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Review

Coronary artery disease and depression

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Coronary artery disease (CAD) as well as depression are both highly prevalent diseases. Both cause a significant decrease in quality of life for the patient and impose a significant economic burden on society. There are several factors that seem to link depression with the development of CAD and with a worse outcome in patients with established CAD: worse adherence to prescribed medication and life style modifications in depressive patients, as well as higher rates in abnormal platelet function, endothelial dysfunction and lowered heart rate variability. The evidence is growing that depression per se is an independent risk factor for cardiac events in a patient population without known CAD and also in patients with established diagnosis of CAD, particularly after myocardial infarction. Treatment of depression has been shown to improve patients' quality of life. However, it did not improve cardiovascular prognosis in depressed patients even though there is open discussion about the trend to better outcome in treated patients. Large scale clinical trials are needed to answer this question. Selective serotonin reuptake inhibitors seem to be preferable to tricyclic antidepressants for treatment of depressive patients with comorbid CAD because of their good tolerability and absence of significant cardiovascular side effects. *Hypericum perforatum* (St. John's wort), an increasingly used herbal antidepressant drug should be used with caution due to severe and possibly dangerous interaction with cardioactive drugs.

Introduction

Recently new risk factors for coronary artery disease (CAD) have been identified, among them emotional distress and depression.[1–5] Taking into account that lifetime prevalence of depression is as high as 17%,[6] it is not surprising that CAD and depression are often comorbid conditions. Both of them cause a significant decrease in quality of life for the patient and impose a significant economic burden on society. The association of depression and CAD has been noted already many years ago. In the mid 19th century a paper about 'nervous and sympathetic palpitations of the heart' was published.[1] This publication was followed by numerous papers describing the concept of neurologically based, or 'neurasthenic', cardiac disorders. In 1910, Sir William Osler described his typical patient with angina pectoris as 'a man whose engine is always set full speed ahead' and called his patients with cardiac disease 'worriers'.[7]

Depression and CAD as comorbid conditions

Major depression is a highly prevalent and disabling mental disorder that is under-diagnosed and under-treated.[6,8] High rates of disease-related disability, and relapse or recurrence are common.[9,10] Major depression is associated with as much physical and social dysfunction as many other common medical illnesses. Similarly, CAD

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is highly prevalent in western populations affecting men and women with increasing age.[11,12] Social dysfunction is twice as high in patients with advanced CAD and depression as in patients with either condition alone.[13–15]

Depression can reliably be diagnosed by psychometric scales and standardized clinical interviews.[16–19] The typical features are the presence of depressed mood and markedly decreased interest in all activities, persisting for at least 2 weeks and accompanied by at least four of the following additional symptoms: changes in appetite, sleep disturbances, fatigue, psychomotor retardation or agitation, feelings of guilt or worthlessness, problems concentrating, and suicidal thoughts.[4] Various well structured questionnaires have been used and validated in the screening process such as the Hamilton Rating Scale for depression,[16] the recent life change questionnaire,[20] and the Beck Depression Inventory.[17,18] In addition, short forms of questionnaires are available which screen for depression and other psychiatric disorders including mood, anxiety, alcohol, eating, and somatoform disorders.[19,21] It is important to utilize these simple validated questionnaires to diagnose depression in primary care settings.

Depression, CAD and outcome

Population without known CAD

Many early studies evaluating the interaction of CAD and depression were secondary analyses of population-based databases and have to be interpreted with caution. Nonetheless, several studies suggest an interaction between depression and the development of CAD after adjustment for traditional cardiovascular risk factors.[22] Relative risk for myocardial infarction in patients with depressive symptoms versus non-depressive patients within the same cohort ranged from 1.5 (95% CI 1.0–2.3) to 4.5 (95% CI 1.7–12.4).[23–27] An increased risk for CAD was not only described in patients with major depression but also in those with minor depressive symptoms and dysphoria.[23,27] In a cohort of 2832 subjects who participated in the National Health Examination Follow-up Study (mean follow-up=12.4 years) and who had no history of CAD or serious illness at baseline, 11% had depressed affect; 10.8% reported moderate hopelessness, and 2.9% reported severe hopelessness. Depressed affect and hopelessness were more common among women, blacks, and persons who were less educated, unmarried, smokers, or physically inactive. After adjustment for demographic and risk factors patients with depressed affect and moderate as well as severe levels of hopelessness had a relative risk to suffer fatal CAD of 1.5 (95% CI 1.0–2.3); 1.6 (95% CI=1.0–2.5) and 2.1 (95% CI=1.1–3.9), respectively. Depressed affect and hopelessness were also associated with an increased risk of non-fatal CAD.[23] Another report in 730 patients showed that significant depression was associated with relative risks of 1.71 (P=0.005) and 1.59 (P<0.001) for myocardial infarction and deaths from all causes, respectively after adjustment for baseline variables.[26]

These findings were confirmed by several prospective studies. The Precursors study evaluated 1190 male medical students who were followed up for 40 years.[28] The cumulative incidence of clinical depression was 12%. Men who reported clinical depression were at significantly greater risk for subsequent CAD and myocardial infarction than men without depression, the relative risk being 2.12 (95% CI 1.24–3.63) and 2.12 (95% CI 1.11–4.6), respectively. Of note, the increased risk associated with clinical depression was present even for myocardial infarction occurring 10 years after the onset of the first depressive episode. The authors concluded that clinical depression appeared to be an independent risk factor for CAD for several decades after the onset of clinical depression.[28] In The Cardiovascular Health Study evaluating 5201 subjects with a follow-up of 6 years, high levels of depressive symptoms were an independent risk factor for mortality in community-residing older adults. The authors hypothesized that motivational depletion which is consistent with vital exhaustion and decreased emotional vitality may be a key underlying mechanism for the depression-mortality effect.[29]

Interaction of depression and known CAD

In patients with angiographically proven CAD and no evidence of myocardial infarction or unstable angina the prevalence of depression was approximately 18% in one study.[30] In patients following acute myocardial infarction, up to 25% had severe, often recurrent major depression, while 27–65% manifested symptoms diagnostic of either major or minor depression.[1,25,26,31,32] The evidence that depression affects prognosis in patients with CAD, especially in patients after myocardial infarction is growing: reported relative risks for adverse outcome (mainly cardiac death) range from 2.5 to 5.7.[33–42] In addition to the mortality risk associated with post-myocardial infarction depression, increased health care costs linked to both readmission and out-patient contact among depressed patients who survived the first year after infarction have been observed.[43]

Of note, not only full blown major depression accounted for worse outcome: multivariate analysis in 222 patients with prior myocardial infarction demonstrated that depressive symptoms, anxiety, and history of major depression each had an impact on outcome independent of each other.[34] This finding was confirmed by other studies in patients after myocardial infarction in which mortality rates increased as a function of the degree of depressive symptoms.[38,44]

Impact of major depression on prognosis was as relevant as left ventricular dysfunction (Killip class) and history of previous myocardial infarction[33] and proved to be a significant predictor of 1-year cardiac mortality for women as well as for men independent of other post-myocardial infarction risks.[35] Recently, it has been suggested that depression had a similar impact on prognosis in patients with unstable angina as in patients post myocardial infarction.[37]

A higher prevalence of ventricular tachycardia during 24-h Holter monitoring among patients with CAD and

depression than among CAD patients without depression has been noted which may contribute to the explanation of the increased risk for cardiac mortality in depressed patients with CAD.[45]

In patients with coronary artery bypass graft surgery, it has been shown that depression diagnosed before surgery was related to higher hospital re-admission rates[46] and was an independent risk factor for cardiac events after surgery,[39,47] suggesting that positive emotions may promote better recovery.[48]

In summary, there is considerable evidence suggesting that depression and comorbid CAD may lead to an increased risk of death, regardless of which illness occurred first.[6] The most prominent finding is the increased mortality in patients with depression after myocardial infarction.

Pathophysiologic factors possibly linking depression and CAD

Several studies indicated that depression may have behavioural and direct pathophysiologic effects on CAD. Depression is associated with non-adherence to risk factor modification in many medical conditions,[49–52] such as smoking cessation,[53,54] poor patient compliance,[55,56] e.g. poor glycaemic control in diabetic patients[57] and poor adherence to prescribed medication in general.[56] In addition direct pathophysiologic effects linking depression to CAD have been postulated.

Abnormal platelet function,[58–62] including increased platelet reactivity, increased levels of platelet factor 4 and β-thromboglobulin, increased platelet reactivity to serotonin and decreased platelet reactivity to adenosine diphosphate[59] have been discussed. In addition, and in contrast to paroxetine administration, nortriptyline did not reverse increased levels of platelet factor 4 and β-thromboglobulin measures of platelet activation in patients with depression and CAD.[60]

It has also been hypothesized that hypercortisolemia and elevated levels of corticotropin-releasing factor may be as relevant as additional pathophysiologic mechanisms of depression linked to CAD [4] as well as Ω-3 fatty acid deficiency and elevated homocysteine levels.[64]

Furthermore, endothelial dysfunction has been reported in depressive patients. Fifteen patients who met the criteria for 'major depressive disorder' and lacked conventional risk factors for CAD were compared to matched control subjects with respect to brachial artery flow-mediated vasodilation.[63] Results showed that the only independent predictor of the amount of reactive hyperaemia was presence or absence of depression indicating that major depression in the absence of other conventional risk factors is associated with abnormal peripheral artery endothelial function.

In addition, patients with anxiety and depressive disorders have been shown to have reduced heart rate variability.[65–68] This finding may have important prognostic implications because low heart rate variability is a powerful predictor of sudden cardiac death.[69,70] Even in healthy subjects, depressed mood was related to the magnitude of decrease in parasympathetic cardiac control during stressors.[71] In patients after a recent myocardial infarction with evidence of depression, four indices of heart rate variability were significantly reduced compared to patients without depression[66] indicating that greater autonomic dysfunction as reflected by decreased heart rate variability might be a plausible mechanism linking depression to increased cardiac mortality in post-myocardial infarction patients.[66] Finally, a direct association between the severity of depressive symptoms and the modulation of cardiovagal activity was found.[65]

Thus, abnormal platelet function, endothelial dysfunction, and reduced heart rate variability have been identified as possible links between depression and CAD, however, more research in large scale clinical trials is needed to confirm these interrelationships and to assess their changes after antidepressant treatment.

Treatment of depression in patients with CAD

In patients with CAD, several small clinical trials suggest that cognitive-behavioural therapy successfully reduced anxiety and depression, and thus facilitated the modification of cardiac risk factors.[72–74] Data of the Enhancing Recovery in Coronary Heart Disease (ENRICHD) trial have been published recently.[75,76] This randomized controlled clinical trial evaluated 2481 patients with evidence of depression after myocardial infarction who either underwent treatment for depression (cognitive behavioural therapy) or usual care. Despite the treatment group's improvements in depression and social support, there was no significant difference in event-free survival (mortality and recurrent infarction) after an average follow-up of 29 months, between usual care (75.9%) and psychosocial intervention (75.8%).

However, several studies suggest that depressive patients with CAD benefit from cardiac rehabilitation programmes by improving coping skills and self image, reducing biological risk factors such as social isolation and smoking, by providing emotional support, and improving quality of life scores,[1,77–79] regardless of patient age and gender.[80,81] Unfortunately, drop-out rates from rehabilitation programmes are higher in depressive patients than in non-depressive patients.[82] Therefore, depressive patients with CAD should be encouraged to participate in cardiac rehabilitation programmes!

Medical therapy of depression

For many years, pharmacologic treatment for patients with depression and stable CAD was based on tricyclic antidepressive agents (TCA), such as amitriptyline, imipramine, nortriptyline, desipramine, and doxepin. TCA's have several adverse effects that complicate their use in patients with cardiac disease.[1] Tricyclic antidepressive agents cause orthostatic hypotension, which may result in haemodynamic instability, especially in patients with conduction system disease and congestive heart failure.[1] Furthermore, TCA's have anticholinergic

effects and a high potential for drug interaction. TCA's also have significant anti-arrhythmic activity and can be classified as type IA anti-arrhythmic agents,[83–85] but also show arrhythmogenic potential.[86,87]

In contrast, selective serotonine reuptake inhibitors (SSRI) have only minimal cardiac side effects: the only effect of citalopram on ECG findings was a small reduction in heart rate (less or equal to 8 beats per minute). There were no significant effects on PQ, QRS, or QTc intervals, indicating that citalopram has no effect on cardiac conduction and repolarization during short- or long-term treatment.[88]

In a study (n=81) comparing paroxetine (aSSRI) and nortriptyline (a TCA) both treatments were similarly effective in reducing depressive symptoms, but paroxetine was better tolerated than nortriptyline and less likely to produce cardiovascular side effects.[89] In patients with recent myocardial infarction or unstable angina and without other life-threatening medical conditions sertraline has been shown to be a safe and effective treatment for recurrent depression.[90]

Another study with paroxetine demonstrated that reduced panic attacks were paralleled by increased parasympathetic activity but preserved baroreflex response. The authors concluded that potential benefits of selective serotonin reuptake inhibitors in decreasing cardiac mortality might be achieved by the increase of heart rate variability.[91] In depressed survivors of acute myocardial infarction sertraline facilitated the rate of recovery of heart rate variability, a recognized predictor of clinical outcome.[92]

To assess the risk of myocardial infarction, 2247 patients who received at least one prescription for an antidepressant were compared with 52750 subjects who did not. Patients were compared with respect to antidepressant treatments they received: TCA's, SSRI's, and others. Over a follow-up of 4.5 years, antidepressant users had a more than twofold risk to suffer a myocardial infarction (relative risk 2.2 (95% CI 1.3 to 3.7)) when compared with nonusers. Patients using TCA's and SSRI's had relative risks of 2.2 (95% CI 1.2 to 3.8) and 0.8 (95% CI 0.2 to 3.5), respectively, suggesting an association between use of TCA's and increased risk to suffer myocardial infarction. In SSRI's, there was no such correlation.[93] However, in another study, SSRI exposure did not substantially decrease the risk of developing first-time acute myocardial infarction in patients free of other factors predisposing to CAD.[94]

Two large prospective trials are currently running and should provide more insight into the interaction of depression, CAD, treatment and prognosis.

The Myocardial Infarction and Depression-Intervention Trial (MIND-IT) will show in 2140 patients admitted for myocardial infarction, whether antidepressant treatment of post-myocardial infarction depression, preferably with mirtazapine, can improve cardiac prognosis.[95] In this regard, the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART Study) has not only provided safety data but also shown a trend to a better outcome in post-myocardial infarction patients who were randomized to treatment with sertraline compared with placebo.[90]

In summary, since quality of life in CAD patients with depression is decreased, screening for psychosocial risk factors and antidepressant therapy may be indicated, although to date there is only limited data from randomized trials whether this treatment effectively reduces morbidity and mortality. Even if survival is not improved by antidepressive therapy, more clinical trials are needed to define the optimal management of patients with CAD and depression.[96,97]

Herbal medication

Hypericum perforatum (St. John's wort) has become a popular alternative treatment for depression and several randomized clinical trials have been published; however with conflicting results.[98–102] It is noteworthy that several drug interactions of cardioactive drugs with St. John's wort were recently published.[103,104] These interactions are probably due to the induction of cytochrome P450 isoenzymes CYP3A4, CYP2C9, CYP1A2 and the transport protein P-glycoprotein by constituent(s) in St. John's wort. The degree of induction is unpredictable due to factors such as the variable quality and quantity of constituent(s) in St. John's wort preparations. In addition, possible pharmacodynamic interactions with SSRI's and serotonin (5-HT(1d)) receptor-agonists such as triptans used to treat migraine were identified. These interactions are associated with an increased risk of adverse reactions.[105] St John's wort also can endanger the success of organ transplantations.[106,107] In summary, the growing use of herbal remedies has far exceeded the available information on their benefits, adverse effects and drug interactions.[108,109]

Conclusions and implications

Coronary artery disease as well as depression are both highly prevalent diseases. Both of them cause a significant decrease in quality of life for the patient and impose a significant economic burden on society. The evidence is growing that depression per se is an independent risk factor to suffer a cardiac event. This has been shown in patients with as well as without known CAD. There are several behavioural and pathophysiologic factors that seem to link depression with development of CAD and with a worse outcome in patients with established diagnosis of CAD. Treatment of depression has been shown to improve quality of life of patients. There are also preliminary results suggesting a trend to better cardiovascular prognosis with antidepressive treatment in CAD patients. One may hypothesize that patients treated for their depression might better adhere to risk factor modifications, prescribed medications and rehabilitation programmes. Patients with known CAD and evidence of depression should therefore be evaluated for antidepressive therapy such as cognitive behavioural therapy, complex cardiac rehabilitation programmes, and pharmacologic treatment. Regarding pharmacologic treatment, SSRI's may be preferred for their good tolerability and absence of significant cardiovascular side effects. Furthermore, one should be aware of the

increasing use of herbal medications such as Saint John's wort which may cause severe and possibly dangerous drug interactions with cardioactive drugs.

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