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ORIGINAL ARTICLE

# Increased inflammation in rheumatoid arthritis patients living where farm soils contain high levels of copper

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*Background/Purpose:* Heavy metal pollution in farm soils is a problem in some parts of Taiwan. Copper can be a factor associated with increased disease activities of rheumatoid arthritis (RA). Thus, the aim of this study was to investigate whether copper pollution in farm soils is associated with worsened RA.
*Methods:* Clinical parameters from 122 RA patients were collected from a medical center in central Taiwan. Levels of heavy metals in the blood were measured using inductively coupled plasma mass spectrometry. Levels of copper in farm soils were retrieved from a national survey. These data were analyzed to find the factors related to RA disease activities.
*Results:* RA patients living where farm soils contained high levels of copper had increased white blood cell counts, erythrocyte sedimentation rate, and disease activity score 28, compared with patients living where copper levels were low. Among the nine types of heavy metal measured in the study, blood levels of copper and nickel correlated with erythrocyte sedimentation rate.
*Conclusion:* Our cross-sectional data suggest a correlation between RA disease activity and the level of copper at township farm soils samples. Further longitudinal studies using more rigorous methodologies are warranted to examine whether this correlation is causal.


Conflicts of interests: The authors have no conflicts of interest relevant to this article.

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## Introduction

It is estimated that 0.5—1.0% of the general population are suffering from rheumatoid arthritis (RA).[1] With the advance of biologics, remission is attainable in many RA patients.[2] This implies that measures that can mitigate or eliminate proinflammatory cytokine production can benefit RA patients.

Some environmental factors for RA are known, including pollution and cigarette smoking.[3] People living in urban areas or in the vicinity of roads had increased incidences of RA than people living in rural areas.[4,5] However, there have been no reports of a strong association between a specific chemical and RA incidence. By contrast, smoking is a factor that is easier to define than pollution. Smoking can increase disease activities in RA patients, and can promote the production of interleukin (IL)-8, matrix metalloproteinase-1, and heat shock protein 70 in synovium tissue.[6—9] Moreover, cigarette smoking can increase the blood levels of cadmium in RA patients and increase the blood levels of copper in healthy people.[10—12] The copper levels in the blood also positively correlated with lipid peroxidation in people who smoke.[13]

Copper is an essential trace element for humans; however, consuming a high-copper diet may promote the production of IL-2 and IL-6, and may alter the composition of white blood cells (WBCs), including an increase in lymphocyte numbers and a decrease in neutrophil numbers.[14—17] In addition, copper can increase the production of proinflammatory cytokines, including IL-1β, tumor necrosis factor-α, and IL-6 production in many types of cells.[18—21]

In RA patients, blood copper levels correlated with disease activity markers such as erythrocyte sedimentation rate (ESR), C-reactive protein, and disease activity score 28 (DAS28).[22,23] In addition, blood copper levels also correlated with blood levels of IL-1 and tumor necrosis factor-α in patients.[24—27] Moreover, the blood copper levels in RA patients were higher than those in osteoarthritis patients and healthy controls.[28,29] These findings imply that copper can be an important factor to determine the levels of inflammation in RA patients.

Heavy metal pollution in the farmland at Changhua County in central Taiwan has been documented and reported.[30,31] We have provided evidence that pollution in the farmland has already exerted a negative effect on the health of people living in Changhua. Changhua had the highest national incidence of oral cancer.[32] Patients living in an area with a high density of electroplating factories had oral cancer at a younger age and had a poorer prognosis than those in other areas with lower factory densities.[33] In addition, the incidence of oral cancer was statistically associated with the levels of heavy metals in the farm soils.[34] The blood levels of certain metals were also increased in oral cancer patients compared with control participants.[35]

In this study, we investigated whether RA patients living where the farm soils contain high levels of copper have increased disease activities. In addition, we studied whether heavy metals other than copper can also associate with increased RA disease activities.

## Methods

### Patients recruited

This study was approved by the Ethical Committee of the Changhua Christian Hospital, Changhua, Taiwan. Informed consent was acquired from all patients participating in the study. RA patients were diagnosed according to the 1987 criteria. Gout patients had at least one attack. Ankylosing spondylitis (AS) patients were diagnosed according to the New York criteria. Clinical information collected from the 122 RA patients is shown in Table 1.

### Grading of copper levels in farm soils

Heavy metal concentrations in the surface (0—15 cm) of farm soils were retrieved from a national survey.[31] Concentrations of copper were obtained with the 0.1N HCl extraction methods. By averaging the results from the same township/precinct, we obtained a value to represent the copper level in farm soils for each township/precinct. The townships were graded according to their copper levels in farm soils and divided into four grades. Townships in Grade 1 had a copper level higher than 23.83 mg/kg; Grade 2,

**Table 1** Clinical parameters in 122 RA patients.[a]

| Clinical parameters, mean ± SD (range) | |
|---|---|
| Age (y) | 55.37 ± 13.51 (16—89) |
| Sex (M/F) | 34/88 |
| WBC count ($10^3$ cells/μL) | 6.73 ± 2.22 (3.5—14.7) |
| Platelet count ($10^3$ cells/μL) | 239.79 ± 66.57 (119—424) |
| Hemoglobin (g/dL) | 13.34 ± 1.51 (8.4—16.7) |
| GPT (U/L) | 24.99 ± 17.18 (4—113) |
| Creatinine (mg/dL) | 0.90 ± 0.53 (0.5—6.3) |
| ESR (mm/h) | 25.84 ± 21.52 (1—129) |
| DAS28 | 3.45 ± 0.96 (1.39—6.17) |
| TJC | 5.01 ± 5.56 (0—28) |
| SJC | 0.51 ± 1.56 (0—10) |
| RF-IgM (positive, %) | 39.67 |
| **Patient number in different townships (*n*)** | |
| Grade 1 township | 14 |
| Grade 2 township | 46 |
| Grade 3 township | 23 |
| Grade 4 township | 39 |
| **Medications (%)** | |
| Prednisolone | 87.2 |
| Methotrexate | 48.7 |
| Hydroxychloroquine | 94.9 |
| Sulfasalazine | 48.72 |
| Celecoxib | 58.21 |
| Etanercept | 12.82 |

DAS28 = disease activity score 28; ESR = erythrocyte sedimentation rate; GPT = glutamic pyruvic transaminase; RF-IgM = rheumatoid factor-immunoglobulin M; SJC = swollen joint count; TJC = tender joint count; WBC count = white blood cell count.

[a] Soil copper levels in different townships (mg/kg): Grade 1, > 23.83; Grade 2, 15.43—23.83; Grade 3, 7.03—15.43; Grade 4, 0—7.03.

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