Association Between Chronic Osteomyelitis and Risk of End-Stage Renal Disease

A Nationwide Population-Based Cohort Study

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Abstract: Inflammation, which initiates endothelial dysfunction, vascular atherosclerosis, and oxidative stress, may negatively influence renal function and accelerate the development of end-stage renal disease (ESRD). The role of chronic osteomyelitis (COM), a chronic inflammatory disease, in the development of ESRD has not been investigated. This study explored whether patients with COM have a higher risk of ESRD than that of patients without COM.

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INTRODUCTION

End-stage renal disease (ESRD) is becoming a major public health concern worldwide. It can cause functional impairment and interfere with work productivity. In addition, the high cost of treatment for patients with ESRD causes a financial burden for health care systems. Hence, early recognition and prevention of risk factors for ESRD could diminish its social and economic cost.

Over the past decade, attention has been focused on identifying the risk factors for ESRD. Age, male sex, diabetes, hypertension, coronary artery disease (CAD), and congestive heart failure (CHF) are currently considered risk factors for ESRD. Inflammation has also been reported to be associated with ESRD risk. The pathophysiological explanation for the ESRD risk associated with inflammation is still unresolved but likely involves a systemic response and vascular atherosclerosis. Exploring and evaluating the ESRD risks associated with chronic inflammation-related diseases is necessary to elucidate the association between ESRD and inflammation.

Chronic osteomyelitis (COM), a lasting infection of the bones, typically evokes intense inflammation within bony structures and nearby soft tissues. COM is difficult to eradicate, and its therapy typically requires weeks, months, or years to complete. COM has been reported to increase the risk of CAD, dementia, stroke, depression, and epilepsy. Because CAD and stroke have many risk factors in common with ESRD, investigating the possible relationship between COM and ESRD is warranted. No study has connected COM with the risk of ESRD. We used a nationwide population database to assess the association of COM and risks of developing ESRD in a cohort study over a follow-up period of 14 years.
MATERIALS AND METHODS

Data Source

Data were extracted from the National Health Insurance Research Database (NHIRD) of the Taiwan National Health Insurance (NHI) program. This insurance program has provided health care for >99% of the >23 million residents of Taiwan and contracted with 97% of Taiwan’s hospitals and clinics. Taiwan launched a NHI in 1995, operated by a single buyer, the government. Medical reimbursement specialists and peer review should scrutinize all insurance claims. The diagnoses were based on the International Classification of Diseases, Ninth Revision (ICD-9) codes that were judged and determined by related specialists and physicians according to the standard clinical criteria. If these hospitals or doctors made the wrong codes or diagnoses, they would be punished to pay a lot of penalty. Therefore, the diagnoses and codes used in this study should be correct and reliable.19 For this study, we used NHI administrative data19 that contains health care data including records of inpatient claims, a registry of catastrophic illness patients, and a registry of beneficiaries. Records were linked using a scrambled, anonymous registry of catastrophic illness patients, and a registry of bene-

Data Source

Age-specific analysis showed that the IRR was the highest in non-COM cohort is 5.29 ± 3.96 years and in non-COM cohort is 6.21 ± 3.88 years. In both the cohorts, more than half of the patients were ≥55 years, and 66.5% were male. Compared with the comparison cohort, patients with COM were more likely to have diabetes (28.0% vs 6.05%; P < 0.001), hypertension (30.1% vs 11.2%; P < 0.001), hyperlipidemia (6.97% vs 2.66%; P < 0.001), CHF (14.1% vs 5.09%; P < 0.001), hyper-

Statistical Analysis

The proportionate distributions of sociodemographic characteristics and comorbidities between the cohorts with and without COM were compared using the χ² test. The sex-

RESULTS

We identified 24,267 patients newly diagnosed with COM between 1997 and 2010 and 97,068 patients in the non-COM comparison cohort (Table 1). The mean follow-up years in COM cohort is 5.29 ± 3.96 years and in non-COM cohort is 6.21 ± 3.88 years. In both the cohorts, more than half of the patients were ≥55 years, and 66.5% were male. Compared with the comparison cohort, patients with COM were more likely to have diabetes (28.0% vs 6.05%; P < 0.001), hypertension (30.1% vs 11.2%; P < 0.001), hyperlipidemia (6.97% vs 2.66%; P < 0.001), CHF (14.1% vs 5.09%; P < 0.001), hyper-

Outcome Measures

Both cohorts were followed until a diagnosis of ESRD or until loss to follow-up, death, termination of insurance, or the end of 2010. ESRD was identified from the Registry for Catastrophic Illness Patient Database. Registration for cata-

Table 3 shows the incidence rate and adjusted HR of ESRD according to the presence of individual comorbidity. A higher incidence rate of ESRD was observed in patients having any comorbidity in both the cohorts. COM patients with no comorbidity had a higher risk of developing ESRD comparing with the non-COM patients with no comorbidity (adjusted HR of diabetes = 1.53, 95% CI: 1.23–1.85; adjusted HR of hyper-

Table 2 shows the incidence rate and adjusted HR of ESRD according to the presence of individual comorbidity. A higher incidence rate of ESRD was observed in patients having any comorbidity in both the cohorts. COM patients with no comorbidity had a higher risk of developing ESRD comparing with the non-COM patients with no comorbidity (adjusted HR of diabetes = 1.53, 95% CI: 1.23–1.85; adjusted HR of hyper-

Table 4 shows the incidence rate and adjusted HR of ESRD stratified by age categorization and the presence of comorbidity. Younger COM adults aged 20 to 34 years without comorbidities have a higher ESRD risk than non-COM adults aged 20 to 34 years without comorbidities (adjusted HR = 8.14, 95% CI: 2.04–32.6).
TABLE 1. Demographic Characteristics and Comorbidities in Cohorts With and Without Chronic Osteomyelitis

| Variable             | Chronic Osteomyelitis | Comorbidity | P Value |
|----------------------|-----------------------|-------------|---------|
|                      | No (N = 97,068)       | Yes (N = 24,267) |         |
| Sex                  |                       |             |         |
| Female               | 32,520 (33.5)         | 8130 (33.5) | 0.99    |
| Male                 | 64,548 (66.5)         | 16,137 (66.5) |         |
| Age, mean (SD)*      | 56.9 (17.7)           | 57.0 (17.7) | 0.51    |
| Stratify age         |                       |             |         |
| 20–34                | 13,236 (13.6)         | 3309 (13.6) | 0.99    |
| 35–44                | 13,304 (13.7)         | 3326 (13.7) |         |
| 45–54                | 16,848 (17.4)         | 4212 (17.4) |         |
| 55–64                | 16,804 (17.3)         | 4201 (17.3) |         |
| 65+                  | 36,876 (38.0)         | 9219 (38.0) |         |
| Comorbidity          |                       |             |         |
| Diabetes             | 5875 (6.05)           | 6786 (28.0) | <0.001  |
| Hypertension         | 10,825 (11.2)         | 7315 (30.1) | <0.001  |
| Hyperlipidemia       | 2582 (2.66)           | 1691 (6.97) | <0.001  |
| CHD                  | 4983 (5.13)           | 2731 (11.3) | <0.001  |
| CHF                  | 4941 (5.09)           | 3431 (14.1) | <0.001  |
| Gout                 | 482 (0.50)            | 613 (2.53)  | <0.001  |
| Proteinuria          | 102 (0.11)            | 90 (0.37)   | <0.001  |

* χ² test. CHD = coronary heart disease, CHF = congestive heart failure, SD = standard deviation.

** Two sample t test.

The Kaplan–Meier survival analysis showed that patients with COM had a significantly higher rate (5.8%) of ESRD development than that of the non-COM cohort (Figure 1).

TABLE 2. Incidence Rate and HR of ESRD by Sex, Age, and the Presence of Comorbidity

| Variables | No | Yes | IRR† (95% CI) | Adjusted HR† (95% CI) |
|-----------|----|-----|--------------|----------------------|
|           | Event | Rate |          | Event | Rate |          |
| All       | 790  | 13.1 | 5.5 (4.3, 7.1)** | 2.01 (1.81, 2.25)** |
| Sex       |       |     |              |         |       |         |
| Female    | 313  | 16.1 | 4.27 (4.02, 4.54)** | 1.81 (1.52, 2.17)** |
| Male      | 477  | 11.7 | 4.73 (4.53, 4.94)** | 2.03 (1.76, 2.34)** |
| Stratify age |     |     |              |         |       |         |
| 20–34     | 3   | 0.31 | 34.0 (28.5, 40.5)** | 17.8 (5.18, 61.4)** |
| 35–44     | 34  | 3.55 | 12.7 (11.4, 16.2)** | 2.91 (1.78, 4.73)** |
| 45–54     | 84  | 7.58 | 11.9 (10.9, 13.0)** | 2.79 (2.05, 3.78)** |
| 55–64     | 190 | 17.1 | 5.27 (4.86, 5.71)** | 1.69 (1.35, 2.12)** |
| 65+       | 479 | 25.3 | 2.45 (2.30, 2.60)** | 1.30 (1.10, 1.54)** |
| Comorbidity |     |     |              |         |       |         |
| No        | 407 | 0.76 | 1.24 (1.17, 1.32)** | 1.57 (1.23, 2.00)** |
| Yes       | 383 | 5.83 | 2.59 (2.42, 2.77)** | 2.25 (1.97, 2.57)** |

CHD = coronary heart disease, CHF = congestive heart failure, CI = confidence interval, ESRD = end-stage renal disease, HR = hazard ratio, IRR = incidence rate ratio, PY = person-years.

* P < 0.05.
** P < 0.01.
*** P < 0.001.
† Adjusted for age, sex, and the presence of comorbidities.
‡ Subjects with 1 of the comorbidities (diabetes, hypertension, hyperlipidemia, CHD, CHF, gout, and proteinuria) were classified as the comorbidity group.
§ Incidence rate, per 10,000 PY.

DISCUSSION

Previous studies have shown a link between chronic inflammatory diseases, such as hepatitis C infection,24,25 hepatitis B infection,26 stroke,27 gout,28 periodontal disease,29 and herpes zoster, and ESRD.30 Systemic inflammation is a suspected mechanism in the relationship between these diseases and an increased risk of ESRD. Using the nationally representative NHIRD to compare patients with COM and controls between 1997 and 2010, this study showed that COM, a chronic inflammatory disease, is associated with an increased risk of ESRD.

Numerous studies have shown a causal link between ESRD risk and old age, sex,31,32 diabetes,33 hypertension,33,35 hyperlipidemia,34,36 CAD,37 and CHF.38 Our data revealed that COM patients with at least 1 of these comorbidities had an increase in ESRD risk compared with non-COM patients without comorbidities. Further analysis of the interaction between COM and individual comorbidity as well as the risk of ESRD in COM patients and matched controls with or without these comorbidities differed. Our results demonstrate that COM is potentially an independent risk factor for ESRD.

There are several possible physiopathological mechanisms accounting for COM cohort that has higher ESRD risk than non-COM cohort. Chronic infection may cause infection-associated glomerulonephritis that would predispose to nephrons damage, glomerulosclerosis, and thus decline of renal function reserve. Antibiotics for treating COM may also have direct nephrotoxicity or interacting drug–drug toxic effects on renal function of COM patients. A prospective long-term follow-up of COM patients with kidney biopsy data would be necessary to help clarify the causality of COM and ESRD.

Old age has been recognized as a crucial risk factor for ESRD.39 However, in the current study, the COM subgroup of patients aged 20 to 34 years had an up to 17.8-fold increased
**TABLE 3.** Incidence Rate and HR of ESRD by the Presence of Each Type of Comorbidity

| Variables | Chronic Osteomyelitis | Compared to Nonosteomyelitis |
|-----------|-----------------------|-----------------------------|
|           | Event PY Rate$^a$     | IRR$^b$ (95% CI)            | Adjusted HR$^c$ (95% CI) |
| Diabetes  |                       |                             |                           |
| No        | 525 579,260 0.91      | 1.64 (1.56, 1.72)$^{***}$   | 1.53 (1.27, 1.85)$^{***}$ |
| Yes       | 265 23,225 11.4       | 2.08 (1.90, 2.29)$^{***}$   | 1.78 (1.53, 2.07)$^{***}$ |
| Hypertension | 515 559,347 9.21     | 4.09 (3.93, 4.25)$^{***}$   | 2.06 (1.77, 2.40)$^{***}$ |
| No        | 275 43,168 63.7      | 2.29 (2.10, 2.48)$^{***}$   | 1.50 (1.27, 1.77)$^{***}$ |
| Yes       | 75 10,824 69.3       | 2.81 (2.44, 3.42)$^{***}$   | 1.76 (1.29, 2.39)$^{***}$ |
| Hyperlipidemia | 715 591,691 12.1    | 3.45 (4.19, 4.51)$^{***}$   | 2.02 (1.80, 2.28)$^{***}$ |
| No        | 275 43,168 63.7      | 2.81 (2.44, 3.42)$^{***}$   | 1.76 (1.29, 2.39)$^{***}$ |
| Yes       | 75 10,824 69.3       | 2.81 (2.44, 3.42)$^{***}$   | 1.76 (1.29, 2.39)$^{***}$ |
| CHD       |                       |                             |                           |
| No        | 690 581,907 1.19     | 4.53 (4.37, 4.70)$^{***}$   | 1.99 (1.76, 2.24)$^{***}$ |
| Yes       | 100 20,608 48.5      | 2.81 (2.46, 3.21)$^{***}$   | 1.75 (1.33, 2.30)$^{***}$ |
| CHF       |                       |                             |                           |
| No        | 646 583,366 1.11     | 4.43 (4.27, 4.59)$^{***}$   | 2.06 (1.82, 2.34)$^{***}$ |
| Yes       | 144 19,149 7.52      | 2.28 (2.02, 2.57)$^{***}$   | 1.43 (1.14, 1.80)$^{***}$ |
| Gout      |                       |                             |                           |
| No        | 769 600,707 1.28     | 4.58 (4.42, 4.74)$^{***}$   | 2.04 (1.82, 2.28)$^{***}$ |
| Yes       | 21 1808 13.6         | 1.03 (0.74, 1.43)           | 1.02 (0.54, 1.93)         |
| Proteinuria | 785 602,147 1.30    | 4.52 (4.36, 4.68)$^{***}$   | 2.02 (1.81, 2.25)$^{***}$ |
| No        | 5 368 13.6           | 2.71 (1.30, 5.68)$^{***}$   | 1.66 (0.45, 6.16)         |
| Yes       |                       |                             |                           |

ESRD = end-stage renal disease, IRR = incidence rate ratio, HR = hazard ratio, PY = person-years.

$^a$ $P < 0.05$.

$^{**} P < 0.01$.

$^{***} P < 0.0001$.

$^b$ Adjusted for age, sex, and comorbidities.

$^c$ Incidence rate, per 10,000 PY.

**TABLE 4.** Incidence Rate and HR of ESRD by Age and the Presence of Comorbidity

| Variables | Chronic Osteomyelitis | Compared to Nonosteomyelitis |
|-----------|-----------------------|-----------------------------|
|           | Event PY Rate$^a$     | IRR$^b$ (95% CI)            | Adjusted HR$^c$ (95% CI) |
| Stratify age Comorbidity$^d$ |                       |                             |                           |
| 20–34     |                       |                             |                           |
| No        | 3 94,859 0.03         | 8.34 (7.38, 9.44)$^{***}$   | 8.14 (2.04, 32.6)$^{**}$ |
| Yes       | 0 448 0.00           | —                            | —                         |
| 35–44     |                       |                             |                           |
| No        | 26 94,172 0.28       | 2.07 (1.82, 2.35)$^{***}$   | 2.07 (1.00, 4.29)         |
| Yes       | 8 1732 4.62         | 4.49 (2.70, 7.46)$^{***}$   | 4.66 (2.26, 9.62)$^{***}$ |
| 45–54     |                       |                             |                           |
| No        | 52 105,684 0.49      | 2.58 (2.31, 2.89)$^{***}$   | 2.59 (1.55, 4.34)$^{***}$ |
| Yes       | 32 5084 6.29         | 3.86 (2.97, 5.01)$^{***}$   | 3.90 (2.68, 5.67)$^{***}$ |
| 55–64     |                       |                             |                           |
| No        | 112 99,775 1.12      | 1.08 (0.92, 1.25)           | 1.08 (0.63, 1.85)         |
| Yes       | 78 11,220 6.95       | 2.64 (2.23, 3.12)$^{***}$   | 2.62 (2.01, 3.41)$^{***}$ |
| 65+       |                       |                             |                           |
| No        | 214 142,357 1.50     | 1.24 (1.10, 1.40)$^{***}$   | 1.26 (0.84, 1.88)         |
| Yes       | 265 47,183 5.62      | 1.62 (1.49, 1.77)$^{***}$   | 1.62 (1.35, 1.95)$^{***}$ |

CI = confidence interval, ESRD = end-stage renal disease, IRR = incidence rate ratio, HR = hazard ratio, PY = person-years.

$^a$ $P < 0.05$.

$^{**} P < 0.01$.

$^{***} P < 0.0001$.

$^b$ Adjusted for sex.

$^c$ Subjects with 1 of comorbidities (diabetes, hypertension, hyperlipidemia, CHD, CHF, and proteinuria) were classified as the comorbidity group.

$^d$ Incidence rate, per 10,000 PY.
ESRD risk compared with the non-COM subgroup of patients aged 20 to 34 years. This result is attributable to at least 2 factors. First, the competing risk between ESRD and death is higher in elderly people compared with younger patients. Therefore, elderly patients might have an increased risk of death from other causes before they are required to initiate dialysis. Second, elderly people have higher possibility to refuse long-term dialysis in consideration of lifespan and underlying complex comorbidities. Finally, we collected data in a retrospective manner and applied strict criteria to enroll patients with and those without COM. The relatively low number of ESRD events in patients without COM aged 20 to 34 years might have caused bias.

Our study has several strengths. First, this retrospective study had a follow-up length of 14 years, and a strict criteria was used to the catastrophic illness registration criteria used to identify ESRD. The long-term follow-up and strict definition of ESRD diagnosis criteria strengthened the time- and severity-dependent effects of COM on ESRD development. Second, COM and age- and sex-matched controls were selected from a dataset exceeding 22 million enrollees and encompassing >99% of the population of Taiwan. This near-total-population sample coupled with a strict case-to-control ratio of 1:4 increased the generalizability, precision, and reliability of its results. Third, an NHI monitoring and auditing system is implemented to supervise insurance claims to prevent overdiagnosis and medical resource waste. This NHI surveillance program ensures the validity of diagnosis. Finally, all recognized comorbidities and risk factors of ESRD (ie, hypertension, diabetes, hyperlipidemia, CHF, CAD, hyperuricemia and gout, and proteinuria) were considered and adjusted in this study, and the results suggest that COM is an independent risk factor for ESRD.

Several limitations of this study should be noted. First, we had no definite information on the levels of blood pressure, serum glucose, and serum lipids of the patients. Our study may thus have a confounding variability bias. The second limitation is that the database used for our research did not provide information on lifestyle and personal health behaviors, including smoking, drinking, and obesity; these variables are known to be related to ESRD. Finally, the results of this study were obtained from insurance claims to calculate the risk of ESRD among the COM patients. Hence, patients who refused long-term dialysis or COM management may have caused us to underestimate or overestimate the effects of COM on ESRD development. This possible bias was minimized because the NHI covers >99% of Taiwan’s population.

Our investigation showed that COM is an independent risk factor for ESRD. Patients with COM have a higher prevalence of conventional risk factors for ESRD. The ESRD risk of patients with COM increases if they have comorbidities (ie, hypertension, diabetes, CAD, CHF, hyperlipidemia, hyperuricemia and gout, and proteinuria). Younger patients with COM have a higher risk of ESRD. Our findings could be used to prompt clinical alerts and develop renal function screening programs for patients with COM, particularly younger patients.

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