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Non-cardiac Chest Pain and Anxiety: A Possible Link to Vitamin D and Calcium

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Abstract
This study was performed to check the hypothesis that low serum vitamin D and reduced calcium intake may contribute to the comorbidity of psychological symptoms (anxiety and depression) and non-cardiac chest pain (NCCP). The design was a case–control study that involved 40 subjects with NCCP and 40 age and gender-matched healthy controls. Serum vitamin D was assessed using electrochemiluminescence immunoassay; anxiety and depression symptoms were assessed using Hospital Anxiety and Depression Scale, and dietary calcium intake was assessed by self-reporting. Subjects with NCCP had higher anxiety and depression scores and lower vitamin D and dietary calcium intake compared to healthy controls ($p < .05$). NCCP was associated with anxiety score (odds ratio = 1.40, $p < .01$). Prevalence of abnormal anxiety score was much higher in subjects with NCCP (47.5%) compared to healthy controls (7.5%). Anxiety score was inversely correlated with vitamin D level and dietary calcium intake ($p < .01$). Anxiety score was inversely associated with vitamin D level ($R^2 = .32$, $p < .05$). In conclusion, development of NCCP can be predicted from increased anxiety score which in turn can be predicted from low vitamin D levels. This suggests physicians to consider anxiety and vitamin D deficiency as possible causes for NCCP.

Keywords Chest pain · Anxiety · Vitamin D · Calcium

Introduction

Chest pain is a serious warning symptom of coronary artery disease and is considered as a leading cause of emergency department visits all over the world (Ruigomez, Rodriguez, Wallander, Johansson, & Jones, 2006). In fact, around 60% of chest pain presentations are of non-cardiac origin (Kachintorn, 2005). These are diagnosed by exclusion of any cardiac cause of chest pain after a comprehensive evaluation that is routinely performed to all patients who present with recurrent or persistent chest pain (Kachintorn, 2005). Because it is indistinguishable from ischemic chest pain and it receives similar medical investigations, non-cardiac chest pain (NCCP) is associated with increased utilization of health resources and increased medical cost (Mourad, Alwin, Strömberg, & Jaarsma, 2013).

Non-cardiac chest pain may result from several etiologies including gastrointestinal, pulmonary, musculoskeletal, and psychological disorders (Fass & Achem, 2011). Although musculoskeletal and psychological disorders are common, they are frequently overlooked as a possible cause of NCCP (Jensen, 2001). Anxiety, depression, and musculoskeletal pain (MSP) have been long recognized to co-exist, exacerbate each other, share biological pathways and neurotransmitters, and respond to similar treatments (Lynch, 2001; Poleshuck et al., 2009). There is a growing body of evidence suggesting that treatment of stress and anxiety should be considered in the treatment of MSP and thus NCCP (Poleshuck et al., 2009; Schey, Villarreal, & Fass, 2007).

Anxiety and depression could be linked to certain nutrients deficiencies including vitamin D and calcium

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(Armstrong et al., 2007; Wintermeyer et al., 2016). Vitamin D has an important role in the central nervous system (CNS) as its receptors are widely distributed in the human brain (Eyles, Smith, Kinobe, Hewison, & McGrath, 2005). So, low vitamin D concentrations were found to be associated with depression in young adults (Ganji, Milone, Cody, McCarty, & Wang, 2010) and associated with anxiety and depression in subjects with fibromyalgia (Armstrong et al., 2007). Similarly, low extracellular calcium could have stimulatory effects on neuromuscular junctions, leading to affective mental disorders including irritability, anxiety, and depression (Foster & Kumar, 2002; Jimerson et al., 1979). Furthermore, dietary calcium intake was reported to be inversely related to the risk of mental diseases (Bae & Kim, 2012) and greater milk and dairy intake was reported to reduce the risk of depression (Miki et al., 2015).

In this study, we hypothesized that low level of vitamin D and reduced daily calcium intake may contribute to the comorbidity of psychological symptoms and NCCP. The aims of this study were (1) to assess the level of vitamin D, dietary calcium intake and anxiety and depression symptoms in subjects with NCCP compared to age- and gender-matched healthy controls and (2) to investigate the association between the vitamin D level and daily calcium intake with psychological symptoms.

Methods

Study Design

This is a case–control observational study that was conducted at King Abdullah University Hospital (KAUH) in Jordan between May 2016 and May 2017 after getting an ethical approval from the Institutional Review Board (IRB). The study involved 40 subjects with NCCP for whom chest pain of cardiac origin was excluded by cardiac catheterization and 40 age and gender matched healthy controls. All participants agreed to participate in the study by signing appropriate consent forms. Controls were recruited from healthy subjects who were visiting KAUH for non-medical purposes. Participants with chronic renal failure, chronic liver disease, those on vitamin D supplementation (during the last 3 months) and who were diagnosed with cardiovascular diseases including heart failure, cardiac arrhythmias, angina pectoris, acute coronary syndrome or myocardial infarction were all excluded from the study.

Data Collection

General information about age, gender, smoking status, previous vitamin D supplementation, history of kidney, liver and cardiovascular diseases and other information were obtained by self-reporting and from patients' medical records. Height (cm) was measured using a metric scale and weight (kg) was measured using a well-calibrated balance after removing heavy clothes and taking the shoes off. Body Mass Index (BMI) was calculated using the formula: BMI = weight (kg)/height (m^2).

Blood Sampling and Vitamin D Determination

Venous blood samples were collected into anticoagulant-free plain test tubes by a well-qualified laboratory technician. Blood samples were then centrifuged at 4000 rpm for 8 min within 1 h of collection using a high-speed centrifuge (centrifuge MR23i, Jouan SA, France) to separate the serum. Serum 25-hydroxyvitamin D concentration was measured by electrochemiluminescence immunoassay using Roche Modular E170 Analyzer (Roche Diagnostics, Basel, Switzerland).

Assessment of Anxiety and Depression

Anxiety and depression symptoms were assessed using the well-validated Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983). This scale was translated from English to Arabic using a standard forward–backward translation method to minimize lingual barriers among participants. Then, it was pilot tested on 30 subjects who were not included in the current study. This scale is a 14-item scale that contained seven items for anxiety assessment and seven items for depression assessment. The score for every item in this scale has the maximum of three points and the total final score is out of 21 points. Scores from 0 to 7 were considered normal, scores from 8 to 10 were considered borderline and scores from 11 to 21 were considered abnormal. The scale was filled by participants themselves after cardiac catheterization, and a well-trained researcher was available to clarify any enquiry about the scale items.

Assessment of Dietary Calcium Intake

Dietary calcium intake was assessed by self-reporting. Participants were asked about their daily frequency and type of dairy products intake (yogurt, milk, cheddar cheese, cream cheese, and labanah). Intake of dairy products was determined on a daily basis as none, single, two, three or more dairy servings per day. A dairy serving was defined as follows: 1 cup (240 mL) of yogurt or milk (~ 300 mg calcium), 2 tablespoons (2 oz) of labanah (100 mg calcium), one ounce piece of cheddar cheese (162 mg calcium), or one ounce of cream cheese (20 mg calcium) (Abdul-Razzak, Obeidat, Al-Farras, & Dauod, 2014).

Statistical Analyses

Data were analyzed using IBM Statistical Analysis Software Package (SPSS) version 20 (Armonk, New York, USA). Qualitative variables were expressed as number (%) while continuous variables were expressed as mean ± standard deviation (SD). Differences between qualitative variables were determined using either Chi-square test or Fisher's Exact test as appropriate. Continuous variables that were not normally distributed were "Ln" transformed prior to analysis. Differences between continuous variables were determined by Student's *t* test. Binary logistic regression analysis was used to detect independent predictors of NCCP. Correlations between HADS-anxiety score and other continuous variables were determined using Spearman's correlation test. Associations between HADS-anxiety score and other correlated continuous variables were determined using multiple linear regression analysis. *p* values were two-sided and considered statistically significant at < .05.

Results

Characteristics of the Study Population

Data were collected from 40 subjects with NCCP and 40 age and gender matched healthy controls. General characteristics of the study population are shown in Table 1. Significant differences between subjects with NCCP and controls (*p* values < .05) were detected in smoking status, HADS-anxiety score, HADS-depression score, Ln (serum 25-hydroxyvitamin D) and Ln (dietary calcium intake). Both subjects with NCCP and healthy controls did not report having diabetes mellitus or any other chronic illness.

Predictors of NCCP

Associations between NCCP and other variables are shown in Table 2. Interestingly, the only detected predictor of NCCP was HADS-anxiety score (odds ratio = 1.40, *p* value < .01). In contrast, there was no significant association between developing NCCP and other variables including age, gender, BMI, smoking, HADS-depression score, dietary calcium intake or serum vitamin D level (*p* values > .05).

Prevalence of Anxiety Among Subjects with NCCP and Controls

47.5%, 20%, and 32.5% of subjects with NCCP were classified as having abnormal, borderline, and normal HADS-anxiety scores, respectively. While, 7.5%, 17.5%, and 75% of controls were classified as having abnormal, borderline, and normal HADS-anxiety scores, respectively.

Correlation Between HADS-Anxiety Score and Other Variables

As shown in Table 3, HADS-anxiety score was significantly and inversely correlated with serum vitamin D level and dietary calcium intake (*p* values < .05). As well, HADS-anxiety score was significantly and positively correlated with HADS-depression score (*p* value < .05) and it had an inverse borderline significant correlation with age (*p* value = .05).

Predictors of Anxiety

Further multiple linear regression analysis was performed to predict HADS-anxiety score from variables that were correlated with it (Table 3). As shown in Table 4, Ln

Table 1 Characteristics of the study sample

	Subjects with NCCP (*n* = 40)	Healthy controls (*n* = 40)	*p* Value*
Gender (male/female)	30/10	30/10	–
Age (years)	43.28 ± 7.91	42.93 ± 8.33	.85
BMI (kg/m^2)	30.25 ± 5.42	28.17 ± 4.48	.08
Smoking			
Smoker	21 (52.5)	11 (27.5)	.04
Non-smoker	19 (47.5)	29 (72.5)	
HADS-anxiety score	10.40 ± 4.30	5.73 ± 3.20	< .01
HADS-depression score	9.50 ± 3.64	6.90 ± 3.13	< .01
Ln (25-hydroxyvitamin D, ng/mL)	2.47 ± 0.56	2.72 ± 0.50	.04
Ln (dietary calcium intake, mg/day)	5.10 ± 1.21	5.78 ± 0.96	< .01

NCCP non-cardiac chest pain, *N* number of participants, *HADS* Hospital Anxiety and Depression Score, *BMI* body mass index, *Ln* natural logarithm

*Statistically significant differences (*p* values < .05) were determined using Chi-square test or Fisher's Exact test for categorical variables and Student's *t* test for continuous variables. Data were expressed as number, mean ± standard deviation or number (%)

Table 2 Predictors of NCCP

Variable	Value	*B* (SE)	Odds ratio	Confidence interval	*p* Value*
Constant		−5.34 (3.82)	–	–	.16
Age (Years)	–	0.06 (0.04)	1.06	0.98–1.15	.15
Gender	Male Female (reference)	−0.51 (0.79)	0.60	0.13–2.83	.60
BMI	–	0.08 (0.06)	1.09	0.96–1.23	.18
Smoking	Smoker Non-smoker (reference)	−0.54 (0.68)	0.58	0.15–2.23	.45
HADS-anxiety score	–	0.30 (0.10)	1.35	1.11–1.64	< .01
HADS-depression score	–	0.08 (0.10)	1.09	0.89–1.32	.41
Ln (dietary calcium intake, mg)	–	−0.28 (0.29)	0.76	0.43–1.33	.34
Ln (25-hydroxyvitamin D, ng/mL)	–	−0.29 (0.62)	0.75	0.22–2.50	.64

B coefficient (intercept), *SE* standard error, *BMI* body mass index, *HADS* hospital anxiety and depression score, *Ln* natural logarithm

*Binary logistic regression (dependent variable: NCCP vs. Controls), $p < .05$ was considered statistically significant

Table 3 Correlation between HADS-anxiety score and other variables

Variables	*r*	*p* Value*
Age	−.43	.05
BMI (kg/m^2)	.07	.57
25-Hydroxyvitamin D (ng/mL)	−.28	.01
Dietary calcium intake (mg)	−.32	< .01
HADS-depression score	.48	< .001

r Spearman's correlation coefficient, *BMI* body mass index, *HADS* Hospital Anxiety and Depression Score

*Spearman correlation test (*p* value < .05 is considered significant)

(25-hydroxyvitamin D) and HADS-depression score were significant predictors of HADS-anxiety score (*p* values < .05). Ln (25-hydroxyvitamin D) was inversely associated with HADS-anxiety score while HADS-depression score was directly associated with HADS-anxiety score.

Discussion

To the best of our knowledge, this is the first study that assessed vitamin D level, dietary calcium intake, and anxiety and depression symptoms in subjects with NCCP compared to healthy controls. Our hypothesis was that low level of vitamin D and reduced daily calcium intake may contribute to the comorbidity of anxiety, depression and NCCP. Interestingly, results of the present study showed that HADS-anxiety and HADS-depression scores were significantly higher in subjects with NCCP compared to healthy controls. In contrast, serum vitamin D level and dietary calcium intake were significantly higher in healthy controls compared to subjects with NCCP. This suggests that symptoms of anxiety and depression, low vitamin D level, and low dietary calcium intake could be implicated in the development of NCCP. So, further investigations were performed to find associations between NCCP and other variables including age, gender, BMI, smoking, anxiety, depression, dietary calcium intake, and vitamin D level. Results showed that NCCP can only be

Table 4 Prediction of HADS-anxiety score

Variable	R^2	ANOVA	Model	*B*	*β*	*p* Value*
HADS-anxiety score	.32	$F = 6.75$, *p* value < .01	Constant	13.41	–	< .01
			Age	−0.09	−0.17	.09
			Gender	−0.06	−0.01	.95
			Ln (dietary calcium intake (mg))	−0.20	−0.05	.63
			Ln (25-hydroxyvitamin D (ng/mL))	−1.74		
			HADS-depression score	0.52	−0.21	.03

R^2 squared coefficient of determination, *B* unstandardized coefficient, *β* standardized coefficient, *F* *F*-statistic, *HADS* Hospital Anxiety and Depression Score, *Ln* normal logarithm

*Multiple linear regression analysis (*p* value < .05 is considered significant)

predicted from HADS-anxiety score as there was a significant association between NCCP and HADS-anxiety score. Therefore, it is expected that subjects with higher anxiety score could be at risk of developing NCCP. Similarly, Smeijers et al. study (2014) demonstrated that NCCP was associated with increased level of anxiety. In addition, Demiryoguran et al. study (2006) showed that around 30% of patients presented to the emergency department with NCCP were suffering from abnormal anxiety scores and they recommended that anxiety disorder should always be considered in patients presenting with NCCP. Even, the prevalence of abnormal anxiety score among patients with NCCP in our study was around 50%, which is higher than that reported by Demiryoguran et al. (2006) taking in consideration that both studies used the same method to assess anxiety. The involvement of anxiety in the development of NCCP is thought to be due to its role in the neuro-behavioral processes that are involved in pain regulation (Smeijers et al., 2014). Anxiety is associated with increased sympathetic neurotransmitters including norepinephrine that is involved in neural mechanisms and acts as a modulator of pain perception (Bremner, Krystal, Southwick, & Charney, 1996; Pertovaara, 2006; Strobel, Hunt, Sullivan, Sun, & Sah, 2014).

Because anxiety could be linked to certain nutrient deficiencies including vitamin D and calcium (Armstrong et al., 2007; Bae & Kim, 2012), we were interested in finding associations between HADS-anxiety score and these nutrients. Our results showed that HADS-anxiety score was inversely correlated with both serum vitamin D level and dietary calcium intake, suggesting that low levels of vitamin D and dietary calcium intake could increase level of anxiety. However, further multiple linear regression analysis including age, gender, vitamin D and dietary calcium intake as independent variables showed that HADS-anxiety score was only associated with vitamin D level. This result was consistent with Bicikova et al. study (2015), which found similar association between serum vitamin D level and anxiety disorders. This association could be explained by the action of vitamin D on its receptors in the brain (Eyles et al., 2005). Previous animal studies showed that mice lacking vitamin D receptors were demonstrating increased anxiety (Kalueff, Lou, Laaksi, & Tuohimaa, 2004). Consequently, it was supposed that any defect in vitamin D level or its binding to its receptors may result in anxiety (Wu et al., 2016).

There is a growing body of evidence demonstrating that vitamin D is neuroprotective, targeting several genes in the brain, including those that have specific relevance to cognitive or behavioral functions such as calcium-binding proteins (calbindin-D28K, parvalbumin, and calretinin), which are involved in intracellular calcium homeostasis (Krishnan et al., 2008; Schwaller, Meyer, & Schiffmann, 2002). Maintaining cellular calcium homeostasis is one of the main roles of vitamin D in the brain. Dysregulation of Ca^{2+} homeostasis can influence neuron excitability, which in turn affects network activity, metabolism, and increases the risk factors for psychiatric diseases (Gleichmann & Mattson, 2011). Similar to vitamin D, calcium plays a significant role in the CNS and may have crucial implications in the etiology of many neuropsychiatric disorders including mood disorders (Balon & Ramesh, 1996; Berridge, 2013; Yarlagadda, Kaushik, & Clayton, 2007). The regulation of calcium in the CNS involves transport mechanisms across blood–brain barrier, Ca^{2+} pumps, Ca^{2+}-binding proteins and others (Mata & Sepulveda, 2005; Yarlagadda et al., 2007). The inverse correlation between anxiety and daily calcium intake in the present study suggests a link between calcium intake and risk of psychological symptoms. Interestingly, subjects with NCCP had significantly low daily calcium intake compared to controls. This finding is in agreement with Abdul-Razzak et al. 2018 study (accepted for publication) in which, anxiety and depression symptoms were inversely associated with vitamin D level and total daily calcium intake in subjects with MSP.

Collectively, the current study tried to find links between the development of NCCP and symptoms of anxiety and depression, dietary calcium intake and serum vitamin D level. Although patients with NCCP had higher HADS-anxiety and HADS-depression scores and lower dietary calcium intake and serum vitamin D levels compared to healthy controls, NCCP was only associated with HADS-anxiety score. Although these findings are reported for the first time, this study has some limitations. Anxiety and depression symptoms were assessed by self-reporting with no diagnosis based on clinical investigations. However, the method used in this study was well validated and approved for clinical research purposes (Zigmond & Snaith, 1983). Dietary calcium was also assessed by self-reporting, which could not be precise enough as an estimate for daily calcium intake. Still, the method used for this estimation was previously validated and used by other researchers (Abdul-Razzak et al., 2014). As well, it is possible that other factors that we did not assess in the current study may contribute to our findings. For instance, we did not assess NCCP that may originate from gastrointestinal or pulmonary causes. In addition, we tried to find a link between vitamin D level and anxiety without investigating the etiology of anxiety, which could be multifactorial. Despite of these limitations, we believe that results of the current study are important and encourage other researchers to do more investigations in this area of research. For example, future experimental and longitudinal studies are required to confirm associations between anxiety, depression, vitamin D status, calcium intake and NCCP. Results from these studies may inform physicians if sufficient vitamin D levels and good calcium intake can reduce anxiety and NCCP.

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Compliance with Ethical Standards

Conflict of interest Mohammad J. Alkhatatbeh, Khalid K. Abdul-Razzak, Noor A. Amara, and Mohamad Al-Jarrah declare that they have no conflict of interest.

Human and Animal Rights All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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