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Research Progress of the Interaction between Depression and Coronary Heart Disease

Review Article

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Abstract

The incidence of depression Combined Coronary Heart Disease (CHD) is increasing, and it is a consensus that depression could increases the incidence of adverse cardiovascular events or mortality. Women under 50 and aging males were the high-risk groups of patients with CHD combined depression, existing researches on the relationship between the depression history, the onset times of depression, the therapeutic schedule and the adverse prognosis of CHD showed great differences; the differences of depression syndromes (somatic/emotional symptoms), CHD subtypes, LVEF levels and estrogen levels in individuals may explain this heterogeneity partly. Autonomic nervous system, limbic system, intestinal micro flora, inflammatory response, metabolism of 5-HT and polyunsaturated fatty acid maybe the main pathological basis for the occurrence and progress of CHD combined depression. In addition, depression severity associate with no nadherence in a gradient fashion, improvement of depression syndromes precedes the improvement of drug compliance.

Key words: Coronary heart disease combined depression; Depression; Acute coronary syndrome; Myocardial infarction; Pathogenesis

Abbreviations: AS, atherosclerosis; ACS, acute coronary syndrome; CAD, Coronary artery disease; CHD, Coronary heart disease; DG, dentate gyrus; GRACE, global registry of acute coronary events ; HADS-D, hospital anxiety and depression scale ; HAMD, Hamilton depression rating scale; IMT, intima-media thickening; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events ; MI, myocardial infarction; SCAD, stable coronary artery disease; SSRIs, Selective serotonin reuptake inhibitor drugs; TRD, treatment resistant depression; TUNEL, terminal 2'-deoxyuridine, and 5'-triphosphate nick-end labelling; OVX, ovariectomized; 5-HT, 5-hydroxytryptamine.

The incidence of depression combined coronary heart disease (CHD) increased year by year, and independent correlation is remarkable between the depression and mortality or adverse cardiovascular events in patients with non-organic myocardial infarction (MI) [27]. Large sample cross-sectional studies [77, 32] and evidence-based studies [5, 12, 25, 60] also proved that depression was a risk factor of adverse cardiovascular events in CHD.

Correlation between onset time and severity of depression and incidence of cardiovascular adverse events

Studies on the relationship between depression and CHD could be divided into two categories: Depression could increase the incidence of CHD or the risk of initial acute coronary syndrome (ACS);in patients with one adverse event, depression increased the risk of ACS recurrence or mortality by 2-4 times, but it has nothing to do with the severity of CHD or other prognostic risk indicators[47, 51].The other kind of results support that cardiovascular outcomes have nothing to do with depression, whether it is lifelong depression or depression before myocardial infarction (MI) admission; compared with the first (sporadic) or recurrent attack of depression, depression that occurred within 1 month after the ACS event, has a strong independent correlation with long-term mortality, which could predict the heart mortality in the next 5-7 years [9, 15, 18, 26,53].

Depressive symptoms or history before ACS aggravate the occurrence of adverse cardiovascular events, but it is still controversial whether the mediating mechanism is related to sports

A 9-year follow-up study in Taiwan showed that depression was associated with an increased risk of CHD (P<0.001) [30], the cardiovascular risk of patients with depression was significantly higher [7], and the depression history could be used as a predictor of post MI depression symptoms [2]. Early studies showed that the mean value of intima-media thickening (IMT) (0.87±0.35mm), in depression patients with CHD risk but without disease, was significantly higher than that in non-depression patients (0.77±0.19mm) (P<0.001) [54]. However, a 5-year follow-up study contained 1017 stable coronary artery disease (SCAD) patients (mainly aging males, about half of them are veterans) in San Francisco was carried out, which showed that the age-adjusted annual rate of cardiovascular events was 10.0% among the 199 participants with depressive symptoms (score>or=10) and 6.7% among the 818 participants without depressive symptoms (P=0.002);an association which remained significant (31%) after adjustment for comorbid conditions and disease severity; additional adjustment for potential biological mediators attenuated this association (P=0.12); then, adjusted the potential behavioral mediators, including physical inactivity, there was no significant association (P=0.75) [73].

In 2014, the American Heart Association proposed to increase depression as a risk factor for poor prognosis among patients with ACS [37]. A meta-analysis studies demonstrated that the adjusted HRs for patients with depression (vs those without) were 1.22 for combined MI and coronary death, 1.31 for MI alone, and 1.36 for coronary mortality alone [76]. The increased risk of MI and coronary death are significantly associated with depression.

Depression incidence increased significantly in post ACS patients, the severity and score of depression syndrome correlated with poor prognosis and mortality positively. LVEF could be used as a predictor of severe depression in post MI

The incidence rate of depression in CHD is 2 times than that of the general, and the incidence rate of MI is nearly 3 times [21, 46, 67]. The prevalence of depression in hospitalized MI patients is close to 20% [65, 67]. A variety of scoring methods on depression showed a significant positive correlation between global registry of acute coronary events (GRACE) and moderate to severe depression symptoms of post MI [48]. Depression scores was directly related to the increase of mortality [16], and the higher scores, the higher mortality [34], further study found that post MI depression could predict death significantly, but can't fully predict adjusted long-term survival. In addition, a 5 years of follow-up study showed that, the predictive correlation between depression and death decreased from significant to insignificant after adjusting for confounding factors and severity of MI [29].

The reduction of left ventricular ejection fraction (LVEF) could be used as a serious index of post MI depression (OR=3.17) [16, 19]. A research, which studied individual depressive symptoms and the all-cause mortality in 6,673 patients with MI, found that LVEF accounted for much of the associations in men≤55 years and women ≥70 years [14]. 632 patients (≤65 years) admitted for first-ever MI was followed up for 10-13 years; and showed that depressive symptoms were significantly associated with days of hospitalization, especially with the cardiac-related admissions [49].

Prognosis heterogeneity across different subtypes of depression, death most closely related to somatic / emotional syndromes

Early studies showed that, among different subtypes

of depression, somatic/emotional symptoms were most closely related to mortality within 5 years [14, 17, 44], which may partly explain the results exhibiting significant correlation between mild depression and mortality. Marian U. Worcester et al. conducteda long follow-up study, found that depression was a significant predictor of mortality independently of age and severity of MI, and mild depression had stronger mortality than others [75]. Besides, great heterogeneity of prognosis across age and genders were found in individuals with post-MI depression, negative self-image (P=0.022) and indecisiveness (P=0.003) were associated with increased mortality in men <55, and dissatisfaction (P=0.003) and fatigue (P<0.001) in men >70; fatigue was associated with mortality in women aged 56-69 (P=0.012), and suicidal ideation in women aged >70 (P=0.037) [14].

Young women and the senior citizens are susceptible and high-risk of depression combined CHD. Estrogen and IL-6 levels may partly expound the difference.

The prevalence of depression in patients with CHD is 15-30%, of which women are about two times as high as men, and the prevalence of post-MI depression in young women is much higher [37, 52, 71]. According to surveys, about half of women under 60, with a history of MI, had a history of major depression, and young women were more likely to die of MI than men [11, 64,70]. Using men as the reference point, women had an elevated risk of having some type of psychiatric disorder (such as depression) (P =0.007), and the hospital anxiety and depression scale (HADS-D)score was notably higher in women [62]; however, some clinical data showed that there were no significant associations between self-rating depression scale (SDS) scores and cardiovascular events among female patients, nevertheless, depression symptoms 1 year after onset of MI are a significant predictor of subsequent cardiovascular events for male patients [63]. In addition, another study found that HADS-D scores shortly post-MI had no predictive value on parameters of coagulation and fibrinolysis in patients 3 months after MI [22].

IL-6 increased significantly with the occurrence of mental and physical stress. Under the condition of similar levels of coronary angiographic and conventional risk factors in different gender groups. Before experiencing stress (including mental and physical), the baseline levels ofIL-6 in women ⩽50 years was two times higher than that of the matched men (3.8 pg/ml vs 1.8 pg/ml, P=0.001); IL-6 concentrations increased after mental/physical stress, with similar multiples as the baseline(womenandmen⩽50 years)at both 60min and 90min; while no difference ofIL-6 concentrations were found between different genders over 50before and after mental stress/physical stress; in addition,IL-6 concentrations of baseline showed no correlations with inducible ischemia. The above evidence indicate that young women post-MI have higher plasma concentrations of IL-6 before and after stress testing [59]. Animal studies showed that, after ovariectomized (OVX), the female rats developed mild depression-like behaviors after MI and were largely prevented by exogenous estrogen(E_2) [50].

The above results of IL-6 and $E_2$are consistent with the results of clinical trials in young women with higher levels of post-MI inflammation and worse prognosis, which may partly explain the differences of gender and age in patients with post-MI depression.

Treatment of depression combined CHD: Effective treatment of depression could reduce the adverse prognosis of patients with post-MI depression

Antidepressants could prevent death or adverse cardiovascular events [31]. Patients with Hamilton depression rating scale (HAMD) score less than 50% lower than baseline and HAMD score greater than 10 are defined as treatment resistant depression (TRD).A clinical trial contained 770 CHD patients showed that proportion of young women were significantly increased among patients with TRD, compared with non-TRD patients, and the mortality of TRD patients was higher in the follow-up period (13%vs. 7%)[4]. This means that effective treatment in depression could reduce the mortality of patients with post-MI depression.

Selective serotonin reuptake inhibitor drugs (SSRIs), norepinephrine (NE) and the combinations are commonly used drugs for depression. Evidence-based researches confirmed that SSRIs could reduce depression symptoms of patients with CHD and depression, and improve the long-term prognosis [56, 68]. Animal experiments demonstrated that the susceptibility of ventricular arrhythmia increased in post-MI depression, fluoxetine reduced the incidence of ventricular arrhythmia and improved the prognosis by increasing Kv4.2 [36]; escitalopram reversed post-MI behavior syndromes in rats by reducing pro-inflammatory cytokines and prostaglandin E2 [3]. According to the

classification of antidepressants, the ACS patients were observed during hospitalization with no switching; the result showed no difference between SSRIs group and non SSRI second generation antidepressants group unless there was a history of more serious depression (P=0.06); major adverse cardiovascular events (MACE)/mortality rates of SSRIs, non-SSRI second-generation antidepressants groups were reduced significantly during the follow-up period; furthermore, significant interaction between antidepressant use (yes/no) and timing of antidepressant use initiation (prior to versus only after the ACS) was showed; but, compared to non-SSRI second-generation antidepressant users, SSRI users had an increased hazard of MACE/mortality but this difference was not statistically significant [58]. The result is consistent with the conclusion that 'SSRIs and tricyclic antidepressants have no significant effect on the risk of composite coronary events in patients with depression [30]; in view of the small sample size and unitary observation index, some results still need to be verified repeatedly.

HAMD scores of 46 patients with CABG history and mild to moderate depression were measured, simvastatin was found to reduce the depressive symptoms more than atorvastatin, and time × treatment interaction had a significant effect on HAMD scores [1].Cognitive behavioral therapy was applied in treatment of 157 SCAD patients with moderate to severe depression also, more than 50% of the participants met the criteria for depression remission (17-item HAMD ≤ 7) at 16 weeks, but none of the inflammatory markers (CRP, IL-6, TNF) predicted post treatment depression or changed with depression[10]. In addition, studies suggested that the estimated costs of mental health care were higher than that of the usual care, but the overall estimated costs had no significantly difference between the two methods [13].

Drug compliance depression severity associate with non-adherence in a gradient fashion, improvement of depression syndromes precedes the improvement of drug compliance

The compliance of cardiology drugs on patients with post-MI depressive reduced significantly, and the incidence rate and mortality rate of CHD increased significantly [20]. An electronic medication monitoring study measured adherence to aspirin in 172 hospitalized ACS patients within 3months [57]. It was showed that depression severity was associated with no adherence in a gradient fashion: 15% of non-depressed patients, 29% of mildly depressed patients, and 37% of patients with moderately-to-severely depressive symptoms took aspirin less than 80% of the time; improvements in depressive symptoms in the first month after the ACS were associated with improvements in adherence rates in the subsequent 2 months. What's more, the improvement of depression was prior to the improvement of drug compliance [24]; to verify this point, Glassman ah et al. conducted clinical study to observe the compliance with sertraline; found that depression symptoms were relieved by sertraline, the medication compliance of patients was improved subsequently [6].

Research limitations

The definition and diagnosis of depression in patients with CHD has been controversial. The core of their dispute is whether depression-like behavior could represent "real" depression, as some symptoms of depression are non-specific; which may lead to low clinical diagnosis rate of depression and false positive results [45]. Therefore, conclusions of some clinical researches with small sample size are still controversial, researches which large sample size and high-quality are still needed to verify these points in the future, which may partly solve disputes on different points or contrary conclusions.

Pathological mechanism

The increase of intima-media thickness (IMT) in patients with depression is related to accelerated atherosclerosis and promotes the occurrence of CHD; inflammation and dysfunction of autonomic nervous system may be the pathophysiological mechanisms between depression and CHD. Early studies suggested that although depression symptoms had no significant predictive effect on heart rate variability (HRV), but HRV was involved in the prognosis of depression and MI [55].Depression was independently associated with HRV damage, inflammation reaction and endothelial function, however, the specific biological pathways and indicators are still controversial[8, 35].

Increased IL-6 and active pro-apoptotic pathway maybe involved in the relationship between MI and depression; increased IL-17a may the pathological product of depression after MI.

In the past ten years, research showed that HRV in patients with depression and CHD was lower than that

in non-depression group, and SDNN and SDANN were significantly lower than those in non-depression group [54]; CRP, IL-6, IL-8, TNF - α in patients with CHD and depression were higher than the non-depression group; depression was positively correlated with CRP, IL-6, IMT, and negatively correlated with SDANN [66, 69].Yiming Wang et al. found that no difference was seen between the MI and post-MI depression groups, there was a greater up-regulated Bax:Bcl-2 ratio in the post-MI depression groups [72]. Further study found that the plasma levels of IL-17a, IL-6, TNF α and IL-12p70 increased significantly in patients with first-time ST segment elevation MI and post-MI depression on the 3rd day, IL-17A and IL-6 increased on the 5th day; IL-17A and IL-6 increased in patients with MI without depression on the 3rd day, and IL-6 remained high on the 5th day only [74]. This suggest that active pro-apoptotic pathway maybe involved in the relationship between MI and depression; a higher degree of inflammatory reaction may induce depression, and the increase of IL-17a may the pathological product of depression after MI. However, there were still some research believed that fibrinogen, atherosclerotic load, hs-CRP and other inflammatory cytokines had no correlation with the occurrence of moderate to severe post-ACS depressive (or HDRS-17 and MADRS); and depression historypre-MI was the only relevant factor [33, 61]. Small sample size, individual differences, or some other reasons may explain the above clinical results.

Vagus nerve involved in the process of MI and post-MI depression, high-PUFA n-3 diet and probiotics abate the arising of depression-like behaviors through intact vagus nerve

Low levels of long-chain omega-3 polyunsaturated fatty acids (PUFA n-3) and increased inflammation were associated with depression and MI. Serum arachidonic acid / eicosapentaenoic acid (AA/EPA) ratio in patients with depression post-MI was significantly increased [61]. Post-MI depression symptoms are related to the apoptosis of amygdala cells, and the combination of probiotics Lactobacillus helveticus and Bifidobacterium longum has been proved to be helpful in reducing the apoptosis of limbic system and prevent depression. K Gilbert et al. [23] fed rats with different doses of PUFA n-3 diet or probiotics (combination of Lactobacillus helveticus R0052 and Bifidobacterium longum R0175)from the onset ofpost-MI reperfusion, found that caspase-3 enzymatic activities, terminal 2'-deoxyuridine, and 5'-triphosphate nick-end labelling (TUNEL)-positive cells of the high-PUFA n-3 diet group decreased most significantly in the CA1, dentate gyrus (DG) and amygdala at the 3rd day post-MI; while probiotics just reduced the activity of caspase-3 and TUNEL-positive cells in DG and medial amygdala. Besides, further research proved that high-PUFA n-3 diet and probiotics during the reperfusion of MI abated the arising of depression-like behaviors at 2 weeks post-MI, and the pathological process mainly depends on intact vagus nerve. Another study [43] showed that probiotics had no effect on infarct size, but vagotomy increased infarct size; activities of caspase-3 and caspase-8 in amygdala of MI rats increased significantly, probiotics reversed this process. Vagotomy could eliminate the beneficial effect of probiotics. These studies indicated that vagus nerve involved in the process of MI and post-MI depression, while the high-PUFA n-3 diet and probiotics just abated the arising of depression-like behaviors through intact vagus nerve.

Metabolism of tryptophan-5-HT maybe related to gastrointestinal dysfunction in post-MI depression

Low level of central 5-hydroxytryptamine (5-HT) is one of the main pathological changes in depressive. Abnormal metabolism of tryptophan-5-HT involved in depressive disorder and gastrointestinal dysfunction after MI, is not only an important substance in the gut-brain axis, but also an important pathological basis for common somatic, cognitive and mental depression after MI. Animal experiments showed that the contents of platelet 5-HT2AR and SERT in peripheral blood of post-MI depression rats were increased consistently [39]; meanwhile, the metabolism of tryptophan-5-HT in rats was significantly decreased, the levels of 5-HT and 5-hydroxyindoleacetic acid in hippocampus were decreased, and the levels of 5-HT and 5-hydroxyindoleacetic acid in ileum were also significantly increased [38, 40, 42]; ALDH2 was activated after the exogenous intervention of Alda-1, depression-like behaviors were improved, VEGF of hippocampus was increased, and the neurotransmitters contents of 5-HT and DA in serum were significantly increased also[41].

Conclusions

All in all, there is interaction between depression and CHD. Depression or depression history are risk factors for the occurrence of CHD, the incidence of CHD or adverse cardiovascular events in patients with depression are higher than that of the healthy; the incidence of depression in patients with CHD is significantly increased, the bad

prognosis (including adverse cardiovascular events or even death) are significantly increased also, the probability of adverse cardiovascular events in patients with post-ACS depression is 2-3 times higher than that of the general population. The proportion of young women and the elderly in CHD patients is relatively high, which is also a high-risk group with poor prognosis or death. The conclusion that "depression history/pre-ACS depression is not associated with adverse cardiovascular events or death" may be related to individual differences of depressive patients (such as cognitive or emotional somatic symptoms), different subtypes of CHD (differences in age, gender, LVEF level, etc.), as well as the sample size, follow-up time, quality of information collected and other factors that related.

Animal experiments and clinical trials confirmed that: brain-gut axis that closely related to the metabolism of 5-HT was involved in the occurrence and development of post-MI depression, which leaded to cognitive impairment and gastrointestinal dysfunction in patients with post-MI depression; through limbic system, autonomic nervous system participated in IMT thickening and atherosclerosis[28], activated immune system, affected metabolism of intestinal flora, promoted inflammation and HRV, and reduced LVEF, ect. However, there is no direct and strong evidence to prove that the sympathetic nervous system participates in the occurrence of post-MI depression or increases the incidence of CHD in patients with depression directly.

In recent 20 years, many clinical studies on SSIRs showed consistent results. Effective treatment of depression could significantly improve the long-term survival rate and quality of life, and SSIRs also have the advantage of higher clinical safety. Depression severity associate with no adherence in a gradient fashion, improvement of depression syndromes precedes the improvement of drug compliance. However, in view of the difficulties in current studies, many results are small sample size/ short-term follow-up or speculative analysis based on existing data. For example, there are still controversies on the medication time and specific medication categories, high-quality studies with large sample size and long follow-up are needed for repeated verification for future.

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Conflict of interest

The authors declare that they have no conflict of interest.

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