Homocysteine level and depression in patients with ischaemic heart disease

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Background
High levels of homocysteine are associated with vascular disease, changes in the levels of monoamine neurotransmitters and depression. A plausible hypothesis for these associations is that high homocysteine levels are implicated in vascular disease and neurotransmitter deficiency, which are in turn linked to depression.

Aim
To investigate the association between elevated homocysteine levels and depressive symptoms in patients with ischaemic heart disease (IHD).

Participants and methods
Eighty patients with a confirmed diagnosis of IHD were consecutively selected in a cross-sectional study from the inpatient and outpatient cardiology department of Kasr-Al-Ainy hospital. All IHD patients were diagnosed according to the criteria of the American College of Cardiology. Depression was evaluated using the Present State Examination-10 Short English–Arabic Version and the Beck Depressive Inventory. The serum level of homocysteine was determined using the chemiluminescent technique.

Results
Thirty-six ischaemic heart patients (45%) had depressive disorders. Depressed patients were older and had a longer duration of the IHD. The level of homocysteine was higher in depressed patients ($P=0.098$). Positive correlations were found between age and the serum level of homocysteine ($P=0.028$) but no correlations were found between the serum level of homocysteine and the severity of depression. Sleep disturbances correlated significantly with homocysteine levels irrespective of age.

Conclusion
Depressive symptoms are common in IHD patients, especially patients with prolonged duration of the disease. They are more apparent in IHD patients at times of emergency and intervention. In IHD patients, the serum level of homocysteine is associated with the occurrence of vegetative depressive symptoms.

Keywords:
depressive symptoms, homocysteine, ischaemic heart disease

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Introduction

Homocysteine is a sulphur-containing amino acid that occurs naturally in all humans. Increased total homocysteine has been associated with an increased risk of several diseases in the general population (Husemoen *et al*., 2009).

Recent epidemiological studies have suggested that hyperhomocysteinaemia is associated with an increased risk of vascular disease (Guilland *et al*., 2003). Homocysteinaemia is a major risk factor in the pathogenesis of coronary heart diseases and a strong predictor of mortality in this group (Kumar and Clark, 2005).

In addition, high levels of homocysteine are associated with cerebrovascular disease, monoamine neurotransmitters and depression of mood. A plausible hypothesis for these associations is that genetic and environmental factors elevate homocysteine levels, which cause vascular disease and neurotransmitter alterations, which in turn cause depression (Folstein *et al*., 2007).

Homocysteine is directly toxic to neurons and blood vessels and can induce DNA strand breakage, oxidative stress and apoptosis. The methionine–homocysteine metabolic pathway intermediaries are *S*-adenosylmethionine (SAMe) and *S*-adenosylhomocysteine (SAH). The pathway produces methyl groups required for the synthesis of catecholamines and DNA. This is accomplished by remethylating homocysteine – using B_{12} and folate as cofactors – back to methionine. Homocysteine is cleared by transulphuration to cysteine and glutathione, an important antioxidant. Transulphuration requires vitamins B_6 and B_{12} (Guilland *et al*., 2003).

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Hyperhomocysteinaemia, vitamin B_{12} deficiency and to a lesser extent folate deficiency have been linked to depressive disorders (Tiemeier *et al.*, 2002). Higher concentrations of homocysteine increase the risk of depression and lowering homocysteine by 0.19 mg/l could reduce the odds of depression by about 20% (Almeida *et al.*, 2008). If a depressed mood is a symptom of disease, confirmation of the aetiology would lead to prevention and confirmation of pathogenesis would lead to a cure (Folstein *et al.*, 2007).

We aimed to detect the relation between homocysteine level and depressive symptoms in patients with ischaemic heart disease.

Participants and methods

This study included a convenience sample of 80 adult patients of both sexes with a confirmed diagnosis of ischaemic heart disease. Informed consent was obtained from the patients participating in the study. They represent consecutive referrals of patients of the cardiology department of Kasr El-Ainy hospitals (inpatient and outpatient) fulfilling the criteria for inclusion in the study. The patients were diagnosed by a professor of cardiology according to the American College of Cardiology (2000) practice guidelines. We excluded patients with a past history of psychiatric disorders that developed before cardiac diseases, substance abuse, patients with chronic systemic diseases (e.g. rheumatoid arthritis, systemic lupus erythematosus), patients on other medications for chronic systemic diseases (e.g. corticosteroids, immunosuppressive drugs), patients receiving vitamin B_{12}, folic acid and anticonvulsants that affect the level of homocysteine and patients with congenital heart diseases or mental retardation.

Men constituted 52.5% of the sample ($N = 42$) and women constituted 47.5% ($N = 38$). The majority (93.8%, $N = 75$) of the patients were married. The mean age was 54.2 years, SD = 10.8 (range: 24–82 years). The duration of the IHD ranged from 1 month to 31 years, with a median of 2 years (25th percentile = 4 months, 75th percentile = 6.7 years).

Tools

(1) Semistructural interview: A specially designed semi structural interview derived from the Kasr El-Ainy psychiatric sheet was used to obtain demographic data, personal data, past history and family history.

(2) Present State Examination depression sections PSE-10 (Short English–Arabic Version; Huxley *et al.*, 1989) (Arabic version, Hamdi *et al.*, 2007): The Short Arabic version of the PSE-10 (Hamdi *et al.*, 2007) has been developed to be more suitable for service delivery and screening purposes. The abridged form of the Arabic version of the PSE-10 was based on the Short English form of the PSE-10 that was translated and expanded by further questions from the long Arabic version (Hamdi *et al.*, 1995), back translated and tested for reliability (Sabry, 2009). We used this test to diagnose depressive disorders and verify the depressive symptoms. We applied the PSE section 5: thinking/concentration/energy/interest. Section 6: depression and section 7: bodily functions: appetite/sleep/libido. The PSE is designed to allow comparison of each respondent's experience and behaviour against the examiner's glossary-defined concepts by a process of controlled clinical 'cross-examination'. The resulting output is in the form of single symptom ratings. This is followed by clinical decision making of the disorders within a section. If the decision of a probable or a definite syndrome is considered, we can use additional questions from Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) to confirm the diagnosis.

(3) Beck Depression Inventory (BDI-II) (Beck *et al.*, 1996) (Arabic version, Abdel-Fattah, 2000): It is a self-report scale designed to assess DSM-IV-defined symptoms of depression such as sadness, guilt, loss of interest, social withdrawal, change in appetite or sleep, suicidal ideation and other behavioural manifestations of depression over the previous 2 weeks. The inventory is composed of 21 groups of statements on a four-point scale, with the participant selecting the one that best matches his or her current state. Each statement group corresponds to a specific behavioural manifestation. The score range varies from 0 to 63, where higher scores indicate greater severity of depression. Scores in the range of (0–13) indicate no or minimal depression, (14–19) mild depression, (20–28) moderate depression and (29–63) severe depression.

(4) Laboratory assessment: Blood samples were collected on an EDTA tube then stored on ice until centrifugation to avoid falsely high values resulting from homocysteine leaching out from erythrocytes. After separation, Plasma samples were stored at -70°C until analysis (a condition under which plasma homocysteine is known to be stable for a long period of time) (Stabler *et al.*, 2004). Plasma Hcy levels were determined using Enzyme Chemiluminescence Immulite 1000 (Siemens Medical Solution Diagnostics, Los Angeles, USA). According to the reagent package insert, normal total plasma homocysteine concentrations range from 5 to 15 μmol/l in the fasting state (Ueland *et al.*, 1993).

Statistical analysis

Data were analysed using the Statistical Package for Social Sciences, version 15 for Microsoft Windows (SPSS Inc., Chicago, IL, USA). Data were presented using descriptive statistics of frequencies and percentages for qualitative variables and a median, mean and SD for quantitative variables. Qualitative variables were compared using the χ^2-test. Quantitative variables were compared using the Student *t*-test, Pearson and Spearman correlations. Stepwise linear regression analysis was used to predict a dependent variable using a set of predictor variables. Each variable was examined at each step of an equation for entry or removal. Statistical significance was considered at a P value less than 0.05.

Results

The patients were divided into three groups on the basis of the homocysteine serum levels. The most frequent (60%, $N = 48$) were patients with a normal (<15 μmol/l) homocysteine level, followed by those with a moderately elevated homocysteine level, 36.25% ($N = 29$), and then those with an elevated homocysteine level 3.75% ($N = 3$). No patients had highly elevated homocysteine levels.

Using PSE and according to the DSM-IV criteria (APA, 2000), 45% ($N = 36$) of patients with IHD had a confirmed diagnosis, with 21.2% ($N = 17$) of the patients fulfilling the criteria for a major depressive disorder single episode. Fifteen percent ($N = 12$) had dysthymia, 8.8% ($N = 7$) had double depression, 33.8% ($N = 27$) had subclinical symptoms of depression and the remaining 21.2% ($N = 17$) had no mood diagnosis. There was no difference in the mean homocysteine level ($F = 1.52$, $P = 0.22$) between the different types of depressive disorders. The mean homocysteine level for all depressed patients (14.838 ± 9.5) was similar to non/subclinically depressed patients (14.034 ± 5.2, $t = 0.46$, $P = 0.65$).

Using BDI, 77.5% ($N = 62$) of the patients had significant depressive symptoms (Beck score ≥14). Thirty-five percent ($N = 28$) had moderate depressive symptoms, 27.5% ($N = 22$) had severe symptoms and 15% ($N = 12$) had mild depressive symptoms. The remaining 22.5% ($N = 18$) of the patients had no or minimal depressive symptoms. Using the BDI cut-off score of at least 14 to divide patients into depressed and nondepressed groups, the mean homocysteine level for the group of depressed patients was 15.134 μmol/l, whereas the mean homocysteine level for the nondepressive group was 11.856 μmol/l. The difference shows a trend towards statistical significance, $P = 0.098$. Depressed and nondepressed patients differed in age and the duration of ischaemic illness (Table 1). No sex difference was found between depressed and nondepressed patients ($\chi^2 = 3.42$, $P = 0.064$).

Using BDI, significantly more depressed patients were admitted to the ICU. More patients with a high homocysteine level were also admitted to the ICU. Similarly, significantly more depressed patients underwent cardiac catheterization procedures at least once as compared with nondepressed patients (Table 2).

There was a positive correlation between the age and the serum level of homocysteine, but no correlations were found between the serum level of homocysteine and the BDI score (Table 3) or the total PSE-10 score (Table 4).

Patients with bodily function problems (PSE-10 section 7) had a homocysteine level that was above the normal levels (Table 4). Homocysteine level and the duration of ischaemic illness predicted impaired bodily function scores independent of age (Table 5). Sleep and libido problems evaluated by the PSE-10 were the symptoms that were correlated with a high homocysteine level the most (Table 4).

Discussion

Heart disease and depression are commonly comorbid and considered to have a bidirectional relationship that is associated with substantial and broadly equivalent physical functional impairment (Surtees *et al.*, 2008). In our study, using BDI, 77.5% of our IHD patients showed depressive symptoms (mild, 15%; moderate, 35% and severe, 27.5%). Using the PSE for assessment and the DSM-IV for diagnosis, the rates of depressive disorders were considerably less (45% overall).

Table 1 Relation of depression as evaluated by Beck Depression Inventory to age, duration of ischaemia and homocysteine level in 80 ischaemic heart disease patients

	Mean (SD)				
	All patients group ($N=80$)	Beck depressed patients ($N=62$)	Beck nondepressed patients ($N=18$)	t	P
Age (years)	54.2 (10.8)	55.8 (9.3)	48.5 (13.8)	2.118	**0.046**
Duration of ischaemia (months)	47.8 (62.8)	58.6 (67.3)	13.9 (18.4)	4.542	**0.000**
Homocysteine level (μmol/l)	14.396 (7.395)	15.134 (7.879)	11.856 (4.755)	1.674	**0.098**

Bold numerals represent P is significant.

Table 2 Relation of intensive care unit admission and cardiac catheterization to homocysteine level and depression in 80 ischaemic heart disease patients

	n (%)				
	Homocysteine groups			Beck Depression Inventory	
	Normal ($N=48$)	Moderate ($N=29$)	Intermediate ($N=3$)	Depressed ($N=62$)	Not depressed ($N=18$)
ICU (yes)	15 (31.2%)	15 (51.7%)	3 (100.0%)	31 (50%)	2 (11.1%)
	$\chi^2=7.566$	***P*=0.023**		$\chi^2=8.705$	***P*=0.003**
Catheterization (yes)	16 (33.3%)	11 (37.9%)	1 (33.3%)	27 (43.5%)	1 (5.6%)
	$\chi^2=0.172$	$P=0.918$		$\chi^2=8.851$	***P*=0.003**

Bold numerals represent P is significant.

The depressive states detected by the BDI were higher than those obtained by Thombs *et al.* (2006), who found the prevalence of significant depressive symptoms on the basis of a BDI score of at least 10 to be 31.1% (CI 29.2–33.0%; $N = 2273$, six studies) in patients with acute myocardial infarction. Frasure-Smith *et al.* (1995), in a study of 887 patients who completed the BDI and the Perceived Social Support Scale at about 7 days after myocardial infarction, found that almost 32% had BDIs of at least 10, indicating mild to moderate depression. Follow-up interviews were conducted with 89% of survivors. There were 39 deaths (35 cardiac). Elevated BDI scores were related to cardiac mortality ($P = 0.0006$). Lespérance *et al.* (2000) assessed depression in 430 patients with unstable angina who did not require a coronary artery bypass surgery before discharge from hospital. Depression was assessed using the 21-item self-report BDI and was defined as a score of 10 or higher. The BDI identified depression in 41.4% of patients. Depressed patients were more likely to experience cardiac death or nonfatal myocardial infarction than other patients.

Table 3 Correlation of serum homocysteine level with age, duration of myocardial ischaemia and the Beck Depression Inventory score in groups of patients with ischaemic heart disease

	Age	Duration of ischaemia	BDI score
Homocysteine level (μmol/l)			
Depressed group, $N=62$			
r^a	0.198	0.127	0.014
P	0.122	0.326	0.912
All patients, $N=80$			
r^a	0.245	0.178	0.157
P	0.028	0.114	0.165

Bold numerals represent P is significant.
BDI, Beck Depression Inventory.
[a]Pearson's correlation.

Table 4 Correlations of homocysteine groups (normal, moderate, intermediate) with Present State Examination-10 section scores and symptoms of section 7

	R^a	P
Total of PSE sections 5, 6 and 7	0.161	0.160
1. PSE section 5 Thinking/concentration/energy/interest	0.067	0.556
2. PSE section 6 Depression	0.076	0.503
3. PSE section 7 Bodily functions: appetite/sleep/libido	0.287	**0.010**
Appetite/weight loss	0.086	0.449
Delayed sleep	0.282	**0.011**
Middle insomnia	0.258	**0.021**
Nightmares	0.257	**0.022**
Early waking	0.215	0.056
Poor quality sleep	0.269	**0.016**
Loss of libido	0.279	**0.012**
Loss of libido associated with depression	−0.072	0.523
Intercourse unpleasant	0.362	**0.001**
Premenstrual exacerbation	−0.030	0.855

Bold numerals represent P is significant.
PSE, Present State Examination.
[a]Spearman's rho.

There are probably multiple genetic and environmental causes of depression. The difference in the psychosocial causes as well as the stressors may have affected our high percentage of depression. Overall, 41.2% of our patients were admitted to the ICU at least once and 35% underwent catheterization. Our results show that those two factors were more associated with depression. The chronicity of the disease may have also accounted for the difference in the results. Fifty percent of our patients had a duration of more than 2 years and 25% had a duration of more than 6 years. Our results show that our patients with IHD who were depressed had a significantly longer duration of the ischaemic heart disease. Only 30% of our sample, however, was diagnosed with major or double depression, a finding that is similar to the findings of previous studies.

There is strong published evidence for the association between homocysteine level and depression, vascular disease and neurotransmitter abnormalities (Folstein *et al.*, 2007).

Our result showed that 40% of our IHD patients had an elevated homocysteine level [29 (36.25%) had a moderate and three (3.75%) had an intermediate homocysteine level]. Patients with elevated homocysteine were admitted to the ICU more than patients with normal homocysteine level, indicating the severity of their cardiac disease. This is supported by the results of Humphrey *et al.* (2008), who reported that each increase of 5 μmol/l in the homocysteine level increases the risk of coronary heart disease events by ~20%, independent of traditional coronary heart disease risk factors. Support for the notion that homocysteine is a cause of vascular disease comes from studies indicating that increasing intake of dietary folate, which effectively reduces homocysteine levels, lowers the risk of ischaemic stroke in men. The results of a recent meta-analysis of prospective studies suggest that lowering the serum homocysteine level by 25% (about 3 μmol/l) (achievable by increasing the intake of folic acid) decreases the risk for ischaemic heart disease. The reduction of levels reduces the risk of heart disease by 11% and that of stroke by 19% (Wolters *et al.*, 2004). Another meta-analysis of 72 studies concluded that 'lowering homocysteine concentrations by 3 μmol/l from current levels would reduce the risk of ischaemic heart disease by 16%, deep vein thrombosis by 5%, and stroke by 24%' (Wald *et al.*, 2002).

Table 5 Stepwise regression analysis of variables predicting Present State Examination scores

Dependant variable	Variables in the equation[a]	β	t	Significant T	Adjusted R^2	F	Significant F
PSE section 7 score	Duration of ischaemia in months	0.329	3.167	0.002	0.173	9.26	0.000
	Homocysteine level (μmol/l)	0.239	2.303	0.024			
Total of PSE sections 5, 6 and 7	Duration of ischaemia in months	0.232	2.079	0.041	0.041	4.484	0.041

[a]Variables entered into the equation: age, duration in months and homocysteine level.

Comparison of the depressive and nondepressive BDI groups in terms of the serum level of homocysteine found the higher homocysteine level in the depressed group approaching significance than in the nondepressed group. This is in agreement with the study measuring the serum level of homocysteine in 924 men aged 46–64 years, which reported that participants with serum total homocysteine concentrations in the highest tertile had a risk of depression that was more than twice that of participants whose serum total homocysteine concentrations were in the lowest tertile (Tolmunen *et al.*, 2004). Bottiglieri (2005) also reported that more than one-third of the depressed participants in a study had high total homocysteine concentrations (cut-off: 11.9 µmol/l). He reported that the patients with more severe depression who require hospitalization had higher concentrations of total homocysteine than outpatients with less severe depression. Our results, however, did not find correlations between the serum level of homocysteine and the severity of depression, which could be because of the small sample size.

The relationship between homocysteine and neurotransmitters is indirectly suggested by studies showing that mood can be modified by alteration of the homocysteine pathway. SAMe, an intermediary in the homocysteine pathway, has been found to function as an antidepressant. Its effects have been shown to be superior to placebo and comparable with standard tricyclic antidepressants (Bottiglieri and Hyland, 1994; Bressa, 1994). Folate, vitamin B_{12} deficiency, hyperhomocysteinaemia and the c677T allele of the methyl-tetrahydro-folate reductase gene, which cause impaired methylation reactions in the central nervous system, have also been associated with depressive disorders (Kim and Becker, 2003). In addition, two randomized trials have suggested supplemental folate as a treatment for depression (Bell *et al.*, 1988; Taylor *et al.*, 2004). The most direct evidence for the association between homocysteine and neurotransmitters is from a study showing that depressed patients with increased total plasma homocysteine levels had significantly lower levels of serum, red cells and cerebrospinal fluid (CSF) folate, as well as lower levels of CSF SAMe. The depressed patients with high total plasma homocysteine levels were also found to have significantly lower mean CSF concentrations of 5-hydroxyindoleacetic acid, homovanillic acid and 3-methoxy-4-hydroxyphenylglycol (Bottiglieri *et al.*, 2000).

Some studies, however, have reported homocysteine not to be related to depression. Penninx *et al.*'s (2000) study included only women and found vitamin B_{12} deficiency to be present in 14.9% of the 478 nondepressed participants, 17.0% of the 100 mildly depressed participants and 27.0% of the 122 severely depressed participants. No association was found between homocysteine and depression or folate and depression. In another study of an ethnically diverse US population sample, ages 15–39 years, participants with any lifetime diagnosis of major depression had serum and red blood cell folate concentrations that were lower than those of participants who had no history of depression. In this young population, serum homocysteine was not found to be associated with diagnoses of lifetime depression (Morris *et al.*, 2003). In their review, Folstein *et al.* (2007) conclude that homocysteine, B_{12}, folate or some combination is related to depression, but age, sex, race and renal function must be specified.

In our study, there were positive correlations between the serum level of homocysteine and the age in IHD patients. In 1160 adults from a Heart Study cohort aged 67–96 years of age, a high homocysteine level (> 14 µmol/l) was present in 29.3% of the patients. Homocysteine levels were found to correlate with age and to correlate inversely with folate and vitamins B_6 and B_{12} (Selhub *et al.*, 1993). Samples of geriatric patients have higher levels of homocysteine than do samples of community dwelling elderly. For example, among patients aged 65 years and older who were admitted into an acute care geriatric ward in Northern Italy, 74.2% of men and 68.9% of women had elevated homocysteine levels. Elevated total plasma homosysteine concentrations were associated with older age, male sex, increasing serum creatinine, a lower Mini-Mental State Examination score and disability (Marengoni *et al.*, 2004).

In our sample, an increased homocysteine level was associated with some sleep insufficiency and nightmares independent of age. The relationship of homocysteine with sleep is not clear. A possible link is through melatonin (MLT). MLT is a hormone that acts as an internal synchronizer for the timing of daily events and plays an important role in circadian rhythms. The final step of MLT synthesis is methylation, with the methyl donor provided by the metabolic pathway involving homocysteine and methionine (Fournier *et al.*, 2002). The levels of plasma homocysteine were found to be increased, whereas the levels of plasma MLT were decreased in diseases characterized by tissue injury because of oxidative stress such as Ulcerative Colitis (Chen *et al.*, 2011). MLT is a strong antioxidant. Its administration in rats together with a methionine-rich diet significantly decreases the homocysteine concentration and the level of oxidative stress and increases NO production (Murawska-Cialowicz *et al.*, 2008). In normal rats, injected at 17.00 h, 7 mg/kg SAH induced a significant increase in paradoxical sleep during the night. In pinealectomized rats, SAH exerted no significant effect on paradoxical sleep amounts (Sarda *et al.*, 1983). Further studies are needed to clarify the effect of homocysteine on sleep, sleep stages and disorders, for example, the relation of homocysteine level and obstructive sleep apnoea is a current field of study, with some studies finding an association between the severity of sleep apnoea and level of homocysteine (Chen *et al.*, 2012).

Implications

(1) Cardiologists should take depression into account in the management of IHD. Current evidence indicates that only approximately half of cardiovascular physicians

report that they treat depression in their patients, and not all patients who are diagnosed with depressed are treated (Feinstein *et al*., 2006). Some physicians are reluctant to treat depression in patients with IHD because they believe that depression after an acute cardiac event is a 'normal' reaction to a stressful life event that will remit when the acute event stabilizes and the individual resumes normal activities. However, in many cases, depression may occur before and continue after an acute cardiac event. (Glassman *et al*., 2006), and in our study, it increased with the prolongation of the cardiac disease condition.

(2) The association between deficiency of vitamins such as folic acid, vitamin B_{12} and B_6, elevated serum homocysteine level and the occurrence of various mental disorders such as dementia, vascular disorders and depression is a promising area where diet can play a role in the prophylaxis and prognosis of those disorders.

Limitations and recommendations

(1) Our study sample had a limited number of participants and as there are many causes of elevated homocysteine levels including genetic predisposition and brain disease and probably many causes of depression in populations of different ages, studies must include a large enough sample to ensure adequate power to demonstrate outcome.

(2) Controlling for age, duration of ischaemia, psychosocial stressors and other physical status such as kidney functions should be included in studies investigating the relation between post-IHD depression and homocysteine level.

(3) Intervention trials are needed to determine whether depression treatment will be enhanced by homocysteine reduction.

(4) Large population-based prospective studies are needed to challenge the idea that elevated homocysteine levels cause vascular disease, which causes depression.

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Conflicts of interest

There are no conflicts of interest.

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