome, and microRNA. Finally, there are several treatment strategies for the comorbidity, involving drugs and psychotherapy, which may provide a theoretical basis for further basic research and clinical investigations on improved therapeutic interventions. (Curr Probl Cardiol 2021;46:100413.)

Introduction

The ancient Chinese theory that the "Heart Governs the Spirit Light" is an expression of the complex spiritual activities of human beings. If the "Heart Governs the Spirit Light"

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appropriately, the spirit is healthy and vigorous; conversely, a dysfunctional heart will cause mental abnormalities such as insomnia, memory loss, and insanity.[1] Traditional Chinese medicine emphasizes that unity of heart and mind (or the harmonization between soma and spirit) is necessary for life fulfillment.

Recently, there has been a shift from specialized medicine to holistic integrative medicine,[2,3] and from a purely biomedical model to a bio-psycho-social medical model.[4] Although the understanding of "heart" is different in Chinese and Western medicine, scientists have long recognized the importance of psychological factors in the pathogenesis, prognosis, and treatment of coronary heart disease (CHD).[5,6] Conversely, the incidences of cardiovascular and cerebrovascular diseases are significantly higher in patients with mental disorders.[7,8] Depression is a common mental illness clinically characterized by loss of willpower, persistent fatigue, and depressed mood. The prevalence of depression in patients with cardiovascular and cerebrovascular diseases is 25%-40%, many times higher than in the general population.[9-11]

Currently, although the relationship between depression and CHD has attracted increasing academic attention, the mechanisms underlying this comorbidity have not yet been fully elaborated. From many cross-sectional studies,[7-11] it is unambiguous that the incidence of depression is significantly increased in patients with CHD, whereas the incidence of CHD is also increased considerably in patients with depression. To explain this phenomenon, several plausible mechanisms have been assumed to underlie the relationship between CHD and depression. In addition to the traditional ones that are well known for decades, some novel potential mechanisms, such as endocrine substances, gut microbiome, and microRNA, are emerging as new therapeutic targets. Moreover, available treatments, involving drugs and/or psychotherapy, could alleviate the patients' condition. In the present review, we summarize recent progress in understanding the pathogenic mechanisms linking CHD with depression.

The Interaction of CHD and Depression

It is commonly recognized that depression plays an important role in the pathogenesis of CHD or is at least a predisposing factor for CHD,[12,13] whereas patients with CHD are prone to experience mental disorders, particularly depression.[14] The causal linkage between the 2 diseases is very intricate.[15]

Comorbidity is Common

The prevalence of depression in patients with CHD varies throughout the world, likely due to different screening tools and population samples, but is nonetheless significantly higher than in the local population. According to several studies in the United States, the prevalence of clinically significant depression in patients with acute coronary syndromes (ACSs) is as high as 31%-45%, and 20% of ACS patients meet the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders criteria for major depression.[16,17] In 2014, a meta-analysis of CHD complicated with psychological disorders enrolling cases at 23 hospitals (a total of 5236 patients) found that the comorbidity rate of CHD and depression was 51%, while a study of 4 community groups including a total of 1353 patients found a comorbidity rate between 34.6% and 45.8%, with major depression found in 3.1%-11.2% of CHD patients.[18] Therefore, the prevalence of depression in CHD patients is far higher than the 4.3% in the general population estimated by the World Health Organization (WHO, 2017).

The K-DEPACS and EsDEPACS studies reported that 46.3% of ACS patients showed persistent depression at the 12-month follow-up.[19] A prospective study by Korbmache et al found that 20.7% of patients scheduled for cardiac coronary artery bypass graft surgery had high depression scores before surgery, and that the rate increased to 28% at reassessment 6 months after surgery.[20] Therefore, there is compelling evidence that depression is common in patients with CHD, and that depressive symptoms persist following treatment.

Lower Quality of Life in Comorbid CHD-Depression

In CHD patients with poor prognosis (such as those with recent myocardial infarction [MI]), quality of life declines sharply when complicated by depression independent of traditional predictors. CHD patients with a history of depression reported a significantly greater frequency of angina pectoris than patients without depression, as well as limited physical activity.[21-23] Moreover, Kim et al found that the decline in quality of life associated with recurrent chest pain and depression was inconsistent with objective evidence of myocardial ischemia.[24]

Increased Healthcare Costs in Comorbid CHD-Depression

Comorbid CHD-depression also increases the probability of ambulance calls, emergency hospitalization, and disability. In a 3-year follow-

up study, Palacios et al evaluated the depression scores of 803 British CHD patients every 6 months, and reported that the medical costs of patients with long-term depressive symptoms were 95.5%-107.2% higher than those of patients without depression after adjusting for demographics, social factors, clinical risk factors, and disease severity.[25]

Multivariate analyses have also found that depression and anxiety are independent predictors of hospitalization expenses for CHD patients, with overall expenses increasing with the severity of depression and anxiety symptoms.[25,26] This may be related to poor treatment compliance, the greater self-reported severity of various symptoms (eg, angina), and more frequent requests for medical examinations in CHD patients with depression and anxiety.

Poor Prognosis of CHD With Comorbid Depression

CHD patients with comorbid depression demonstrate higher readmission rates, increased frequency of chest pain, and higher risk of major cardiovascular events.[27,28] Meijer et al conducted a meta-analysis of 29 studies between 1975 and 2011 in which a total of 16,889 patients with MI were followed-up for an average of 16 months. They concluded that all-cause mortality was 2.25 times higher in MI patients with depression, while cardiac mortality was 2.71 times greater and the risk of cardiovascular events 1.59 times greater.[29] Moreover, another meta-analysis of 4037 MI patients with major depression followed up for a mean of 39 months concluded that the risk of death was 3.04 (95% confidence intervals, 2.12-4.35) times higher in those with untreated or treatment-refractory depression than in treatment-responsive patients; likewise, all-cause mortality was higher in patients with refractory depression.[30]

CHD Results in Depression

Psychological Factors

Given the long disease course and unsatisfactory prognosis, it is unsurprising that the majority of CHD patients have to deal with negative emotions, such as depression and anxiety, which may manifest as asthenia, distraction, irritability, and poor sleep. In particular, patients with unfavorable living conditions and poor education are more vulnerable, which exacerbates psychological problems and has a marked impact on normal life, ultimately leading to more depressive symptoms.[31] In addition, A-type personalities, characterized by a sense of urgency and hostility,

are often tense and thus more prone to CHD as well as to anxiety, depression, and other mental disorders.[32]

Physiological Factors

Numerous clinical investigations have reported chronic brain hypoxia in CHD, which can eventually lead to neurological symptoms and mental disorders, including depressive symptoms.[33-35] We speculate that there are several possible mechanisms: (1) coronary atherosclerosis—coronary atherosclerosis causes myocardial ischemia and hypoxia, and the weakened heart cannot deliver enough blood to the brain, resulting in cerebral anoxia and abnormal brain function, including depression; (2) cerebral arteriosclerosis—coronary arteriosclerosis is often accompanied by cerebral arteriosclerosis, which decreases brain blood flow and thereby leads to brain dysfunction; (3) alterations in blood oxygen content—decreased arterial oxygen content as a consequence of poor cardiopulmonary circulation contributes to cerebral anoxia and psychiatric symptoms; and (4) cardiac emboli—during a heart attack or myocardial infarct, blood pressure drops sharply and blood coagulation deteriorates, contributing to cerebral thrombosis.

Depression is an Independent Risk Factor for CHD

Depression is not only associated with CHD, but is also an independent predictor that increases the Framingham risk score for CHD.[36,37] Depression severity, duration, and responsiveness to treatment are all associated with adverse outcomes in CHD patients. Moreover, a number of potential mechanisms have been proposed to explain this association, including inflammation, endothelial dysfunction, and platelet activation, hypothalamic-pituitary-adrenal (HPA) axis hyperactivity, autonomic dysfunction, and various behavioral factors.

Abnormalities in the Inflammatory Response

Since the 1980s, the prevailing theory on immune dysfunction in depression has shifted from immunosuppression to overactivation of neuroinflammatory processes.[38,39] Indeed, a multitude of studies have found a close association between depression and the inflammatory response, including dramatically increased levels of certain inflammatory cytokines such as interleukin (IL)-6, C-reactive protein, and tumor necrosis factor-α in patients with depression.[38,40] Further, a meta-analysis of patients with chronic physical illnesses concluded

that tumor necrosis factor inhibitors ameliorate depressive symptoms by alleviating severe and chronic inflammatory conditions.[41] Moreover, inflammatory cytokines are directly associated with the formation and rupture of atherosclerotic plaques, which accelerates atherosclerosis and leads to CHD, as well as angina pectoris and MI.[42,43]

Many studies have indicated that depression accompanied by elevated inflammatory factors is a significant risk factor for mortality from CHD. Whooley et al reported that depression (as indicated by patient health questionnaire-9 score $\geq$ 10) predicted adverse cardiovascular outcomes in CHD patients. This association was reduced by 11.3% after adjustment for inflammatory cytokine concentrations, suggesting that inflammatory factors are associated with adverse cardiovascular events in patients with symptoms of depression.[44] Similarly, Vaccarino et al found that the association between depression and cardiovascular events was reduced by 20% after controlling for inflammatory cytokines.[45] These findings strongly implicate inflammation associated with depression as a major factor leading to poor cardiovascular outcomes.

Endothelial Dysfunction and Excessive Platelet Activation

The effect of depression on subsequent cardiac events may be mediated by endothelial dysfunction and excessive platelet activation. Cai et al reported that average platelet volume (an indicator of platelet activity and chronic inflammation) was significantly higher in major depression patients compared to healthy controls.[46,47] In addition, adenosine diphosphate-induced platelet activity was higher in patients with comorbid ACS and moderate depression compared to ACS patients without depression.[48,49] Depression can also cause vascular endothelial dysfunction in healthy people, CHD risk groups, and CHD patients.[50] Moreover, flow-mediated vasodilation of the brachial artery, an indicator of normal vascular endothelial function, is reduced in depressed patients.[51]

Endothelial dysfunction and excessive platelet activation are also directly related to myocardial ischemia and atherosclerosis. Vascular endothelial cells induced by 5-hydroxytryptamine (serotonin, 5-HT) release nitric oxide, which in turn triggers blood vessel dilation. Thus, the decreased serum 5-HT associated with depression could exacerbate vasoconstriction in atherosclerotic vessels, leading to platelet aggregation and thrombosis.[52] Selective serotonin reuptake inhibitors can attenuate vascular endothelial dysfunction in CHD patients with anxiety and depression, thereby improving adverse cardiovascular prognosis.[53,54]

Hyperactive HPA Axis

It has been confirmed that depression is associated with hyperactivity of the HPA axis and autonomic nervous system dysregulation through enhanced release of corticotropin releasing hormone.[55,56] The ensuing sustained release of glucocorticoids (GC) is known to damage hippocampal neurons via activation of HPA axis. In addition, persistent GC elevation reduces the number and impairs the function of glucocorticoid receptors, which weakens negative feedback inhibition of the HPA axis and promotes HPA axis hyperactivity, ultimately forming a vicious cycle of uncontrolled GC release.[57] Elevated plasma cortisol from excessive corticotropin releasing hormone release is linked to the development of hypertension, diabetes, and atherosclerosis, major risk factors for poor outcome in CHD patients. Thus, HPA axis hyperactivity may link depression to poor cardiovascular outcomes.[58,59]

Elevated norepinephrine in cerebrospinal fluid and plasma has also been reported in patients with major depression, which could in turn increase the contractility, oxygen consumption, and excitability of cardiac muscle, potentially leading to adverse cardiovascular events.[60] Similarly, a large-sample study of CHD patients by Otte et al ($n = 693$) found significantly higher 24-hour urinary cortisol levels in those with comorbid depression,[61] which could lead to abnormalities in glucose and lipid metabolism, resulting in hyperlipidemia and insulin resistance. In addition, HPA axis dysfunction may contribute to metabolic syndrome by promoting the release of proinflammatory factors, thereby further increasing the risk of cardiovascular disease.

Autonomic Dysfunction

Autonomic dysfunction may also contribute to the association between depression and CHD. The heart is innervated by sympathetic and parasympathetic nerves, which cooperatively regulate the response of the heart to stress and other external factors.[62] Patients with a history of CHD or congestive heart failure always show increased sympathetic activity and decreased parasympathetic activity, which leads to reduced heart rate variability (HRV), an independent risk factor for cardiac death, and lower baroreflex sensitivity.[63] Autonomic dysfunction increases the mortality of patients with acute myocardial infarction (AMI), and the occurrence of complications after cardiac surgery.[64]

HRV, indicative of a shift in the autonomic balance toward increased sympathetic activity, is also reduced in depressed patients with or without heart diseases.[65,66] Furthermore, there is a linear

relationship between HRV reduction and depression severity; that is, symptoms of depression may be aggravated as the HRVfalls.[66] A case-control study of CHD patients with or without comorbid depression found that HRV was significantly lower in the depressive group, indicating that depression may affect the prognosis of CHD patients through autonomic dysfunction.[67] Worse still, a recent meta-analysis revealed that antidepressant (AD) drugs failed to increase HRV or improve the prognosis of CHD patients; in fact, ADs may further reduce HRV in depressed patients.[68]

Behavioral Factors

Patients with comorbid CHD and depression are prone to several unhealthy behaviors and lifestyles, such as (1) smoking, (2) poor dietary habits, (3) lack of regular exercise, and (4) poor treatment compliance.

(1) Smoking: Depression increases the risk of smoking and the difficulty quitting.[69] (2) Poor diet: Low intake of fruits and vegetables may contribute to the relationship between depression and cardiovascular disease.[70] (3) Lack of exercise: CHD patients with major depression are less likely to exercise regularly. Moreover, in a study of 1017 patients with stable CHD, physical inactivity was the strongest factor contributing to the association between depressive symptoms and cardiovascular events.[44,71] (4) Poor treatment compliance: Drug nonadherence for secondary prevention of CHD may be 1 reason for poor cardiovascular outcomes in comorbid patients.[72,73] Depression was associated with poor adherence to aspirin therapy among patients with recent ACS, while treatment of depressive symptoms improved medication compliance.[74] These unhealthy behaviors and lifestyles may also increase the frequency and severity of traditional CHD high-risk factors such as obesity, metabolic syndrome, diabetes, hypercholesterolemia, and hypertension.[69]

These potential mechanisms for CHD-depression comorbidity are stronger inter-related, forming a complex pathogenic network that promotes depression in CHD and enhances CDH risk among depressive patients (Fig 1).[75] However, the predominant mechanisms in specific contexts (eg, different clinical and demographic populations) are still unclear. Such information is essential for treatment guidance and lifestyle management to improve prognosis. Much additional research is needed to identify potential causal links between depression and CHD and to elucidate how these mechanisms interact.

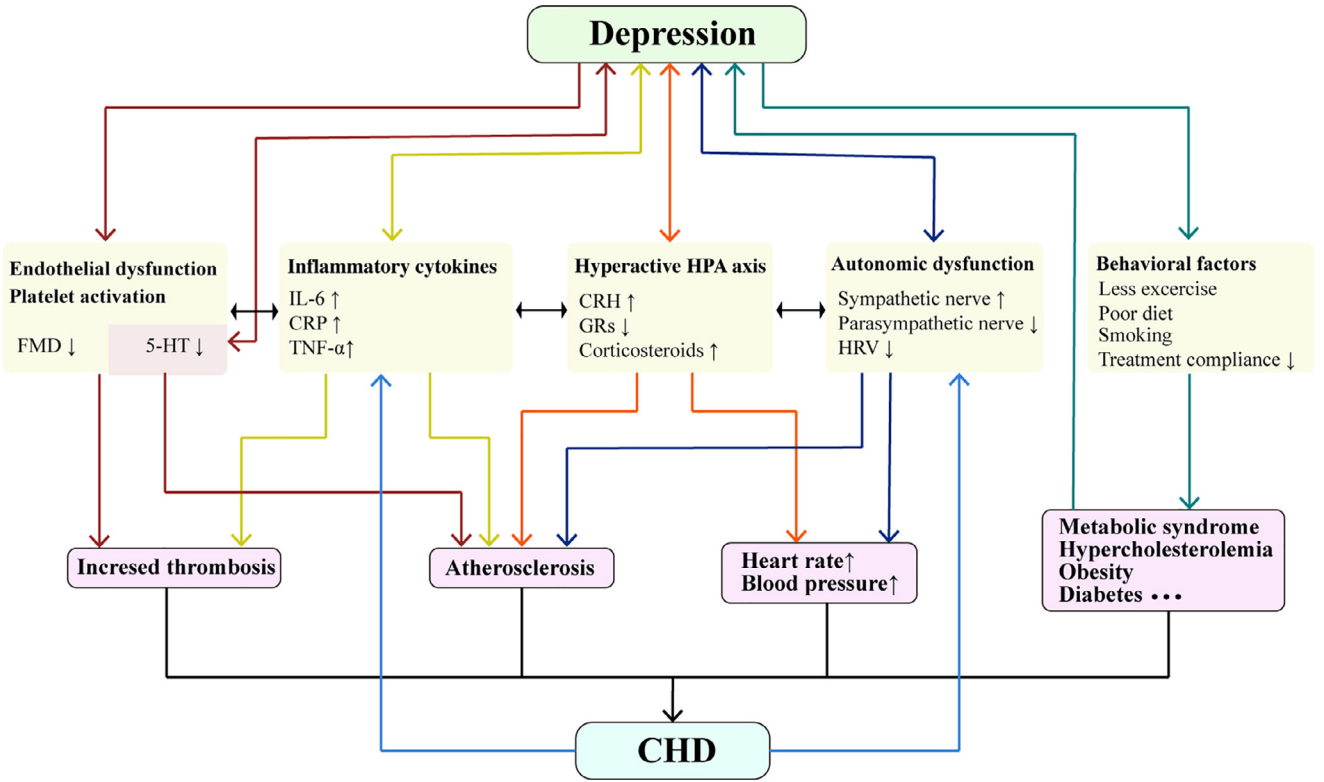

FIG 1. Relationship between depression and CHD. 5-HT, 5-hydroxytryptamine; CHD, coronary heart disease; CRH, corticotropin releasing hormone; CRP, C-reactive protein; FMD, flow-mediated vasodilation; GRs, glucocorticoid receptors; HPA axis, hypothalamic-pituitary-adrenal axis; HRV, heart rate variability; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α.

New Insights Into the Crosstalk Between CHD and Depression

Gut Microbiota

Gut microbiota play important roles in adjusting metabolism, regulating immune responses, and fighting illness, and are critical for maintaining the stability of the intestinal environment. These microbes can be divided into beneficial probiotics such as the genera *Bifidobacterium*, *Lactobacillus*, and *Bacteroides*, and opportunistic pathogens such as Gram-negative aerobes, anaerobic pathogens, *Clostridium difficile*, and *Candida albicans*. Recent studies have reported that the gut microbiota profile is closely related to the occurrence and development of Parkinson's disease, inflammatory bowel disease, depression, metabolic syndrome, and cardiovascular disease.[76-78] Given that gut microbiota constitute 90% of the total number of cells in the human body and that there are 3.3 million unique microbial genes in the human gut, 150 times more than in the human genome, this "second genome" is believed to regulate numerous normal physiological processes and contribute to homeostatic maintenance of the internal environment.[79-81]

The gut microbiota can affect the brain development and function through release of metabolites such as valerate or by stimulating the production of neuroactive substances from gastrointestinal endocrine cells. The brain can in turn monitor and regulate the composition of the gut microbiota via nerve, immune, and endocrine pathways, to either maintain the normal species profile or adjust the microbial profile according to changes in the environment.[78] However, this interactive "microbiota-gut-brain axis" may also change the microbial environment and impact neural activity and function with pathologic results, such as depression.[82,83] Indeed, clinical studies have confirmed that the composition and relative abundance of gut phyla such as *Bacteroidetes*, *Proteobacteria*, *Actinobacteria*, and *Firmicutes* are altered in depression,[84-87] while basic research studies have demonstrated that these changes alter central nervous system function through inflammatory responses, HPA axis activity, and neurotransmitter signaling, resulting in depression.[88,89] Accordingly, directly changing the composition and function of the gut microbiota such as through probiotic supplementation can improve depressed behaviors by restoring physiological cortisol levels, inflammatory factors, and neurotransmitter regulation in the central nervous system.[90,91] Bravo et al observed that the beneficial effects of probiotic supplementation were not

found in vagotomized mice, identifying the vagus nerve as a major modulatory pathway linking gut bacteria to brain function.[92]

Currently, there is increasing interest in the relationship between gut microbiota and cardiovascular diseases. A decline in gut microbial diversity increases the incidence of diabetes, obesity, and metabolic syndrome, all of which are risk factors for cardiovascular disease.[93,94] In addition, gut microbiota directly contribute to coronary atherosclerosis.[95,96] Intestinal bacteria can transform internal choline, phosphatidylcholine, and L-carnitine into trimethylamine (TMA), which is then oxidized to trimethylamino oxide (TMAO) in the liver.[97,98] High levels of TMAO enhance platelet activity and thrombosis,[99] which may in turn enhance atherosclerosis and heart disease risks.[96] Inhibition of TMAO production by adjusting the gut microbiota profile is a promising strategy for the treatment of atherosclerosis.[100] Also, significant differences in the diversity and composition of gut microbiota have been found between CHD patients and healthy controls, including decreases in the phyla *Bacteroidetes* and *Proteobacteria* and increases in the phyla *Firmicutes* and *Fusobacteria*.[101,102] Furthermore, blood *Proteobacteria* are strongly associated with cardiovascular complications and may be an independent risk marker for cardiovascular disease.[103] A risk prediction model for CHD patients including only 47 intestinal microbes based on a metagenome-wide association study of a Chinese population yielded a high degree of specificity and selectivity (area under receiver operating curve up to 0.86).[77]

The aforementioned studies have established strong associations between gut microbiota, such as *Bacteroidetes*, *Proteobacteria,* and *Firmicutes*, and the development of depression and CHD. It is therefore likely that gut microbiota contribute to the comorbid condition (Fig 2). Our tea mare undertaking the preliminary research. Improving CHD, depression, and comorbid CHD-depression outcomes by manipulating the gut microbiota profile warrants further study.

Endocrine Signaling

Whole-body homeostasis is maintained by interactions among 3 major regulatory systems, nerve, endocrine, and immune, and CHD and depression result from imbalances among these homeostatic systems. In the past few decades, the definition of the endocrine system has expanded beyond the traditional endocrine glands and extracellular cells that secrete hormones (thyroid, pituitary, adrenal, etc.) to include other organs such as the liver (which secretes hepatokines-like fetuin-A, insulin-like growth

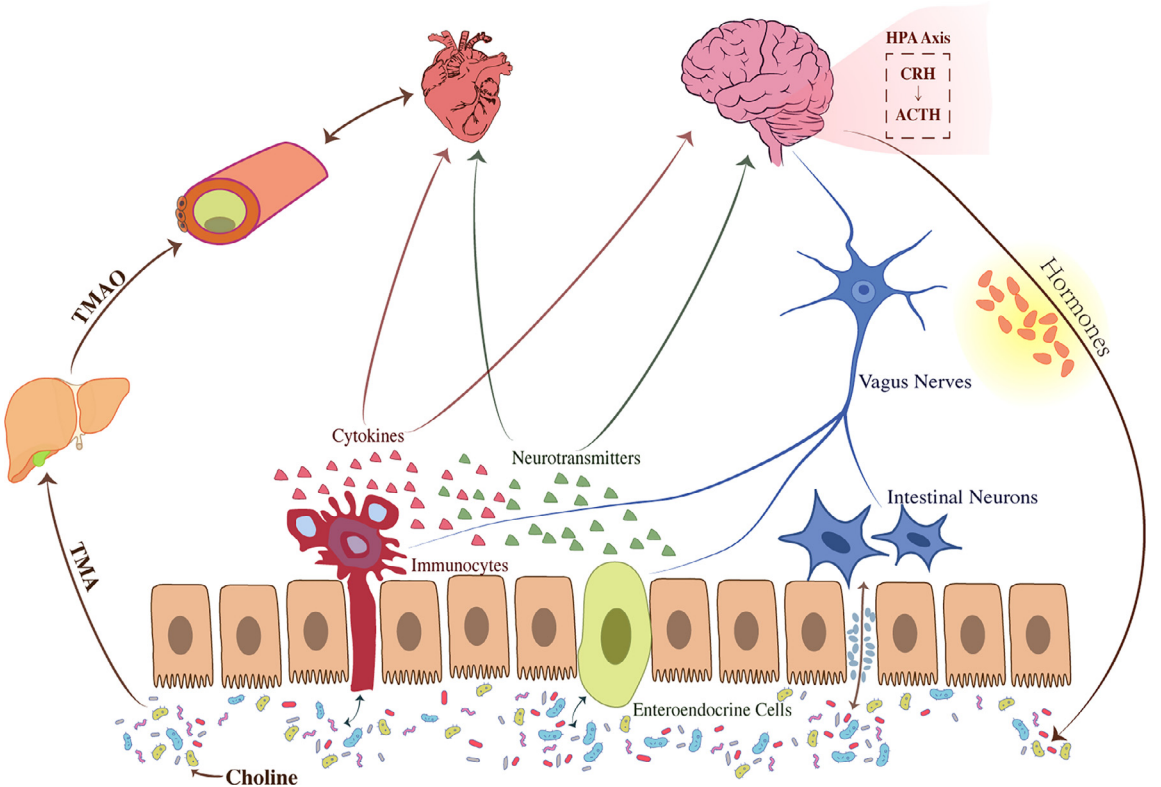

FIG 2. Gut microbiota in comorbid CHD and depression. ACTH, adrenocorticotropic hormone; CRH, corticotropin releasing hormone; HPA axis, hypothalamic-pituitary-adrenal axis; TMA, trimethylamine; TMAO, trimethylamino oxide.

factor (IGF), and others), the heart (which secretes cardiokines-like brain natriuretic peptide and fibroblast growth factor 21 [FGF21]), and skeletal muscle (which secretes mytokines-like irisin and follistatin-like 1).[104-106] These secreted substances regulate the growth, metabolism, and function of the source organ through paracrine and autocrine pathways, and regulate distant organs or tissues through blood circulation as canonical endocrine factors. As endocrine factors, these substances also contribute to the pathogenesis of certain systemic diseases.[107,108] Many of these substances demonstrate a lack of source specificity; for instance FGF21 is synthesized and secreted by the liver, skeletal muscle, and heart. The possible pathophysiological significance of these endocrine substances in comorbidity CHD-depression is described below.

IGF-1 is a single-chain polypeptide with a molecular structure similar to insulin. It is synthesized by the liver, kidney, and skeletal muscle, then secreted into the circulation. Expression of IGF-1 is regulated by growth hormone.[109] IGF-1 functions mainly through IGF binding proteins and the IGF-1 receptor (IGF-1R), both of which are widely expressed in different organs and tissues including the cardiovascular system. Therefore, IGF-1 participates in a variety of physiological and pathologic processes in the heart through endocrine, autocrine, or paracrine pathways.[110,111] According to several reports, specific IGF-1R and IGF binding proteins alleles are strong risk factors for arteriosclerosis and ischemic heart disease,[112,113] while IGF-1 is an effective protective factor against CHD.[114,115] Alternatively, excessively high or low serum IGF-I levels increase the risk of CHD in older men.[114] In addition to peripheral effects, circulating IGF-1 was found to pass through the rat blood-brain barrier and bind to brain IGF-1Rs,[116,117] which are mainly distributed in the olfactory bulb and hippocampus. Furthermore, IGF-1 secretion is abnormally low in patients with depression,[118] and individuals with lower cognitive ability are more likely to suffer from depression if they have lower levels of IGF-1.[119,120]

FGF21 is synthesized by the liver, kidneys, and cardiomyocytes, and then secreted into the circulation.[121] FGF21 specifically binds FGFR, which in turn activates the coreceptor β-klotho, forming a stable FGF21/β-Klotho/FGFR complex that activates the extracellular regulated protein kinases signaling pathway.[122] The expression of FGF21 in various organs is significantly affected by β-Klotho, while β-Klotho exhibits tissue-specific expression in the liver, heart, and nervous system. FGF21 has been shown to protect vascular endothelial cells and slow down the progression of cardiovascular disease.[123,124] It can also inhibit accumulation of reactive oxygen species and ensuing oxidative stress by inducing the

expression of antioxidant genes such as *Ucp3*, *Ucp2*, and *Sod2*.[124] In addition, FGF21 contributes to the regulation of lipid metabolism and anti-inflammatory responses, thereby improving atherosclerosis and reducing myocardial ischemia-reperfusion injury.[125] Intriguingly, Liu et al demonstrated a significant negative association between FGF21 levels and Beck Depression Inventory scores in male subjects, suggesting that FGF21 functions to prevent depression.[126] However, Chang et al reported that central and peripheral FGF21 may play opposing roles in patients with major depression, as metabolic disorders caused by high peripheral FGF21 levels were associated with resistance to AD treatment in patients with bipolar disorder.[127]

Irisin is a peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC-1α)-dependent mytokine. In skeletal muscle cells, PGC-1α activates the transcription of fibronectin type III domain-containing protein 5 (FNDC5), which is processed by proteolytic enzymes to form the secreted protein fragment irisin.[128] In addition to skeletal muscle, cardiomyocytes, adipose tissue, brain, and other tissues can also express FNDC5 and secrete irisin, with highest relative expression in cardiomyocytes.[129] Recent clinical studies have identified a close relationship between irisin and cardiovascular disease. Aydin et al found that serum levels of irisin in AMI patients were significantly lower than in healthy individuals. Conversely, irisin levels were negatively correlated with cardiac troponin I and creatinine kinase-MB, suggesting serum irisin as a potential diagnostic biomarker for AMI.[130] Kuloglu et al drew the same conclusions.[131] Irisin also appears to link exercise to brain health.[132] The improved cognitive function associated with exercise is related to the increased expression of brain-derived neurotrophic factor (BDNF) induced by irisin. In turn, BDNF regulates adult neurogenesis, synapse formation, and synaptic plasticity, all processes associated with cognition and disrupted in depression.[133] PGC-1α regulates the expression of the gene encoding FNDC5 in mouse cortical neurons by increasing transcription factor ERRα activity. Increased FNDC5 then promotes the expression of BDNF in hippocampus.[129,134] Therefore, exercise can exert an AD effect through the irisin-BDNF axis, and this signaling pathway is affected by exercise intensity.[135]

Collectively, these results provide strong evidence that dysregulation of the endocrine factors IGF-1, FGF21, and irisin all contribute to the pathogenesis of CHD and depression. In other words, CHD and depression share common endocrine mechanisms. These circulating endocrine substances are delivered throughout the body, forming a complex regulatory network among different organs and organ systems, thereby

contributing to multiple disease processes. However, there is still a lack of systematic and comprehensive research on the specific contributions of these factors to individual diseases.

MicroRNAs

MicroRNAs (miRNAs) are a class of eukaryotic small noncoding RNAs with a length of about 22 nucleotides that regulate the expression of genes at the post-transcriptional level. Studies over the past decade have implicated various miRNAs in the regulation of development, proliferation, differentiation, and apoptosis among other processes.[136] Since the first report in 1993,[137] more than 2000 distinct miRNAs have been identified, which collectively may regulate nearly 30% of all human genes.[136] In addition to regulation of genes in the miRNA-expressing cell, microRNAs are released into plasma, interstitial fluids, and cerebrospinal fluid.[138] These circulating miRNAs not only participate in normal physiological processes, but also in the pathogenesis of diabetes, cardiovascular diseases, tumors, and psychiatric disorders.[139]

The expression levels of multiple miRNAs change during cardiovascular diseases such as atherosclerosis, MI, and heart failure. Moreover, miRNAs related to various risk factors have been shown to contribute to CHD development.[140,141] For instance, abnormal lipid metabolism is one of the most important independent risk factors for CHD. The accumulation of cholesterol in the arterial wall gradually reduces the elasticity of blood vessels, further promoting inflammation and thrombosis. MicroRNAs regulate lipid metabolism-related gene expression, which is reported to affect the development of lipid metabolism-related diseases, including atherosclerosis.[142-144] Nearly 100 miRNAs that participate in lipid metabolism have been identified. Through gene-expression profiling, Tsai et al suggested that miRNA-122 could reduce the expression of genes involved in triacylglycerol metabolism in liver via an adenosine monophosphate-dependent protein kinase pathway.[145] Similarly, Hiopoulos et al confirmed that overexpression of miRNA-122 could inhibit cholesterol biosynthesis. Moreover, the related gene transcription products, including acyl-CoA carboxylase 1, were reduced to 25%-70% of their initial levels, thereby to degrade blood lipids.[146] External factors affecting lipid metabolism can also cause changes in related miRNAs. The expression levels of interferon regulatory factor-1 and miRNA-126 were increased in serum of animals on a high-fat diet, which further raised the level of vascular cell adhesion molecule 1, thereby enhancing the adhesion of leukocytes to endothelium and promoting the occurrence and development of

CHD.[147] In addition, miRNAs associated with smooth muscle cells, macrophages, and endothelial cells contribute to the pathogenesis of atherosclerosis.[148] Cordes et al demonstrated that miRNA-143 and miRNA-145 regulate expression of the transcription factor EIK-1 and the cell cycle inhibitor KFL-4, while further experiments in vitro found that these 2 miRNAs inhibited the proliferation of smooth muscle cells and promoted cell differentiation.[149] Intravascular macrophages can phagocytize lipids and form foam cells, an important event in the progression of atherosclerosis. A study by Tian et al revealed that YYl/HDAC2/4 complex negatively regulated the expression of miRNA-155 to suppress oxidized low-density lipoprotein-induced foam cell formation. More importantly, the lipid-loading capacity of macrophages and the formation of atherosclerotic plaques were significantly reducing by anti-miRNA-155.[150] In addition, endovascular blood flow shear stress can induce the expression of endothelial miRNA-92a and miRNA-21, and miRNA-21 upregulates endothelial nitric oxide synthase and reduces endothelial cell apoptosis.[151]

Recent studies suggest that circulating miRNAs may be novel biomarkers for cardiovascular diseases. More than 200 miRNAs have been detected in the heart, of which about 20 are considered potential diagnostic markers for AMI. These miRNAs are specifically expressed in the myocardium, and can be released into the peripheral blood circulation during AMI, thereby prompting myocardial damage.[152,153] When CHD patients are in the stable state, the serum levels of these miRNAs are in the normal range. When atherosclerotic plaques are unstable, however, miRNAs in the plaque cells or infarcted myocardium will be released into the blood, resulting in substantial changes to the profile of circulating miRNAs.[152,154] Moreover, recent research has demonstrated that miRNAs are closely related to plaque stability. Bazan et al reported that the acute decline of miRNA-221/222 levels was accompanied by plaque rupture.[155] Leistner et al used optical coherence tomography to evaluate the coronary atherosclerotic plaque burden in 52 CHD patients, and simultaneously measured the serum concentrations of miRNAs. Results revealed that plaque burden was closely related to the serum levels of miRNA-126-3p ($P = 0.04$), miRNA-145-5p ($P = 0.01$), miRNA-155-5p ($P < 0.01$), and miRNA-29b-3p ($P = 0.02$).[156]

Dysfunctional miRNA regulation has also been observed in depression.[157,158] MicroRNAs may be involved in the pathophysiological processes of depression through HPA axis hyperactivity, 5-HT signaling, and BDNF signaling among other pathways. Hyperfunction of the HPA axis and decreased expression of glucocorticoid receptors are 2 of the

most widely observed pathogenic changes in depression. Cellular studies suggest that miRNA-124 may play an important role in regulating GR expression and thus HPA functional state.[159] MicroRNA-16 exerts AD activity by inhibiting the expression of the 5-HT transporter, thereby reducing the reuptake of 5-HT at the synaptic cleft and promoting 5-HT signaling.[160-162] In addition, it has been reported that some miRNAs, such as miRNA-30a-5p and miRNA-195 in the prefrontal cortex and miRNA-206 in the temporal cortex, specifically inhibit the expression of BDNF.[163-165] In addition, BDNF also regulates the expression of miRNAs. In cultured rat cerebral cortical neurons, BDNF selectively upregulated the expression of miRNA-132 through activation of the mitogen-activated protein kinase (MAPK)/extracellular regulated protein kinases signaling pathway, resulting in axonal growth and increased numbers of dendritic spines, suggesting that miR-132 may regulate BDNF-mediated neural plasticity.[166-168] Given the important role of BDNF in the pathogenesis of depression, dysregulation of miRNAs associated with BDNF may also be strongly related to depression.

The studies cited on miRNA changes in CHD and depression are in a growing field implicating miRNA function and dysfunction in both systemic and psychiatric diseases. It appears that miRNAs can indirectly promote or suppress CHD-depression comorbidity through modulation of traditional risk pathways such as lipid metabolism and HPA axis hyperactivity or through direct influences on CHD and depression-related signaling pathways such as BDNF (Fig 3). Therefore, CHD and depression appear to share some common pathologic mechanisms dependent on miRNA regulation. While there is still no evidence for this in patients with comorbidity CHD and depression using miRNA gene chip detection and related methods, these studies have just begun. Thus, it is believed that in the near future miRNAs will be directly implicated in CHD and depression comorbidity and become valuable tools for research and possibly also for therapy.

Suggestions for Therapeutic Strategies

Pharmacologic Strategies

The long-term health effects of ADs are debated. A meta-analysis by Maslej et al showed that the risk of AD prescription was significantly lower in patients with cardiovascular diseases than in the general population,[169] whereas there is little evidence showing improvements of ADs in the prognosis of cardiovascular disease after long-term follow-up. To

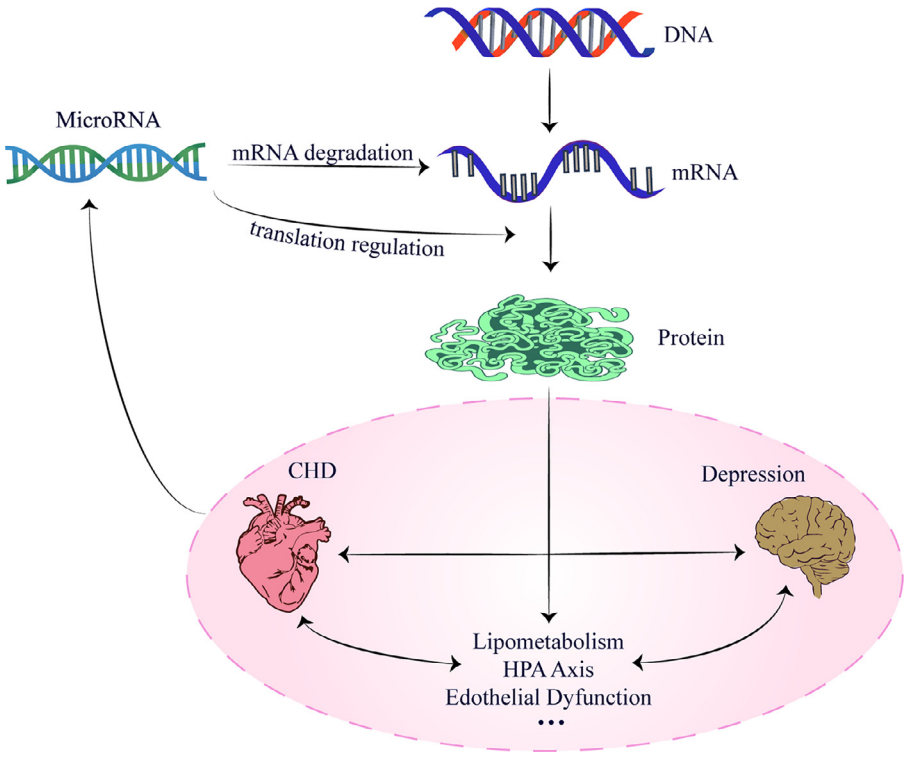

FIG 3. MicroRNAs in comorbid CHD and depression. CHD, coronary heart disease; HPA axis, hypothalamic-pituitary-adrenal axis.

reduce the cardiovascular adverse effects and help clinicians to make better choices, ADs could be divided into 3 categories by clinical outcomes[170]: (1) safe agents that are capable of providing protective effects on ventricular function and cardiac conduction system, such as selective serotonin reuptake inhibitors (SSRIs)[171]; (2) neutral agents that fail to show pharmacologic effects on the cardiovascular system, such as serotonin-norepinephrine reuptake inhibitors; and (3) harmful agents that are a category of ADs that have a deleterious impact on heart function, hemodynamic stability, and HRV, such as tricyclic ADs and monoamine oxidase inhibitors.

However, it is inappropriate to purely increase the dose of ADs or combined use of ADs to alleviate depressive symptoms in patients with CHD. When the symptoms are not alleviated satisfactorily, personality disorders or lack of proper psychological interventions should be sufficiently considered. Thus, the rational selection of ADs and the innovation of alternative treatments are both clinically significant.

Psychotherapy Strategies

Psychotherapy can arouse the patients' initiative to alleviate the disease, including explanatory therapy, lifestyle modifications, cognitive behavioral therapy (CBT), well-being therapy, etc. CBT focuses on changing the patients' thoughts, feelings, and behaviors to treat depression or other adverse symptoms, whereas well-being therapy can reduce the occurrence of stress-related diseases by preventing unhealthy psychological behaviors and promote the recovery of diseases by improving mental health and adjusting lifestyle.[172] In this regard, these strategies support the patients to improve their lifestyles and self-management, thereby improving the ability to cope with psychological distress.

Pharmacotherapy and psychotherapy both play important roles in the treatment of depression in CHD (Fig 4), and the combination therapy of both, such as the sequential integration of CBT and pharmacotherapy, may be more effective.[173] Moreover, physical symptoms caused by CHD also require traditional treatments, such as chemical drugs (clopidogrel, aspirin, and isosorbide dinitrate, etc.), percutaneous coronary intervention, and coronary artery bypass graft.[174] Interestingly, most interventions for depression have not been found to be beneficial for reducing mortality and cardiac events in patients with CHD, which even show negative therapeutic consequences in some cases. Further studies on the role of pharmacotherapy and psychotherapy in CHD patients with depression are greatly required.

Summary

Comorbid depression in CHD and elevated cardiovascular disease risk in depression are now widely recognized as substantial healthcare burdens that worsen prognosis, increase medical expenditures, and reduce patient quality of life. Moreover, there is substantial evidence that comorbidity results from shared pathomechanisms at system, cellular, and genetic levels. Here, we review evidence for the involvement and interactions among inflammation, unhealthy lifestyle factors, and HPA hyperactivity among other factors in comorbid CHD and depression. In addition, we discuss factors more recently implicated in CHD and depression comorbidity, including the gut microbiome, novel endocrine substances, and miRNAs. In clinical treatment, the specific contributions and interventional methods of AD therapy (including pharmacotherapy and psychotherapy) are still underway. Currently, psychocardiology, which regards mental and psychological factors as integral to the prevention and treatment of heart disease, is advancing at a rapid pace. Given that the

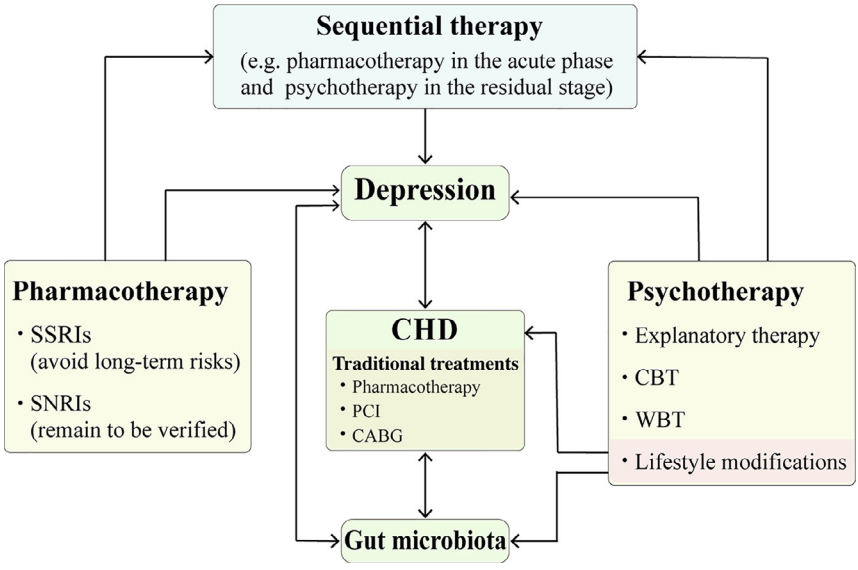

FIG 4. Suggestions for therapeutic strategies. CABG, coronary artery bypass graft; CBT, cognitive behavioral therapy; CHD, coronary heart disease; PCI, percutaneous coronary intervention; SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; WBT, well-being therapy.

intervention of mental illness is conducive to cardiovascular diseases, clinicians should pay closer attention to psychiatric comorbidities.

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Author Contributions

All authors critically reviewed and approved the final version of the paper.

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