Clin. Cardiol. 29, 170–174 (2006)

Depression and Thyroid Axis Function in Coronary Artery Disease: Impact of Cardiac Impairment and Gender

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Summary

Background: Increased rates of depression are reported in coronary artery disease (CAD). In heart disease, depression increases disability, reduces quality of life, and increases mortality.

Hypothesis: The study was undertaken to examine the relationship between depression and thyroid axis function in patients with CAD.

Methods: In all, 73 patients with CAD, consecutively admitted to a cardiac rehabilitation hospital, were assessed for depression using the Hospital Anxiety and Depression scale (HADS). Blood was drawn for assessment of thyroid axis hormones and the N-amino terminal fragment of the pro-B-type natriuretic peptide (NT-pro BNP).

Results: The patients with CAD with depressive symptoms had a higher prevalence of cardiac failure ($p = 0.04$), higher NT-pro BNP concentrations ($p = 0.02$), and lower free triiodothyronine (T_3) concentrations ($p = 0.04$) than patients with CAD but without depressive symptoms. They also showed a strong trend ($p = 0.058$) toward a higher incidence of the low T_3 syndrome. Higher NT-pro BNP concentrations were related to lower total T_3 concentrations ($r = -0.294$, $p = 0.011$) and to higher reverse T_3 concentrations ($r = 0.353$, $p = 0.002$). In men, higher scores of depression were related to lower total T_3 concentration ($r = -0.289$, $p = 0.034$) and to higher NT-pro BNP concentration ($r = 0.380$, $p = 0.005$).

Conclusion: These findings suggest that symptoms of depression in patients with CAD are associated with changes in thyroid axis function and with cardiac impairment, especially in men.

Key words: depression, coronary artery disease, low T_3 syndrome, cardiac impairment, N-amino terminal fragment of the pro-B-type natriuretic peptide, gender

Introduction

Increased rates of depression are reported in coronary artery disease (CAD).[1] In heart disease, depression increases disability,[2] reduces quality of life,[3] and increases mortality.[4] The mechanisms by which depression interacts with CAD are not fully understood. Moreover, some potentially important factors have only begun to be examined. Dysfunction of the thyroid axis is such a factor.

Thyroid hormones have profound effects on the cardiovascular system[5] and brain.[6] A reduced concentration of serum triiodothyronine (T_3), called the low T_3 syndrome, is the most often reported thyroid function abnormality in serious physical and mental diseases.[7] Serum T_3 concentration declines after myocardial infarction (MI),[8] cardiac surgery,[9] and in congestive heart failure,[10] and is a strong predictor of early death.[11, 12] It is related to decreased functional capacity of the heart[13] and to increased concentration of the B-type natriuretic peptide (BNP),[14] a cardiac neurohormone secreted mainly from the ventricles of the heart in response to cardiac dysfunction.[15]

Relationships between thyroid function and mental function abound,[6] and even subclinical hypothyroidism is considered as a risk factor for depression.[16] The low T_3 syndrome is reported to occur in up to 21% of depressed patients.[17]

The primary goal of the present study was to examine relationships between depression and thyroid axis function in patients with CAD. The secondary goals were to examine the po-

The study was supported in part by grants RO1-MH051246 and GCRC RR00046.

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Received: November 18, 2005
Accepted with revision: January 5, 2006

tential role of gender and functional cardiac capacity, assessed by the N-amino terminal fragment of the prohormone BNP (NT-pro BNP) concentration, in this association.

Methods

Patients

In all, 106 patients with CAD consecutively admitted to the cardiac rehabilitation hospital at the Institute of Psychophysiology and Rehabilitation of the Kaunas University of Medicine in Palanga, Lithuania, were enrolled in the study. Seventeen patients treated with psychiatric medication, 2 patients treated with thyroid medications, 6 patients with elevated titers of thyroid peroxidase antibodies (> 60 U/ml), and 8 patients with recent coronary artery bypass surgery were excluded from the analysis. Seventy-three patients, 54 men and 19 women, were admitted to the study and completed it. Fifty-four patients were recovering from an acute MI and 19 patients were recovering from unstable angina; 46 patients (63%) had a history of heart failure. Cardiac functional capacity according to the criteria of the New York Heart Association (NYHA) was assessed in all patients. Based on these criteria, 7 patients were assigned to functional class I, 59 patients to class II, 7 patients to class III, and no patients to class IV. Clinical details are provided in Table I. The protocol was approved by the Regional Committee of Biomedical Ethics, Kaunas University of Medicine, and written informed consent was obtained from all study patients.

Evaluations

All assessments were performed on the second and third day after admission to the rehabilitation hospital. Demographic data and medical histories were obtained during an initial interview and from medical documents.

All patients were assessed for depression and anxiety symptoms using the Hospital Anxiety and Depression Scale (HADS).[18] The HADS comprises 14 items scored from 0 to 3 to which patients respond based on their experience over the past week. Seven items comprise a subscale for depression with a score range from 0 to 21; seven other items comprise a subscale for anxiety. The HADS is a self-rating scale for non-psychiatric clinical settings and is frequently used in cardiac clinics.[19] A cut-off value of > 10 defines patients with severe symptoms of depression or anxiety.

The 36-item Short Form Medical Outcome Questionnaire (SF-36)[20] was used to evaluate the general health status of the patients. The SF-36 includes eight multi-item scales that assess eight health concepts: physical functioning, social functioning, role limitations due to physical problems, role limitations due to emotional problems, mental health, energy/vitality, pain, and general health perception, with higher scores (range from 0–100) reflecting better perceived health.

Blood for hormone assessment was drawn about 8 A.M. before breakfast and within 10 min after patients awoke.

TABLE I Demographic and clinical characteristics of 73 patients with coronary artery disease

	Men n = 54	Women n = 19
	Mean ± SD; n (%)	
Age (years)	56 ± 11	57 ± 8
Cardiac diagnosis		
Myocardial infarction	43 (80)	11 (58)
Unstable angina	11 (20)	8 (42)
Medical history		
Hypertension	33 (61)	15 (79)
Heart failure	34 (63)	12 (63)
Diabetes	2 (4)	3 (16)
NYHA functional capacity class		
I	6 (11)	1 (5)
II	43 (80)	16 (84)
III	5 (9)	2 (11)
Medication use		
Angiotensin-converting enzyme inhibitors	45 (83)	16 (84)
Amiodarone	3 (6)	3 (16)
Beta blockers	46 (85)	14 (74)
Calcium-channel antagonists	7 (13)	5 (26)
Diuretics	5 (9)	4 (21)
Nitrates	40 (74)	11 (58)
Hospital anxiety and depression scale		
Depression	4.1 ± 3.0 [a]	6.3 ± 4.3 [a]
Anxiety	5.7 ± 3.6 [b]	10.0 ± 4.5 [b]
36-Item Short Form Medical Outcome Questionnaire		
Physical functioning	56 ± 22	49 ± 25
Social functioning	60 ± 27	45 ± 30
Role limitations due to physical problems	38 ± 41	33 ± 39
Role limitations due to emotional problems	61 ± 43	44 ± 41
Mental health	66 ± 18 [a]	55 ± 23 [a]
Energy/vitality	59 ± 18 [a]	49 ± 18 [a]
Pain	47 ± 25	39 ± 31
General health perception	45 ± 14 [a]	36 ± 15 [a]
Thyroid axis hormones		
Free T_3 (pg/ml)	3.5 ± 1.0	3.1 ± 0.5
Free T_4 (ng/dl)	1.1 ± 0.2	1.0 ± 0.2
Total T_3 (ng/dl)	110 ± 24	119 ± 27
Total T_4 (μg/dl)	8.2 ± 1.6	8.7 ± 2.2
Reverse T_3 (ng/dl)	27 ± 13	26 ± 13
TSH (mU/l)	2.1 ± 1.4 [a]	2.8 ± 1.3 [a]
Low T_3 syndrome (T_3 < 100 ng/dl)	22 (41)	6 (32)
NT-pro B-type natriuretic peptide (fmol/ml)	590 ± 229	563 ± 169

[a] $p < 0.05$.
[b] $p < 0.001$.
T_3 and rT_3 conversion factor to mmol/l, 0.0154.
T_4 conversion factor to mmol/l, 12.9.
Abbreviations: SD = standard deviation, NYHA = New York Heart Association, T_3 = triiodothyronine, T_4 = thyroxine, TSH = thyroid-stimulating hormone.

Blood was centrifuged and serum was deeply frozen and later shipped to the University of North Carolina at Chapel Hill-General Clinical Research Center Core Laboratory, where the samples from all patients for each parameter were analyzed in a single batch. Serum concentrations of free T_3, free T_4, total T_3, total T_4, reverse T_3, thyroid-stimulating hormone (TSH), and autoantibodies to thyroid peroxidase (anti-TPO) were measured by radioimmunoassay, and the concentration of the NT-pro BNP was measured by enzyme immunoassay. Normal values for free T_3 are from 3.0 to 5.2 pg/ml; for free T_4, from 0.7 to 1.7 ng/dl; for total T_3, from 100 to 190 ng/dl; for total T_4, from 5 to 12 µg/dl; for reverse T_3, from 9 to 35 ng/dl; for TSH, from 0.5 to 3.7 mU/l; for anti-TPO, < 60 U/ml; and for NT-pro BNP, < 350 fmol/ml. Patients with a total T_3 concentration < 100 ng/dl were considered to have the low T_3 syndrome.

Statistical Analysis

Statistical evaluation was preceded by one-sample Kalmogorov-Smirnov test to ascertain normality of the distribution of the continuous variables. Unpaired *t*-test (2-tailed) or the Mann-Whitney U test (2-tailed) was used when appropriate for comparison of continuous data. Pearson's chi-square test was used to compare categorical data. Data are expressed as mean ± standard deviation or as number and percent. A probability value (p) of < 0.05 was considered as statistically significant. Pearson's test of correlations (r) was used to evaluate relationships. All tests were performed using software from Statistical Package for Social Sciences 12.0 for Windows (SPSS, Inc., Chicago, Ill., USA).

Results

Assessment of the 73 patients with CAD for depressive symptoms using the HADS revealed 7 patients (10%) with symptoms of depression (HADS depression score > 10) and 16 patients (22%) with symptoms of anxiety (HADS anxiety score > 10). The low T_3 syndrome was found in 28 (38%) patients. Functional decline was relatively mild, as it was limited to NYHA functional class II in the majority of patients (81%).

In this study, men comprised about 75% of the total sample. Psychological state and thyroid axis hormone concentrations showed significant gender differences (Table I). Women had higher scores on the subscales for depression ($p = 0.018$) and anxiety ($p = 0.001$) of the HADS. On the SF-36 questionnaire, women compared with men had lower scores on subscales pertaining to psychosocial functioning and general health perception, but not on subscales pertaining to physical functioning. Compared with men, women also had significantly higher TSH concentrations ($p = 0.036$).

Table II sorts all 73 patients according to the presence or absence of symptoms of depression and anxiety. Patients with depressive symptoms had higher NT-pro BNP concentrations ($p = 0.02$), higher prevalence of histories of cardiac failure ($p = 0.04$), and lower free T_3 concentrations ($p = 0.04$) than patients without depression. Patients with symptoms of depression also showed a strong trend ($p = 0.058$) toward a higher incidence of low T_3 syndrome.

Patients with depressive symptoms scored lower on those subscales of the SF-36 Medical Outcomes Questionnaire that related to psychological health with no difference on general health perception. Patients with compared with those without anxiety symptoms showed worse scores on the SF-36 questionnaire related to psychological health as well as to general health perception. Among patients with anxiety symptoms, the proportion of women was higher ($p = 0.001$) and the proportion of patients receiving treatment with beta blockers was lower ($p = 0.005$) compared with patients without anxiety symptoms. Amiodarone use was unrelated to the incidence of anxiety and depressive symptoms.

We found significant correlations between NT-pro BNP concentrations and thyroid hormone concentrations in the total sample of patients. Higher NT-pro BNP concentrations were related to lower total T_3 concentrations ($r = -0.294$, $p = 0.011$), to higher reverse T_3 concentrations ($r = 0.353$, $p = 0.002$), and to higher free T_4 concentrations ($r = 0.272$, $p = 0.020$). There were no significant correlations between depression and hormonal variables in the total sample of patients. However, in men, higher scores of depression were related to lower total T_3 concentration ($r = -0.289$, $p = 0.034$) and to higher NT-pro BNP concentration ($r = 0.380$, $p = 0.005$).

Discussion

In this study, we found that symptoms of depression but not symptoms of anxiety are related to alterations in thyroid hormone variables and to cardiac impairment in patients with CAD: depressed patients with CAD had lower free T_3 concentrations and higher NT-pro BNP concentrations; they also demonstrated a higher prevalence of low T_3 syndrome and a higher prevalence of a history of heart failure. The interaction between the thyroid axis and depression in CAD may be direct or indirect. Direct effects of decreased T_3 concentration on depression may be explained by well-established data that the brain is very sensitive to even mild fluctuations in thyroid hormone concentration.[16] On the other hand, it is also possible that CAD and heart failure may activate some other system, such as the inflammatory system,[21] that may be responsible for both depression and low T_3 syndrome. In this model, depression and the low T_3 syndrome would be only markers of a primary mechanism without necessarily any direct interaction.

We also demonstrated a significant relationship between increased NT-pro BNP concentration and suppression of thyroid axis function that defines the low T_3 syndrome—decreased T_3 and increased reverse T_3 concentrations. These data replicate earlier findings, suggesting that even relatively mild cardiac impairment, as it was found in our sample of patients, is related to low T_3 syndrome in patients with CAD with compensated heart failure.[22]

Another important factor that may affect an association between depression and thyroid axis function are medications used by patients with CAD. Amiodarone, an iodine-contain-

TABLE II Scores on two subscales of the Hospital Anxiety and Depression Scale, clinical characteristics, and hormone concentrations in patients with coronary artery disease

	Hospital Anxiety and Depression Scale			
	Depression ≤ 10	Depression > 10	Anxiety ≤ 10	Anxiety >10
Number of patients	66	7	57	16
Age	57 ± 10	60 ± 9	57 ± 11	57 ± 8
Women	16 (24)	3 (43)	9 (16) [c]	10 (62) [c]
Medications				
Amiodarone	5 (8)	1 (14)	3 (5)	3 (19)
Beta blockers	56 (85)	4 (57)	51 (90) [b]	9 (56) [b]
Free T_3 (pg/ml)	3.4 ± 0.9 [a]	2.9 ± 0.5 [a]	3.4 ± 0.9	3.4 ± 0.8
Free T_4 (ng/dl)	1.0 ± 0.2	1.1 ± 0.3	1.0 ± 0.2	1.1 ± 0.3
Total T_3 (ng/dl)	113 ± 25	101 ± 27	110 ± 24	120 ± 29
Total T_4 (µg/dl)	8.3 ± 1.8	8.0 ± 1.4	8.2 ± 1.8	8.7 ± 1.7
Reverse T_3 (ng/dl)	26 ± 11	31 ± 22	26 ± 11	31 ± 18
TSH (mU/l)	2.3 ± 1.4	2.4 ± 1.8	2.2 ± 1.4	2.7 ± 1.3
Low T_3 syndrome	23 (35)	5 (71)	22 (39)	6 (38)
History of heart failure	39 (59) [a]	7 (100) [a]	34 (60)	12 (75)
NT-pro B-type natriuretic peptide (fmol/ml);	564 ± 170 [a]	761 ± 446 [a]	577 ± 179	605 ± 316
36-Item Short Form Medical Outcome Questionnaire				
Physical functioning	55 ± 24	57 ± 10	57 ± 23	45 ± 24
Social functioning	58 ± 29 [a]	31 ± 18 [a]	62 ± 27 [c]	28 ± 21 [c]
Role limitations due to physical problems	39 ± 41	17 ± 30	39 ± 40	27 ± 39
Role limitations due to emotional problems	61 ± 42 [b]	7 ± 15 [b]	63 ± 41 [a]	27 ± 39 [a]
Mental health	65 ± 20 [b]	42 ± 10 [b]	67 ± 17 [c]	41 ± 16 [c]
Energy/vitality	57 ± 19	45 ± 11	60 ± 17 [c]	38 ± 12 [c]
Pain	46 ± 28	33 ± 14	48 ± 26	32 ± 30
General health perception	42 ± 15	41 ± 10	44 ± 14 [a]	34 ± 15 [a]

[a] $p < 0.05$.
[b] $p < 0.005$.
[c] $p < 0.001$.
Abbreviation: NT-pro = N-amino terminal fragment of prohormone. Other abbreviations as in Table I.

ing drug often used to treat cardiac arrhythmia, exerts complicated effects on thyroid function.[23] In this study, amiodarone was used in about equal proportions of patients with and without symptoms of depression and thus was unlikely to have accounted for the mood-related findings. Other medications that may affect mood symptoms and thyroid function are beta blockers.[24] In this study, the proportion of patients receiving beta blockers was about equal in those with and without symptoms of depression; however, this proportion was significantly higher among patients without than among those with symptoms of anxiety. These data suggest that use of beta blockers had no impact on symptoms of depression and may have improved symptoms of anxiety.

The present findings resemble the findings of previous studies regarding gender differences, including the data that men are more likely than women to be referred to cardiac rehabilitation programs and are more likely to attend such programs when referred.[25] Like other investigators, we found a higher prevalence of depression and anxiety in women with CAD than in men.[26]

It is well known that in the general population women more often than men suffer from thyroid diseases.[27] Consistent with this, when we used elevated TSH as the criterion for thyroid dysfunction, we found a preponderance of women with higher TSH concentration, in spite of the exclusion of patients (mostly women) who received thyroid medications or had thyroid disease. Thus, the presence of thyroid disease may contribute to the gender differences in correlations between scores of depression and concentrations of T_3 found in our male study patients, but not in female study patients. On the other hand, this gender difference may arise from the small number of women typically seen in studies like ours[28] and may reflect a chance finding with such a small sample size.

Conclusion

Our study is constrained by certain limitations. Our sample of patients with CAD was not free of potentially confounding variables, such as treatment with amiodarone and beta block-

ers. Statistical power was weakened by the underrepresentation of women. The lack of patients with severe cardiac impairment precluded the exploration of the significance of this variable. The uses of structured diagnostic clinical interviews would have enhanced the evaluation of mood disorders. Thus, the results of this study, suggesting that thyroid axis disturbance may mediate the link between depression and poor function in patients with CAD, should be considered as preliminary. Despite the limitations cited above, our study does strongly suggest certain relationships not addressed in previous studies. The low T_3 syndrome, frequently found in heart disease, is associated with depression in patients with CAD. This relationship is more evident in men, perhaps because more men were studied.

Acknowledgment

The authors are grateful to Dr. Robert D. Utiger for his comments and suggestions preparing the manuscript.

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