Significantly lower mean serum vitamin B12 and folic acid levels and a significantly higher frequency of serum iron deficiency in younger than in older atrophic glossitis patients

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Abstract  Background/purpose: Our previous study found that 19.0%, 16.9%, 5.3%, 2.3%, and 11.9% of 1064 atrophic glossitis (AG) patients have anemia, serum iron, vitamin B12, and folic acid deficiencies, and hyperhomocysteinemia, respectively. This study mainly evaluated the anemia, hematinic deficiencies, and hyperhomocysteinemia in 224 younger (<50 years old) and 840 older (>50 years old) AG patients.

Materials and methods: The blood hemoglobin (Hb) and serum iron, vitamin B12, folic acid, and homocysteine levels in 224 younger and 840 older AG patients were measured and compared with the corresponding levels in 112 younger (<50 years old) and 420 older (>50 years old) AG patients.
years old) healthy control subjects (HCSs), respectively.

Results: We found that 224 younger AG patients had significantly lower mean blood Hb and serum iron levels than 112 younger HCSs. Moreover, 840 older AG patients had significantly lower mean blood Hb and serum iron levels and a significantly higher mean serum homocysteine level than 420 older HCSs. In addition, 224 younger AG patients had significantly lower mean serum vitamin B12 and folic acid levels, a lower mean serum homocysteine level (marginal significance, \( P = 0.056 \)), a significantly higher frequency of serum iron deficiency, and a significantly lower frequency of hyperhomocysteinemia than 840 older AG patients.

Conclusion: The younger AG patients have significantly lower mean serum vitamin B12 and folic acid levels, a significantly higher frequency of serum iron deficiency, and a significantly lower frequency of hyperhomocysteinemia than the older AG patients.


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Comparisons of means of parameters between 224 younger or 840 older AG patients and 112 younger or 420 older HCSs by Student’s t-test, respectively, as well as between 224 younger and 840 older AG patients were performed by Student’s t-test. The differences in frequencies of microcytosis (MCV < 80 fl)\(^22,23\), macrocytosis (MCV ≥ 100 fl)\(^24-26\), blood Hb and serum iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum GPCA positivity between 224 younger or 840 older AG patients and 112 younger or 420 older HCSs, respectively, as well as between 224 younger and 840 older AG patients were compared by chi-square test. In addition, the differences in frequencies of 6 different types of anemia between 224 younger and 840 older AG patients were also compared by chi-square test. The result was considered to be significant if the P-value was less than 0.05.

**Results**

The MCV, mean blood Hb and serum iron, vitamin B12, folic acid, and homocysteine levels in 224 younger and 840 older AG patients and in 112 younger and 420 older HCSs are shown in Table 1. We found that 224 younger AG patients had significantly lower MCV, mean blood Hb and serum iron levels than 112 younger HCSs (all P-values < 0.005, Table 1). Although the 224 younger AG patients also had a higher mean serum homocysteine level than 112 younger HCSs, the difference was not significant (P = 0.171) (Table 1). Moreover, 840 older AG patients had significantly lower mean blood Hb and serum iron levels, and a significantly higher mean serum homocysteine level than 420 older HCSs (all P-values < 0.01, Table 1). In addition, 224 younger AG patients had significantly lower MCV and mean serum vitamin B12 and folic acid levels than 840 older AG patients (all P-values < 0.001, Table 1). The 224 younger AG patients also had a lower mean serum homocysteine level (marginal significance, P = 0.056) than 840 older AG patients. However, no significant differences in the mean blood Hb and serum iron levels were found between 224 younger and 840 older AG patients (Table 1).

According to the World Health Organization (WHO) criteria, microcytosis of erythrocyte was defined as having MCV < 80 fl\(^22,23\), macrocytosis of erythrocyte was defined as having MCV ≥ 100 fl\(^24-26\), and men with Hb < 13 g/dL and women with Hb < 12 g/dL were defined as having Hb deficiency or anemia.\(^27\) Furthermore, patients with the serum iron level < 60 µg/dL,\(^28\) the serum vitamin B12 level < 200 pg/mL,\(^29\) or the folic acid level < 4 ng/mL\(^10\) were defined as having serum iron, vitamin B12 or folic acid deficiency, respectively. In addition, patients with the blood homocysteine level > 12.1 µM (which was the mean serum homocysteine level of healthy control subjects plus two standard deviations) were defined as having hyperhomocysteinemia.\(^1\) By the above-mentioned definitions, 13.4%, 1.8%, 18.8%, 28.1%, 4.0%, 3.6%, 7.1%, and 21.0% of 224 younger AG patients and 5.8%, 4.4%, 19.0%, 13.9%, 5.6%, 1.9%, 13.2%, and 28.2% of 840 older AG patients were diagnosed as having microcytosis, macrocytosis, blood Hb and serum iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum GPCA positivity, respectively (Table 2). Moreover, 224 younger AG patients had significantly higher frequencies of microcytosis, blood Hb and serum iron deficiencies, hyperhomocysteinemia, and serum GPCA positivity than 112 younger HCSs (all P-values < 0.05, Table 2). Furthermore, 840 older AG patients had significantly higher frequencies of microcytosis, macrocytosis, blood Hb and serum iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum

| Group                  | MCV (fl) | Hb (g/dL) | Iron (µg/dL) | Vitamin B12 (pg/mL) | Follic acid (ng/mL) | Homocysteine (µM) |
|------------------------|----------|-----------|--------------|---------------------|---------------------|-------------------|
| Younger AG patients (n = 224) | 87.3 ± 9.0 | 13.1 ± 1.9 | 85.0 ± 39.8 | 628.4 ± 258.3 | 13.2 ± 6.3 | 8.3 ± 7.6 |
| P-value                 | 0.003 | <0.001   | <0.001       | 0.964              | 0.886              | 0.171              |
| Younger AG patients (n = 840) | 90.7 ± 7.5 | 13.1 ± 1.3 | 89.3 ± 28.9 | 702.0 ± 280.9 | 15.6 ± 6.6 | 9.7 ± 10.2 |
| P-value                 | <0.001 | <0.001   | <0.001       | 0.348              | 0.598              | 0.005              |
| Younger HCSSs (n = 112)  | 89.9 ± 3.4 | 13.8 ± 0.9 | 104.0 ± 31.3 | 627.1 ± 217.7 | 13.1 ± 5.5 | 7.3 ± 1.8 |
| Older HCSSs (n = 420)   | 90.6 ± 3.6 | 13.8 ± 0.9 | 98.1 ± 26.6 | 716.8 ± 224.8 | 15.4 ± 5.8 | 8.3 ± 2.1 |

a. Comparisons of means of parameters between 224 younger or 840 older AG patients and 112 younger or 420 older HCSs by Student’s t-test, respectively.
b. Comparisons of means of parameters between 224 younger and 840 older AG patients by Student’s t-test.
Comparisons of frequencies of parameters between 224 younger or 840 older AG patients and 112 younger or 420 older HCSs by chi-square test, respectively.

Comparisons of frequencies of parameters between 224 younger and 840 older AG patients by chi-square test.

### Table 2

| Group                        | Patient number (%) | Iron deficiency (%) | Folic acid deficiency (%) | Hyperhomocysteinemia (%) |
|------------------------------|-------------------|---------------------|--------------------------|--------------------------|
| **Younger AG patients (n = 224)** |                   |                     |                          |                          |
| Iron deficiency              | 13 (5.8)          | 0.001               | <0.001                   | <0.001                   |
| Folic acid deficiency        | 9 (4.0)           | 0.100               | 0.073                    | 0.001                    |
| Hyperhomocysteinemia         | 17 (7.6)          | 0.001               | <0.001                   | 0.001                    |
| **Older AG patients (n = 840)** |                   |                     |                          |                          |
| Iron deficiency              | 49 (5.8)          | 0.001               | <0.001                   | <0.001                   |
| Folic acid deficiency        | 44 (5.3)          | 0.001               | 0.001                    | 0.001                    |
| Hyperhomocysteinemia         | 60 (7.1)          | 0.001               | <0.001                   | 0.001                    |
| **Younger HCSs (n = 112)**   |                   |                     |                          |                          |
| Iron deficiency              | 0 (0.0)           | 0.001               | <0.001                   | <0.001                   |
| Folic acid deficiency        | 0 (0.0)           | 0.001               | 0.001                    | 0.001                    |
| Hyperhomocysteinemia         | 2 (1.8)           | 0.001               | <0.001                   | 0.001                    |
| **Older HCSs (n = 420)**     |                   |                     |                          |                          |
| Iron deficiency              | 19 (4.5)          | 0.001               | <0.001                   | <0.001                   |
| Folic acid deficiency        | 0 (0.0)           | 0.001               | 0.001                    | 0.001                    |
| Hyperhomocysteinemia         | 12 (2.9)          | 0.001               | <0.001                   | 0.001                    |

**Discussion**

This study found that the younger AG patients had significantly lower mean blood vitamin B12 and folic acid levels, a lower mean serum homocysteine level (marginal significance, \( P = 0.056 \)), a significantly higher frequency of serum iron deficiency, a significantly lower frequencies of hyperhomocysteinemia and serum GPCA positivity than the older AG patients. To explain why we had these findings, first, we had to understand the composition of our two groups of AG patients. The younger (\( \leq 50 \) years old) AG patients consisted of 42 men and 182 women, with a male to female ratio of approximately 1:4.3 and a mean age of 44.0 years. Thus, the majority of our male, younger AG patients might have sufficient total body androgen levels, and the majority of our female, younger AG patients might still have menstrual cycles and enough total body estrogen levels. The older (\( > 50 \) years old) AG patients was composed of 108 men and 732 women, with a male to female ratio of approximately 1:6.8 and a mean age of 67.6 years. Thus, our male, older AG patients might have slightly
decreased total body androgen level and nearly all the female, older AG patients might be in the menopause status and had a reduced total body estrogen level. It is well known that androgens can stimulate erythropoiesis and increase levels of red blood cells (RBCs) and Hb through the mechanisms of stimulation of erythropoietin release, increase in bone marrow activity, and augmentation of iron incorporation into the RBCs. However, estrogens do not have this erythropoiesis-enhancement effect and even have a striking negative effect on the erythropoiesis, especially in patients with chronic mountain sickness (Monge’s disease). In menopause women, total body estrogen level decreases because of the cessation of ovarian functions and iron increases as a result of cease of menstrual blood loss. Nevertheless, estrogen deficiency up-regulates hepcidin, which inhibits intestinal iron absorption, leading to lower serum iron levels. In general, each healthy pregnancy depletes the mother of approximately 500 mg of iron. Menstrual blood losses are highly variable, ranging from 10 to 250 mL (4–100 mg of iron) per period. During childbearing years, an adult female loses an average of 2 mg of iron daily. However, in the postmenopausal women, iron deficiency is uncommon in the absence of menstrual bleeding. Furthermore, because women eat less food than men, they must be more than twice as efficient as men in the absorption of iron to avoid iron deficiency. Therefore, anemia is twice as prevalent in females as in males. This difference is significantly greater during the childbearing years due to pregnancies and menses. In this study, men constituted approximately one-fifth of younger AG patients and approximately one-eighth of older AG patients, suggesting that the androgen factor may play a more important role in the group of our younger AG patients than in the group of our older AG patients. On the contrary, menopausal women constituted seven-eighths of our older AG patients, indicating that the menopause is a relevant factor influencing the blood Hb and serum iron levels in the group of our older AG patients. Moreover, younger women consisted of four-fifths of our younger AG patients, indicating pregnancies and menses are two important factors influencing the blood Hb and serum iron levels in the group of our younger AG patients. Taken the above-mentioned evidences together, for the younger AG patients, the active total body physiological function and relatively high total body androgen level are positive factors that increase the blood Hb and serum iron levels, but the repeated menstrual blood losses and one or more times of pregnancy are negative factors that decrease the blood Hb and serum iron levels. Moreover, for the older AG patients, the menopause is the positive factor that enhances the blood Hb and serum iron levels, whereas the slightly decrease total body physiological function and relatively low total body androgen level are negative factors that reduce the blood Hb and serum iron levels. Therefore, the overall effects of these positive and negative factors could finally explain why the younger AG patients had lower mean serum iron level and significantly higher frequency of serum iron deficiency than the older AG patients.

We further explained why the younger AG patients had the significantly lower mean serum vitamin B12 and folic acid levels and a non-significantly higher frequency of folic acid deficiency than the older AG patients. Previous studies discovered significantly lower mean folate levels in buccal mucosal cells and sera of 25 smokers than in those of 34 non-smokers. Pivathilake et al. also demonstrated lower buccal mucosal cell folate and vitamin B12 concentrations in 39 current smokers than in 60 noncurrent smokers. Our previous study of serum folic acid levels in oral precancer patients also found significantly lower mean serum folic acid levels in cigarette smokers or heavy smokers than in non-smokers, and in betel quid chewers than in non-chewers. The findings of above-mentioned studies indicate the existence of vitamin B12 and folic acid deficiencies in the sera and oral mucosal cells of the smokers and betel quid chewers. We suggest that the mechanisms of vitamin B12 and folic acid deficiencies may result from elevated vitamin B12 and folic acid consumption in response to rapid cell proliferation or tissue repair caused by the irritation or damage of oral mucosal cells by the carcinogens in tobacco or betel quid. In this study, we did not assess the frequencies of cigarette smoking and betel quid chewing habits in our 224 younger and 840 older AG patients. However, in the Taiwan population, the males ≥18 years of age had a significantly higher prevalence of smoking habit.

### Table 3 Comparison of frequencies of 6 different types of anemia between 224 younger (<50 years old) and 840 older (>50 years old) atrophic glossitis (AG) patients.

| Anemia type                        | Younger AG patients (n = 224) | Older AG patients (n = 840) | P-value |
|-----------------------------------|-------------------------------|-----------------------------|---------|
| Pernicious anemia                 | 2 (0.9)                       | 20 (2.4)                    | 0.260   |
| Other macrocytic anemia           | 1 (0.4)                       | 7 (0.8)                     | 0.873   |
| Normocytic anemia                 | 15 (6.7)                      | 102 (12.1)                  | 0.028   |
| Iron deficiency anemia            | 22 (9.8)                      | 8 (1.0)                     | <0.001  |
| Thalassemia trait-induced anemia  | 2 (0.9)                       | 19 (2.3)                    | 0.299   |
| Other microcytic anemia           | 0 (0.0)                       | 4 (0.5)                     | 0.674   |
| Total                             | 42 (18.8)                     | 160 (19.0)                  | 0.996   |

* Comparison of frequencies of 6 different types of anemia between 224 younger and 840 older AG patients by chi-square test.
(23.1% for men and 2.9% for women) or betel quid chewing habit (16.8% for men and 1.2% for women) than the females ≥18 years of age.48 Because there is a significantly higher prevalence of smoking or betel quid chewing habit in men than in women in the Taiwan population as well as in younger people than in older people, we strongly suggest that the smoking or betel quid chewing habit may be the major factors that result in the lower mean serum vitamin B12 and folic acid levels and higher frequency of folic acid deficiency in the younger AG patients than in the older AG patients.13–48 In addition, although the younger people tend to have more active physiological function including relatively higher intestinal absorption rate and better regeneration and tissue repair functions, these younger AG patients should have more severe deficiencies of vitamin B12 and folic acid to express the symptoms of AG. Thus, it is not surprised to see the significantly lower mean serum vitamin B12 and folic acid levels and a significantly higher frequency of folic acid deficiency in the younger AG patients than in the older AG patients. Homocysteine is formed during methionine metabolism.49 Both vitamin B12 and folic acid function as co-enzymes for the conversion of homocysteine to methionine.50 Thus, patients with vitamin B12 and/or folic acid deficiencies may have hyperhomocysteinemia. A previous study has shown that a supplementation with folic acid and vitamins B12 and B6 can reduce blood homocysteine levels.51 Our previous studies also demonstrated that supplemetations with vitamin BC capsules plus corresponding deficient vitamin B12 and/or folic acid can reduce the abnormally high serum homocysteine level to significantly lower levels in patients with either AG or burning mouth syndrome.20,21 In this study, although significantly lower mean serum vitamin B12 and folic acid levels and a higher frequency of serum folic acid deficiency in the younger AG patients than in the older AG patients were found, there were a marginally significant lower mean serum homocysteine level and a significantly lower frequency of hyperhomocysteinemia in the younger AG patients than in the older AG patients. We suggest that these results may be also due to the relatively minor deviations of the mean serum vitamin B12 and folic acid levels of the younger or older AG patients from those of the younger or older HCSs, respectively (Table 1).

In this study, the younger AG patients had a significantly higher frequency of IDA (9.8%) than the older AG patients (1.0%, \( P < 0.001 \)). This could be due to the finding that the younger AG patients had a higher frequency of serum iron deficiency (28.1%) than the older AG patients (13.9%, \( P < 0.001 \)). On the contrary, the older AG patients had a significantly higher frequency of normocytic anemia (12.1%) than the younger AG patients (6.7%, \( P = 0.028 \)). We suggest that the significantly higher frequency of normocytic anemia in the older AG patients than in the younger AG patients may result from the relatively higher frequencies of chronic or inflammatory diseases in the older AG patients than in the younger AG patients.31–34

The results of this study conclude that the younger AG patients do have significantly lower mean serum vitamin B12 and folic acid levels, a significantly higher frequency of serum iron deficiency, and a significantly lower frequency of hyperhomocysteinemia than the older AG patients.

### Declaration of competing interest

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

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