Review Article :
DEPRESSION IN POST-MYOCARDIAL INFARCTION PATIENTS

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ABSTRACT

Most patients with myocardial infarction (MI) experience a certain degree of underdiagnosed and undertreated depression. Pathophysiologically, depression is associated with other cardiovascular risk factors, increased platelet aggregability, inflammation, and autonomic dysregulation. In respect to behavioural risk factors, depression has been linked with increased smoking and alcohol use, non-compliance to prescribed medical treatment, and physical inactivity. Evidence showed that there is a strong interconnection between depression and cardiac events. Recently, depression has been recognised a risk factor for cardiac morbidity and mortality for patients with established coronary disease. Furthermore, high levels of depressive symptoms are associated with increased risks of mortality from all causes, including MI.

Keywords: depression, myocardial infarction

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INTRODUCTION

Depression and depressive symptoms are commonly found in patients after cardiac events, particularly post myocardial infarction (MI). However, this condition is often under-diagnosed and under-treated in clinical and rehabilitation settings. In fact, depression plays an important role in pathogenesis MI and has strong relationship with mortality due to MI (Musselman et al. 1998). This paper attempts to dig deeper the relationship between depression and MI as well as its pathophysiological mechanisms to gain better and comprehensive understanding in dealing with post MI patients associated with depression in clinical and rehabilitation settings.

Definition

According to DSM IV, 'depression' (major depressive episodes) is characterized by the presence of a depressed mood or markedly decreased interest/pleasure in all activities, persisting for at least 2 weeks and accompanied by at least 4 of the following additional symptoms: change in appetite or weight, sleep disturbance, fatigue, psychomotor retardation or agitation, feelings of guilt or worthlessness, problems concentrating, and suicidal thoughts (American Psychiatric Association & American Psychiatric

Association Task Force on DSM-IV 2000, Rozanski et al. 1999).

The term 'myocardial infarction' reflects a loss of cardiac myocytes (necrosis) caused by prolonged ischemia. The traditional acute myocardial infarction definition based on the revised WHO criteria is defined as the presence of two out of three typical criteria: ischemic symptoms (i.e., chest pain and discomfort), electrocardiographic changes consistent with ischemia and the rise of cardiac enzyme level which is usually creatine kinase-MB (CK-MB) (Hare 2001, 1979). The Joint Committee of European Society of Cardiology and American College of Cardiology (ESC/ACC 2000) has redefined MI into two classifications: acute, evolving or recent MI and established MI. The first type of MI is diagnosed by the presence of either one of the following criteria: 1) elevation of biochemical markers of myocardial necrosis (preferably troponin) with at least one of the following: a) ischemic symptoms; b) development of pathologic Q waves on the ECG; c) ECG changes indicative of ischemia (ST segment elevation or depression); d) coronary artery intervention (e.g., coronary angioplasty). Established MI is diagnosed if someone satisfies either of the following criteria:1) development of new pathologic Q waves on serial ECGs, or 2) pathologic findings of a healed or healing MI (Galvani et al. 2002).

EPIDEMIOLOGY

The association between depression cardiac events was shown in some studies (Carney et al. 1988; Lehto et al. 2000). Some examples of cardiac events are angina, heart failure requiring admission to hospital, myocardial infarction, cardiac arrest, percutaneus transluminal coronary angioplasty (PTCA), coronary artery bypass surgery (CABG), and cardiac mortality (Connerney et al. 2001). In one of the EUROASPIRE study (European Action on Secondary Prevention through Intervention to Reduce Events) in Finland consisting of 414 patients post cardiac events (i.e., CABG, PTCA, MI and myocardial ischemia without infarction) younger than 71 years, Lehto et al. (2002) reported that one-sixth of the patients (14-19%) suffered from depression (Lehto et al. 2000).

One of strong relationship between depression and cardiac event can be seen in patients with MI (Forrester et al. 1992; Lane et al. 2002; Lehto et al. 2000; Schleifer et al. 1989). The interview of 283 patients admitted to cardiac care units for myocardial infarction, 8 to 10 days after infarction showed that 45% of the patients met diagnostic criteria for minor or major depression, including 18% with major depressive syndromes. When 171 of them were re-interviewed 3 to 4 months later, 33% of patients met criteria for minor or major depression (Schleifer et al. 1989). Further more, in a prospective study of 288 MI patients, more than half the patients with complete Beck Depression Inventory (BDI) and state anxiety data experienced either elevated symptoms of anxiety or depression throughout the first year following MI (Lane et al. 2002). In a systematic review of studies within late 1980s up to end 1990s, Musselman et al. (1998) found a relative consistent prevalence rates of depression in cardiovascular disease patients ranging from 16% to 23 % (mean,19 %; median 18 %) (Musselman et al. 1998). Romanelli et al. (2002), in a prospective study, documented that almost one in four patients older than 65 experienced depression soon after MI (Romanelli et al. 2002). Depressive symptoms that are not sufficient to meet the criteria for major depression episodes are also commonly occur among patients with cardiac disease, and is also associated with an increased risk for cardiac events (Rozanski et al. 1999).

RELATIONSHIP BETWEEN DEPRESSION AND HEART DISEASE

Depression and heart disease are two independent conditions that may influence each other and any one may develop secondary to another. Many patients with post myocardial infarction and coronary artery bypass surgery (CABG) experience depressive symptoms after the events. Depression post MI is potentially resulted from some psychosocial condition including actual stress and anxiety from the event, life stress, low education level, social isolation (Frasure-Smith et al. 1993), and low social class (Ickovics et al. 1997).

On the other hand, literatures indicate that persons with depression tend to develop heart diseases much easier than persons without depression do (Barefoot & Schroll 1996). A prospective study during a 27-year follow-up on more than a total of 700 men and women in Glostrup, Denmark, showed that high scores on a measure of depressive symptoms were associated with increased risks for AMI. The study did not show different impacts of depressed affects on health between men and women. These results were among the first to demonstrate that depression could play a role in the development of initial coronary events (Barefoot & Schroll 1996).

The cardiovascular effects of antidepressant drugs

Some antidepressant medications are recognized having cardiovascular effects. The using tricyclic antidepressant (e.g., Amitriptyline) may cause conduction prolongation, AV block, orthostatic hypotension, anticholinergic effects (e.g., tachycardia and palpitation), and cardiovascular death in overdose. Dopamine and norepinephrine reuptake inhibitors have side effect of hypertension. This effect may also be found in the usage of serotonin and norepinephrine reuptake inhibitors. Antidepressant medications with no major cardiovascular effects are selective serotonin reuptake inhibitors (SSRIs) (Glassman et al. 2003). Hippisley-Cox et al. (2001), in a case-control study performed on more than 900 participants with heart disease found that there was a dose-response relationship and a significant increased risk of ischemic heart disease on patients who had ever taken dosulepin (antidepressant) (Hippisley-Cox et al. 2001).

The psychological effect of cardiovascular medication

Likewise, cardiovascular medications may also have implications on depression. Among cardiac medication, beta blockers are probably the most commonly associated with depression. Avorn, Everitt and Weiss (1986) documented a significant higher use of antidepressant in patients taking beta blockers (23%) compared to those taking other antihypertensive medication. This finding indicated that beta-Blocker use may be an important cause of iatrogenic depression among patients with hypertension (Avorn et al. 1986). Another cardio-active medication commonly associated

with depressive symptoms is digitalis. In a prospective study of 335 patients post-MI depression, Schleifer et al. (1991) found that treatment with digitalis predicted depression at 3 to 4 months and digitalis may have CNS effects that contribute to depression post-MI (Schleifer et al. 1991).

DEPRESSION AND PROGNOSIS OF MI

There is substantial evidence that depression is a risk factor for cardiac morbidity and mortality for patients with established coronary disease. The relationship is most apparent for patients with a recent acute myocardial infarction (Carney & Freedland 2003). Frasure-Smith, Francois and Mario (1993), in a prospective study which was the first ever done to demonstrate an independent impact of major depression on post-MI prognosis, documented 12 deaths, including 6 patient with depression (17%) and 6 patients without depression (3%), from among 222 hospitalized patients post MI after a 6-month follow-up (Figure 1) (Frasure-Smith et al. 1993). A continued observation up to 18 months on these patients supported the previous result that depression while in the hospital after an MI is a significant predictor of post-MI cardiac mortality. In addition, Frasure-Smith and colleagues (1995) found that the risk associated with depression is greatest among patients experiencing premature ventricular contractions equal or more than 10 times per hour. This results agreed with the hypothesis that arrhythmia acts as a potential mechanism underlying high mortality in patients with depression after MI (Frasure-Smith et al. 1995).

Barefoot and Schroll (1996) reported that high levels of depressive symptoms are associated with increased risks of mortality from all causes, including MI (Barefoot & Schroll 1996). A study assessing 817 patients undergoing CABG at Duke University Medical Centre between May, 1989, and May, 2001 showed that patients with moderate to severe depression at baseline and mild or moderate to severe depression that persisted from baseline to 6 months had higher rates of death than did those with no depression (Blumenthal et al. 2003). In addition, depression increases the risk of re-infarction on patients with post-MI (Frasure-Smith et al. 1993), and is the risk factor for the new cardiac event for people without previous myocardial infarction history (Vaccarino 2000).

Compared with younger patients, older post-MI patients with depression had more co-morbidity and had almost four times the risk of dying (26.4% vs 7.3%) within the first 4 months after discharge. Although many factors may affect this increased risk, Romanelli et al. suggested that sicker patients who were older and depressed might less often be prescribed medications known to reduce post-MI mortality and might also have greater difficulty following recommendations to reduce cardiac risk than their counterparts without depression (Romanelli et al. 2002).
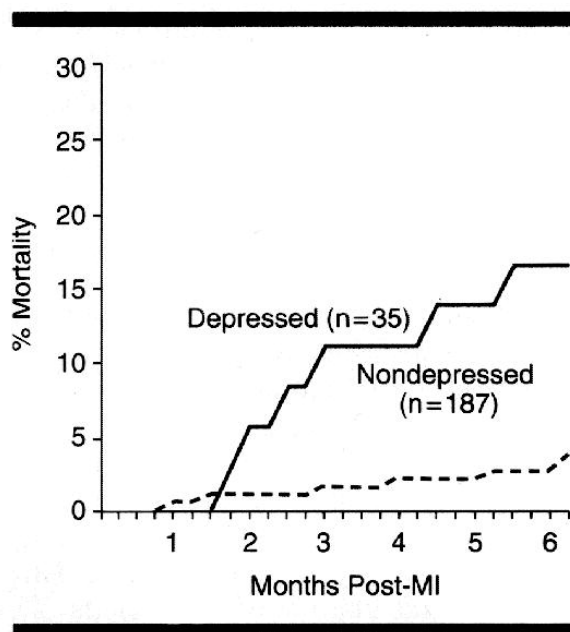

Figure 1. Depression and mortality (Frasure-Smith et al. 1993)

PATHOPHYSIOLOGICAL IMPACTS OF DEPRESSION

In general, depression has behavioural and direct pathophysiological and behavioural effects (Rozanski et al. 1999). Pathophysiologically, depression is associated with other cardiovascular risk factors, increased platelet aggregability, inflammation, and autonomic dysregulation (Blumenthal et al. 2003). In respect to behavioural risk factors, depression has been associated with increased smoking (Lehto et al. 2000) and alcohol use, non-compliance to prescribed medical treatment, and physical inactivity (Blumenthal et al. 2003).

Platelet activation

Platelets are one of blood cell elements. Platelets, also called thrombocytes, are formed in bone marrow from megakaryocytes which fragment into platelets either in bone marrow or in the pulmonary capillaries. The normal concentration of platelets in blood is between 150,000 and 300,000 per microliter. It has a half-life time in the blood of 8-12 days (Guyton & Hall 2000).

Platelets have many functional characteristic factors, even though they do not have nuclei and cannot reproduce (Guyton & Hall 2000). Platelet cytoplasm contains high concentration of 5-hydroxytryptamine (5-HT, serotonin), adenosine triphosphate (ATP), adenosine diphosphate (ADP), calcium, and alpha granules which are the most abundant organelles. The alpha granules secrete a large amount of proteins and products during their activation such as platelet factor-4 (PF-4) and beta-thromboglobulin; adhesive glycoproteins such as von Willebrand factor and fibronectin; coagulation factors, such as factor V, factor XI, protein S, and factor XIII; mitogenic factors, such as platelet-derived growth factor (PDGF) and transforming growth factor (TGF)-[beta]; and fibrinolytic inhibitors, such as [alpha]-2 plasmin inhibitor, plasminogen activator inhibitor-1, and P selectin. PDGF, PF-4 [beta]-TG, and thrombospondin are synthesized by platelets, whereas other factors are taken up from the plasma (Camacho & Dimsdale 2000). Growth factors secreted by platelet cause vascular endothelial cells, vascular smooth muscle cells, and fibroblasts to multiply and grow, thus causing cellular growth that helps repairs damaged vascular walls (Guyton & Hall 2000).

Platelets play key roles in hemostasis. When the blood vessels injure, the following events may occur and involve platelets: adhesion activation and aggregation. Platelets adhere to the collagen-containing subendothelial tissue within 15 to 20 second after the vessel injury. This adhesion is promoted by a plasma protein, the von Willebrand factor, factor VII and ADP.

Erythrocytes apparently increase platelet adherence rate by facilitating migration of circulating platelets toward vascular surfaces and by releasing ADP which enables platelets to stick to exposed collagen (McCance & Huether 2002). In activation phase, platelets experience several biochemical changes before secreting their components. The platelet membrane fibrinogen receptor (GPIIb-IIIa) serves as adhesion molecule to fibrinogen, fibronectin, and von Willebrand factor. This complex also binds collagen and GPIb-IX and forms a "sandwich". At this stage, platelets undergo dynamic changes in shape from smooth to spiny spheres that develops protrusions (pseudopods). Several physiological and pathological platelet activators are collagen, components of the atherosclerotic wall vessel, thrombin (these three are the strong ones), ADP, epinephrine, thromboxane A2 (TXA2), prostaglandin H2, 5-HT, and platelet-activating factor (Camacho & Dimsdale 2000; McCance & Huether 2002).

During aggregation, platelets' shape changes continually, preparing the them to expel components contained in granules (Camacho & Dimsdale 2000). This process is induced by TXA2 released by endothelial cells (McCance & Huether 2002). Fibrinogen and von Willebrand factor are the principal adhesive macromolecules that link the platelets together by binding to glycoprotein IIb/IIIa molecules on adjacent platelets. As a result of multiple reactions of this type, the platelets become aggregated into a hemostatic plug (Lefkovits et al. 1995).

Platelets play important role in thrombosis, atherosclerosis and acute coronary syndrome (Lefkovits et al. 1995). Exposure of platelets to damaged endothelium, shear stress, hypercholesterolemia, and circulating substances, like serotonin, can all initiate platelet activation similar to the hemostasis cascade initiated by endothelium injury (Schins et al. 2003). As platelets contain adrenergic receptors on their surfaces, stimulation those receptors increase the levels of circulating catecholamines, then potentiate the effect of other agonists, and at a higher concentrations, may initiate platelet responses including secretion, aggregation and activation of arachidonate pathway (Musselman et al. 1998). Platelets also contribute to vascular damage by stimulating lipoprotein uptake by macrophages and mediating vasoconstriction through the production and / or release of substances such as TXA2, platelet-activating factor, and serotonin (Musselman et al. 1998).

Increased platelet activation has been considered as one of mechanism linking depression and myocardial infarction. Markovitz and Matthews (1991) first proposed that enhanced platelet response to

psychological stress might trigger adverse coronary artery ischemic events (Markovitz & Matthews 1991). Clinical studies on platelet activation in depressed patients with or without cardiovascular disease performed mostly found increases in: 1) concentration of platelet-specific released products, such as beta-thromboglobulin (TG) and Platelet Factor (PF)-4, 2) molecules that are expressed on and shed from the platelet surface, such as P-selectin, glycoprotein IIb/IIIa, phosphatidylserine, and activated factor V, and 3) agonist-induced platelet aggregation (Schins et al. 2003).

It has been suggested that psychological stress induces platelet activation. Musselman et al. (2000) found that compared to the control group, 15 patients with major depression diagnosed with DSM-IV exhibited greater procoagulant activity under basal condition as detected by increased bindings of the monoclonal antibodies (mAb) anti–ligand-induced binding site (LIBS) to platelet surface and the mAb GA6 to granule membrane protein P-selectin, and increased plasma concentrations of platelet factor 4 (Musselman et al. 2000).

Depression and autonomic dysregulation

Some studies like the one conducted by Frasure-Smith and colleagues (1995) suggested that an autonomic dysfunction which may manifest in cardiac arrhythmias, commonly occurred in patients with post-MI depression. In this regard, the effect of depression has contributed to a sympathetic-parasympathetic stability alteration leading to changes in heart rate variability (Frasure-Smith et al. 1995).

Heart rate variability (HRV) is a term used to describe the variation of both heart rate and RR intervals. Some other terms have been used in literature for this purpose are cycle length variability, heart period variability, RR variability, and RR interval tachogram (1996). Heart rate and rhythm are controlled by intrinsic system of SA node and autonomic system of sympathetic and parasympathetic nerves (Boron & Boulpaep 2003; Ganong 2001; Guyton & Hall 2000). RR interval is thought to represent the balance between sympathetic and parasympathetic input to the heart. Low HRV reflects excessive sympathetic or inadequate parasympathetic tones (1996). This may lower the threshold for ventricular fibrillation during myocardial ischemia (Kleiger et al. 1987), and may put patients with post MI depression on increased risk for ventricular arrhythmia and sudden death (Seiner & Mallya 1999).

A high degree of heart rate variability is found in persons with normal hearts, whereas low HR variability can be found in patients with severe coronary artery disease, congestive heart failure and diabetic neuropathy (Bigger, Jr. et al. 1988). In a matched-pair study of 10 patients with low HR variability and 10 control patients with high HR variability, Bigger et all (1988) found that, based on 24-hour electrocardiograms, compared to the high HRV group, the low HR variability group showed: (1) the daytime and night time average HR was faster; (2) the difference between daytime and night time HR was less; (3) the proportion of differences greater than 50 ms between successive N-N intervals was smaller; and (4) the number of HR "spikes" per day (increase in HR greater than or equal to 10 beats/min, lasting from 3 to 15 minutes) was less (Bigger, Jr. et al. 1988)

HRV change has been a predictor of post-MI mortality. Kleiger et al. (1987) found that HRV had the strongest univariate correlation with mortality in patients with post-MI. The relative risk of mortality was 5.3 times higher in the group with HR variability of less than 50 ms than the group with HR variability of more than 100 ms (Kleiger et al. 1987).

The alteration in HRV is one of the most plausible mechanisms underlying increased mortality rate among patients with post-MI depression. A study done by Carney et al. (2001) involving 380 acute MI patients with depression and 424 AMI patients without depression showed that all four indices of 24 hour HRV (ultra low frequency, very low frequency, low frequency and high frequency) were significantly lower in patients with depression than in patients without depression (Carney et al. 2001).

Depression and behaviour risk factors

Depression as one of the psychosocial stressors may promote atherosclerosis in two ways: maintenance of bad lifestyle behaviours that promote atherosclerosis, for example, smoking and poor diet; and the discouragement of their modification (Rozanski et al. 1999). Glassman et al. (1990) observed that individuals who had experienced major depressive disorder at some time in their lives were more frequently had history of regular smoking than were individuals who had never experienced major depression or among individuals with no psychiatric diagnosis. In addition, smokers with major depression were also less successful to quit smoking than were either of the comparison groups (Glassman et al. 1990). The level of depression was significantly correlated with poor medication adherence and poor dietary compliance (Kim et al. 2003). In regard to alcohol intake behaviour, Weitzman (2004) reported that students with poor mental health and depression (PMHD) were less likely to report never

drinking; as likely to report frequent, heavy, and heavy episodic drinking; and more likely to report drinking to get drunk. Students with PMHD-especially females-were more likely to report drinking-related harms and alcohol abuse (Weitzmal 2004).

Inflammation

Depression could increase dhe risk of coronary heart disease by inducing or promoding inflammation process& This process can be detected by finding increased systemic inflammation marker, such aa C-reactive protein (Gabay & Kushner 1999). Analysed the third National Health and Nutrition Examination

Survey, a representative sample of the US population from 1988 to 1994, Danner et al. (2003) found correlation between history of a major depressive episode and elevated CRP among men aged 17 to 39, particularly for recent episodes (up to 6 months before assessment). In multivariate analyses, men with a history of major depressive episode had 2.77 times higher odds of elevated CRP compared with never-depressed men (Figure 2) (Danner et al. 2003). Atherosclerosis, a mechanisms suggested underlying increased mortality among patients with post-MI depression, basically is an inflammatory disease (Ross 1999).
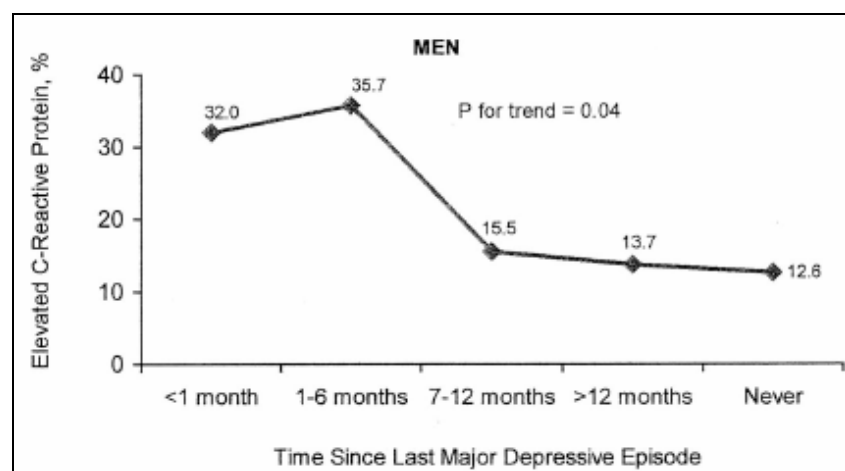

Figure 2. Prevalence of elevated C-reactive protein in men (Dannep et al. 2003)

TREATMENT OF DEPRESSION IN POST-MI PATIENTS

Once the diagnosis of depression is established, the patient shoeld be treated. However, research documented that most patients with post-MI depression are receiving inadequate treatment. A sdudy by Luutonen et al. (2002) indicated that none of patients were receiving adequate antidepressive medication 18 moths after myocardial infarction, even though 33.9 % of them were having depressive symptoms (BDI $\geq$ 10) (Luutonen et al. 2002).

There are a variety of reasons why most post-MI patient with depression is undertreated. First, diagnosis of depression among cardiac patient might be difficult. This possibly because the depressive symptoms performed by cardiac patients such as sadness and low self esteem are less typical compared to what are

usually performed by patients with extreme psychiatric disorder. Also, cardiac patients and their doctors may think depression is part of normal response after cardiac events (Luutonen et al. 2002). Second, treating depressive symptoms in cardiac patient is problematic. Some of antidepressive medications have side effect that may compromise heart problems. For example, Amitriptyline may cause postural hypotension and tachycardia (Glassman et al. 2003). On the other hand, some cardiac drugs may also have some psychological effects (Avorn et al. 1986). Third, the efficacy of psychotherapy for cardiac patients is not well documented by sufficient amount of research, event though Jones and West (1996) found that patients who received psychosocial treatment in addition to the standard cardiac rehabilitation have a lower cardiac mortality than those who did not receive psychosocial treatment (Jones & West 1996).

Pharmacotherapy is one of treatment approach responded well by Individuals with mood disorders. Antidepressants such as monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), and selective serotonin reuptake inhibitors (SSRIs), through different mechanisms work by increasing the level of monoamines (norepinephrine and serotonin) (McCance & Huether 2002). However the best pharmacological treatment for depression recently is derived from SSRIs, as they may decrease the risk of a cardiovascular event by reducing platelet activation and by restoring heart rate variability (Davies et al. 2004). The high affinity of most selective serotonin reuptake inhibitors for the serotonin transporters leading to reduced storage of serotonin in platelets has been suggested as an explanation for the cardioprotective action of these drugs (Sauer et al. 2003).

Cardiac Rehabilitation Program

The overall aims of cardiac rehabilitation are to optimize patients' functioning, enhance quality of life, and minimise the risk of recurrent cardiac events. Comprehensive rehabilitation programmes include exercise training, behavioural changes, education, and psychological support (Dalal et al. 2004). In a study of 338 patients in whom a major cardiac event had occurred 4 to 6 weeks previously and who were participating in outpatient cardiac rehabilitation consisting of 36 sessions over a 3-month period, Milani, Lavie, and Cassidy (1996) found that, after cardiac rehabilitation, patients with depression had marked improvements in depression scores and other behavioural parameters (anxiety, somatization, and hostility) as well as in quality of life (QoL). Two thirds of the patients who were initially depressed resolved their symptoms by study completion (Milani et al. 1996). Improvement of quality of life components such as mood, hopefulness and the ability to enjoy life lead to improvement of mental health. Other QOL component improvement such as sleep, appetite, and energy lead to improvement of physical function and task performance ability. In addition, reduced depressive symptoms in patient post MI may lead to enhanced patient's adherence to treatment regimes and cardiac rehabilitation programs (Glassman et al. 2003).

CONCLUSION

Depression is an independent risk factor for pathogenesis of acute myocardial infarction, rather than merely a secondary emotional response to the illness. The identification and treatment of depression should be one of the elements in the rehabilitation of patients with myocardial infarction.

REFERENCES

American Psychiatric Association & American Psychiatric Association, Task Force on DSM-IV, 2000, *Diagnostic and statistical manual of mental disorders : DSM-IV-TR* (4th edn, text revision ed.). American Psychiatric Association, Washington DC.

Avorn, J, Everitt, DE & Weiss, S 1986, 'Increased antidepressant use in patients prescribed beta-blockers', *Jama,* vol. 255, no. 3, pp. 357-360.

Barefoot, JC & Schroll, M 1996, 'Symptoms of depression, acute myocardial infarction, and total mortality in a community sample', *Circulation,* vol. 93, no. 11, pp. 1976-1980.

Bigger, JT, Jr., Kleiger, RE, Fleiss, JL, Rolnitzky, LM, Steinman, RC & Miller, JP 1988, 'Components of heart rate variability measured during healing of acute myocardial infarction', *Am J Cardiol,* vol. 61, no. 4, pp. 208-215.

Blumenthal, JA, Lett, HS, Babyak, MA, White, W, Smith, PK & Mark, DB et al. 2003, 'Depression as a risk factor for mortality after coronary artery bypass surgery', *Lancet,* vol. 362, no. 9384, pp. 604-609.

Boron, WF & Boulpaep, EL 2003, *Medical physiology: a cellular and molecular approach*, W.B. Saunders, Philadelphia, PA.

Camacho, A & Dimsdale, JE 2000, 'Platelets and Psychiatry: Lessons Learned From Old and New Studies', *Psychosom Med,* vol. 62, no. 3, pp. 326-336.

Carney, RM, Blumenthal, JA, Stein, PK, Watkins, L, Catellier, D & Berkman, LF et al. 2001, 'Depression, Heart Rate Variability, and Acute Myocardial Infarction', *Circulation,* vol. 104, no. 17, pp. 2024-2028.

Carney, RM & Freedland, KE 2003, 'Depression, mortality, and medical morbidity in patients with coronary heart disease', *Biol Psychiatry,* vol. 54, no. 3, pp. 241-247.

Carney, RM, Rich, MW, Freedland, KE, Saini, J, teVelde, A & Simeone, C et al. 1988, 'Major depressive disorder predicts cardiac events in patients with coronary artery disease', *Psychosom Med,* vol. 50, no. 6, pp. 627-633.

Connerney, I, Shapiro, PA, McLaughlin, JS, Bagiella, E & Sloan, RP 2001, 'Relation between depression after coronary artery bypass surgery and 12-month outcome: a prospective study', *Lancet,* vol. 358, no. 9295, pp. 1766-1771.

Dalal, H, Evans, PH & Campbell, JL 2004, 'Recent developments in secondary prevention and cardiac rehabilitation after acute myocardial infarction', *BMJ,* vol. 328, no. 7441, pp. 693-697.

Danner, M, Kasl, SV, Abramson, JL & Vaccarino, V, 2003, 'Association Between Depression and Elevated C-Reactive Protein', *Psychosom Med,* vol. 65, no. 3, pp. 347-356.

Davies, SJC, Jackson, PR, Potokar, J & Nutt, DJ 2004, 'Treatment of anxiety and depressive disorders in patients with cardiovascular disease', *BMJ,* vol. 328, no. 7445, pp. 939-943.

Forrester, AW, Lipsey, JR, Teitelbaum, ML, DePaulo, JR & Andrzejewski, PL 1992, 'Depression following myocardial infarction', *Int J Psychiatry Med,* vol. 22, no. 1, pp. 33-46.

Frasure-Smith, N, Lesperance, F & Talajic, M 1993, 'Depression following myocardial infarction. Impact on 6-month survival', *Jama,* vol. 270, no. 15, pp. 1819-1825.

Frasure-Smith, N, Lesperance, F & Talajic, M 1995, 'Depression and 18-month prognosis after myocardial infarction', *Circulation,* vol. 91, no. 4, pp. 999-1005.

Gabay, C & Kushner, I 1999, 'Acute-phase proteins and other systemic responses to inflammation', *N Engl J Med,* vol. 340, no. 6, pp. 448-454.

Galvani, M, Panteghini, M, Ottani, F, Cappelletti, P, Chiarella, F & Chiariello, M et al. 2002, 'The new definition of myocardial infarction: analysis of the ESC/ACC Consensus Document and reflections on its applicability to the Italian Health System', *Ital Heart J,* vol. 3, no. 9, pp. 543-557.

Ganong, WF 2001, *Review of Medical Physiology,* 20th edn, Lange Medical Book/McGraw-Hill, New York.

Glassman, A, Shapiro, PA, Ford, DE, Culpepper, L, Finkel, MS & Swenson, JR et al. 2003, 'Cardiovascular Health and Depression', *Journal of Psychiatric Practice,* vol. 9, no. 6, pp. 409-421.

Glassman, AH, Helzer, JE, Covey, LS, Cottler, LB, Stetner, F & Tipp, JE et al. 1990, 'Smoking, smoking cessation, and major depression', *Jama,* vol. 264, no. 12, pp. 1546-1549.

Guyton, AC & Hall, JE 2000, *Textbook of Medical Physiology,* 10th edn, WB Saunders Company, Philadelphia.

Hare, DL 2001, 'Recovery from acute coronary syndromes', *Australian Family Physician,* vol. 30, no. 10, pp. 959-963.

Hippisley-Cox, J, Pringle, M, Hammersley, V, Crown, N, Wynn, A & Meal, A et al. 2001, 'Antidepressants as risk factor for ischaemic heart disease: case-control study in primary care', *BMJ,* vol. 323, no. 7314, pp. 666-669.

Ickovics, JR, Viscoli, CM & Horwitz, RI 1997, 'Functional recovery after myocardial infarction in men: the independent effects of social class', *Ann Intern Med,* vol. 127, no. 7, pp. 518-525.

Joint International Society and Federation of Cardiology/ \World Health Organization Task Force, 1979, 'Nomenclature and criteria for diagnosis of ischemic heart disease. Report of the Joint International Society and Federation of Cardiology/ World Health Organization task force on standardization of clinical nomenclature. *Circulation,* vol. 59, no. 3, pp. 607-609.

Jones, DA & West, RR 1996, 'Psychological rehabilitation after myocardial infarction: multicentre randomised controlled trial', *BMJ,* vol. 313, no. 7071, pp. 1517-1521.

Kim, MT, Han, HR, Hill, MN, Rose, L & Roary, M 2003, 'Depression, substance use, adherence behaviors, and blood pressure in urban hypertensive black men', *Ann Behav Med,* vol. 26, no. 1, pp. 24-31.

Kleiger, RE, Miller, JP, Bigger, JT, Jr. & Moss, AJ 1987, 'Decreased heart rate variability and its association with increased mortality after acute myocardial infarction', *Am J Cardiol,* vol. 59, no. 4, pp. 256-262.

Lane, D, Carroll, D, Ring, C, Beevers, DG & Lip, GY 2002, 'The prevalence and persistence of depression and anxiety following myocardial infarction', *Br J Health Psychol,* vol. 7, part 1, pp. 11-21.

Lefkovits, J, Plow, EF & Topol, EJ 1995, 'Platelet glycoprotein IIb/IIIa receptors in cardiovascular medicine', *N Engl J Med,* vol. 332, no. 23, pp. 1553-1559.

Lehto, S, Koukkunen, H, Hintikka, J, Viinamaki, H, Laakso, M & Pyorala, K 2000, 'Depression after coronary heart disease events', *Scand Cardiovasc J,* vol. 34, no. 6, pp. 580-583.

Luutonen, S, Holm, H, Salminen, JK, Risla, A & Salokangas, RK 2002, 'Inadequate treatment of depression after myocardial infarction', *Acta Psychiatr Scand,* vol. 106, no. 6, pp. 434-439.

Markovitz, JH & Matthews, KA 1991, 'Platelets and coronary heart disease: potential psychophysiologic mechanisms', *Psychosom Med,* vol. 53, no. 6, pp. 643-668.

McCance, KL & Huether, SE 2002, *Pathophysiology : the biologic basis for disease in adults & children,* 4th edn, Mosby, St. Louis, Mo, London.

Milani, RV, Lavie, CJ & Cassidy, MM 1996, 'Effects of cardiac rehabilitation and exercise training programs on depression in patients after major coronary events', *Am Heart J,* vol. 132, no. 4, pp. 726-732.

Musselman, DL, Evans, DL & Nemeroff, CB 1998, 'The relationship of depression to cardiovascular disease: epidemiology, biology, and treatment', *Arch Gen Psychiatry,* vol. 55, no. 7, pp. 580-592.

Musselman, DL, Marzec, UM, Manatunga, A, Penna, S, Reemsnyder, A & Knight, BT et al. 2000, 'Platelet reactivity in depressed patients treated with paroxetine: preliminary findings', *Arch Gen Psychiatry,* vol. 57, no. 9, pp. 875-882.

Romanelli, J, Fauerbach, JA, Bush, DE & Ziegelstein, RC 2002, 'The significance of depression in older patients after myocardial infarction', *J Am Geriatr Soc,* vol. 50, no. 5, pp. 817-822.

Ross, R 1999, 'Atherosclerosis-an inflammatory disease', *N Engl J Med,* vol. 340, no. 2, pp. 115-126.

Rozanski, A, Blumenthal, JA & Kaplan, J 1999, 'Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy', *Circulation,* vol. 99, no. 16, pp. 2192-2217.

Sauer, WH, Berlin, JA & Kimmel, SE 2003, 'Effect of Antidepressants and Their Relative Affinity for the Serotonin Transporter on the Risk of Myocardial Infarction', *Circulation,* vol. 108, no. 1, pp. 32-36.

Schins, A, Honig, A, Crijns, H, Baur, L & Hamulyak, K 2003, 'Increased coronary events in depressed cardiovascular patients: 5-HT2A receptor as missing link?', *Psychosom Med,* vol. 65, no. 5, pp. 729-737.

Schleifer, SJ, Macari-Hinson, MM, Coyle, DA, Slater, WR, Kahn, M & Gorlin, R et al. 1989, 'The nature and course of depression following myocardial infarction', *Arch Intern Med,* vol. 149, no. 8, pp. 1785-1789.

Schleifer, SJ, Slater, WR, Macari-Hinson, MM, Coyle, DA, Kahn, M & Zucke, HD et al. 1991, 'Digitalis and beta-blocking agents: effects on depression following myocardial infarction', *Am Heart J,* vol. 121, no. 5, pp. 1397-1402.

Seiner, SJ & Mallya, G 1999, 'Treating depression in patients with cardiovascular disease', *Harv Rev Psychiatry,* vol. 7, no. 2, pp. 85-93.

Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996, 'Heart rate variability: standards of measurement, physiological interpretation and clinical use', *Circulation,* vol. 93, no. 5, pp. 1043-1065.

Vaccarino, V 2000, 'The association between depression and coronary heart disease incidence', *Drugs Today (Barc),* vol. 36, no. 10, pp. 715-724.

Weitzman, ER 2004, 'Poor mental health, depression, and associations with alcohol consumption, harm, and abuse in a national sample of young adults in college', *J Nerv Ment Dis,* vol. 192, no. 4, pp. 269-277.