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# Increased depression risk among patients with chronic osteomyelitis

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ABSTRACT

*Objective:* Inflammatory processes, which provoke alternations of neurotransmitter metabolism, neuroendocrine function, and neuroplasticity in the brain, might promote depression. In depression patients who do not exhibit risk factors, including hypertension, diabetes, coronary heart disease, stroke, Parkinson's disease and dementia, particularly in young people, inflammation is a likely risk factor for depression. We explored whether chronic osteomyelitis (COM), a chronic inflammatory disease, increases depression risk.

*Methods:* A Taiwanese national insurance claims data set of more than 22 million enrollees was used to select 15,529 COM patients without depression history and 62,116 randomly selected age- and gender-matched controls without depression and COM history to trace depression development for an 12-year follow-up period from January 1, 1999 to December 31, 2010. The depression risk was analyzed using the Cox proportional hazards regression model.

*Results:* The above-mentioned risk factors for depression were more frequent in the COM cohort, who exhibited significantly higher depression risk than the control group did. Comparing only those without comorbidities, the COM group exhibited higher depression risk than the control group did (hazard ratio [HR] = 3.04, 95% confidence interval [CI]: 2.55–3.62). The younger population carried even greater risk (age < 45: HR = 6.08, 95% CI: 1.71–7.85; age > 65: HR = 1.75, 95% CI: 1.39–2.19).

*Conclusions:* This is the first study connecting COM to increased risk of developing depression. The outcomes suggest that COM is a substantial depression predictor and call for a closer focus on these patients for more rigorous depression prevention, particularly in young people.



## Introduction

Depression is a relatively common mood disorder that has become a primary cause of functional impairment, disability, or loss of work productivity [1–3]. Therefore, early recognition of risk factors for depression prevention is a prime factor for decreasing depression-related social and economic burdens. Through the mechanisms involving afferent nerves and humoral pathways, inflammatory substances formed by peripheral inflammations could induce certain pathophysiological changes, such as a change in neurotransmitter metabolism, varied neuroendocrine function and alternating neuroplasticity in the brain, and depression formation [4–7]. Because of similar pathophysiological effects on the brain, depression, including vascular depression, can also be triggered by certain chronic medical disorders associated with chronic inflammatory processes, such as hypertension [8–10], diabetes [4,8–10], coronary heart disease (CHD) [4,8–10], stroke [8–10], and neurodegenerative courses, including Parkinson's disease (PD) [11,12] and dementia [13,14]. However, surveys have evidenced no traditional medical risk factors for depression in certain depression patients [6,15,16]. Therefore, exploring depression risk factors beyond those that are well documented, including hypertension [8,9], diabetes [4,8–10], CHD [4,8–10], stroke [8–10], PD [11,12], and dementia [13,14], is necessary.

The potential role of chronic inflammatory processes in altering neurotransmitter metabolism, varied neuroendocrine function, and alternating neuroplasticity in the brain is well evidenced [4–7]. Chronic osteomyelitis (COM), a condition involving powerful chronic inflammation caused by bone infection, can last for weeks, months, or years and involve pathological processes that sustain intense inflammation in the foci because of the formation of abscesses, bone debris, and sinus tracts [17]. COM can occur at the long bone and spine after a period of bacteremia or fungemia and later can spread to adjacent vertebra or into the meninges [17]. The COM patients are characterized by male predominance and the majority of them are older in age [18,19]. COM could increase the risk of some medical conditions, such as ischemic

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stroke [20], coronary artery disease [21], epilepsy [22], and dementia [23]. Certain autoimmune disorders have also exhibited increased depression risk, including rheumatoid arthritis (RA) [4,24,25], systemic lupus erythematosus (SLE) [24,25], and infectious diseases, such as human immunodeficiency virus (HIV) [26,27] and hepatitis C virus (HCV) [26,27] infections. However, the degree to which diseases exhibiting chronic inflammation contribute to depression pathogenesis beyond conventional risk factors for depression, particularly for vascular depression, such as hypertension [8–10], diabetes [4,8–10], CHD [4, 8–10], and stroke [8–10], is unknown.

There have been no studies ever connecting COM, a well-known chronic inflammatory disease, to the development of depression. Our nationwide study was based on a large National Health Insurance (NHI) claims database, available in Taiwan, to investigate the linkage of COM and depression in a cohort exceeding 22 million enrollees for an 8-year period from January 1, 1999 to December 31, 2006.

## Methods

### *Data source*

This nationwide retrospective cohort study used the NHI beneficiary files of the inpatient claims database obtained for the 1996–2010 period from in Taiwan, which began in 1995. The inpatient claims database used in this study was extracted from the NHI Research Database (NHIRD) [28]. NHI covers over 98% of the Taiwanese population. The *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) was used for coding the diseases of interest in the present study.

### *Study subjects*

Based on the NHI database, enrollees who were newly diagnosed with COM (ICD-9-CM code 730.1) from January 1, 1999, to December 31, 2006, without a history of previous depression (ICD-9-CM codes 296.36, 296.82, 298.0, 300.4, 301.12, and 311) before COM diagnoses were collected and their dates of COM diagnoses were defined as the entry dates. The study group comprised 15,529 patients with COM. The control group was compiled from the NHIRD, using a random selection of age- and gender-matched participants without COM and depression with corresponding entry dates, at a ratio of 4:1 in the study group ($n = 62{,}116$).

### *Ethics statement*

Because identification numbers of patients had been encrypted, patient consent was not required for this study. This study was approved by the Research Ethic Committee at China Medical University (CMU-REC-101-012). The committee waived the requirement for consent.

### *Outcome and relevant variables*

In this study, the end point was depression (ICD-9-CM codes 300.4, 296.36, 296.20-296.36, 298.0, 301.12, and 311) during the study period. The variables of relevance were age, gender, and comorbidities, including hypertension (ICD-9-CM codes 401–405), diabetes (ICD-9-CM codes 250), CHD (ICD-9-CM codes 410–414), stroke (ICD-9-CM codes 430–438 at discharge), PD (ICD-9-CM codes 332), and dementia (ICD-9-CM codes 290.0-290.4, 291.2, 292.82, 294.10, 294.11, 331.0).

### *Statistical analysis*

The chi-square test and the *t*-test were used to assess the differences of discrete and continuous variables between the COM cohort and the control group. Person-years were calculated from the entry dates to the first dates of the occurrence of depression, withdrawal from the insurance program, death, or the end of 2010. The gender- and age-specific incidence rates (per 1000 person-years) of depression were compared between the 2 groups. Using the Cox proportional hazards regression model, hazard ratios (HRs) were derived to compare the risk of developing depression between the groups. The demographic factors and comorbidities relevant to depression were retrieved for group comparison. HRs for depression were stratified by age and gender (Table 2), and the risk of depression with the stratification of each of the 6 depression-relevant comorbidities was also compared between groups (Table 3). The association between COM severity and depression was analyzed according to COM severity, which was defined as the total length of hospital stay because of COM during the follow-up duration, divided by the length of follow-up duration (Table 5). Using the tertile, COM severity was further classified as mild (the first tertile in COM severity), moderate (the second tertile in COM severity), and severe (the third tertile in COM severity) [20]. The cumulative incidences for depression were plotted using the Kaplan–Meier model and the difference between groups was calculated by applying the log-rank test (Fig. 1). A 2-tailed $P$ value $< 0.05$ was considered significant. SAS Version 9.1 (SAS Institute Inc., Carey, NC, USA) was used in the present study.

## Results

Men were more likely than women were to be infected with COM (66.9% vs. 33.1%) (Table 1). Compared with the control group, the prevalence of comorbidities considered to be depression risk factors, including hypertension, diabetes mellitus, CHD, stroke, PD, and dementia, was significantly higher in the osteomyelitis group ($p < 0.0001$) (Table 1). The overall incidence rates for depression in the study and in the control groups were 3.94 and 1.21 per 1000 person-years, respectively (Table 2). In both groups, women had a higher incidence of depression than men did (Table 2). We observed a U-shaped distribution of depression incidence with higher rates in both the youngest (age < 45) and oldest (age > 65) age-groups in the COM group, which increased with age in the control group (Table 2). The depression risk was 3.22-fold [95% confidence interval (CI): 2.82–3.67] higher in the COM group than in the control cohort (Table 2). When adjusting for age, gender, hypertension, diabetes, CHD, stroke, PD, and dementia, using the Cox proportional-hazards regression, the risk was 2.84-fold (95% CI: 2.47–3.26) significantly higher in the COM group than the control cohort (Table 2). The age-specific adjusted hazard ratios (aHRs) were highest in the youngest age-group (<45: 6.08, 95% CI: 1.71–7.85) with a steady decline with increasing age (>65: 1.75, 95% CI: 1.39–2.19) (Table 2). The Kaplan–Meier analysis in the 2 groups showed that depression risk rose during follow-up in both groups, with a significantly higher cumulative incidences for depression in the study group than in the control group (log-rank $p < .0001$) (Fig. 1).

Table 3 shows the comorbidity stratification analyses of the Cox proportional-hazards regression model adjusted for age and gender. In the absence of any of the 6 relevant

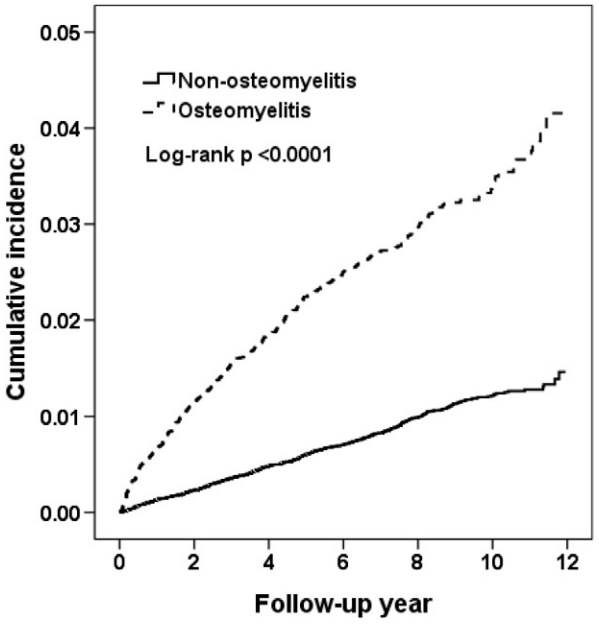


**Fig. 1.** The comparison of cumulative incidences for depression between chronic osteomyelitis and control groups using the Kaplan–Meier model.