INTRODUCTION

Fatigue is a commonly seen symptom in primary care. The prevalence of chronic fatigue lasting more than 6 months is 30%, and approximately half of these patients visit a primary care clinic [1]. Chronic fatigue is often caused by mood disorders and, therefore, the use of antidepressants and anxiolytic medications is 3 times higher in patients with chronic fatigue as compared to the general population [2]. Furthermore, depression in patients presenting at primary care sites can appear similar to other medical conditions such as chronic pain, fatigue, or gastrointestinal disorders rather than as classic depressive symptoms [3].

Micronutrient deficiency is also considered to be a cause of fatigue. These are involved in cell metabolism, including mitochondrial function. Mitochondrial dysfunction is a cause of the chronic fatigue syndrome [4,5]. A lack of minerals related to oxidative stress, such as magnesium (Mg), is associated with chronic fatigue [6]. Depression is also affected by nutritional status. Depressive patients have low vitamin and minerals intake [7]. Therefore, this study aimed to identify the association of micronutrients such as minerals with chronic fatigue and depression.

METHODS

A retrospective cross-sectional study was performed using the medical records of chronic fatigue patients aged 20–64 years old who visited the integrated medical center of a university hospital in Gyeongju, South Korea, from June 2013 to August 2016. All fatigue patients who visited the integrated medical center had a medical interview were taken laboratory tests and completed the Korean versions (K) of the fatigue severity scale, Beck depression inventory, and concentrations of mineral in hair samples.

The subjects were classified into three groups according to their fatigue and depression scores: 21 patients (21.6%) were free of fatigue and depression, 55 (56.8%) experienced fatigue without depression, and 21 (21.6%) experienced fatigue with depression. The potassium (K) concentration in hair significantly decreased in the groups of fatigue or fatigue with depression compared to the group with free of fatigue and depression (p=0.042). The trend of sodium (Na), K concentration, and Na/magnesium (Mg) ratios in hair gradually decreased with fatigue and depression (p for trends=0.027, 0.037, and 0.03).

Conclusion: The status of hair minerals in chronic fatigue and depressed women are associated with the concentrations of hair minerals, especially Na, K, and Na/Mg ratios.

Keywords: Fatigue, Depression, Sodium, Potassium, Hair.
statistics were used for adjusting age. Adjusted for age, partial correlation analysis was performed between concentrations of hair mineral and the score of FSS or BDI-K. The subjects were divided into three groups: Fatigue and depression free, fatigue without depression, and fatigue with depression. A general linear model adjusted for age was used to compare the differences in hair mineral density among these three groups. In addition, linear contrast analysis was used to analyze trends in mineral concentration among the three groups. Statistical analysis was performed using Statistics is a Software Package Version 20.0 Inc., TX, USA. Statistical significance was set at p<0.05.

RESULTS

The mean age of the subjects was 45.9±9.64 years (range: 20–64 years). The mean FSS score for all subjects was 4.39±1.55 (range: 1.0–7.67) and the mean BDI-K score was 16.12±9.86 (0–41). According to these scores, 76 (78.4%) of the 97 patients were fatigued and 21 (21.6%) were depressed. All depressed patients included the group of fatigue. When the subjects were classified into three groups according to fatigue and depression, 21 patients (21.6%) were free of both fatigue and depression, 55 (56.7%) had fatigue without depression, and 21 (21.6%) had fatigue with depression.

Table 1 shows negative correlations between the concentrations of hair Na, K, and the score of FSS. The Na/Mg ratio was also negatively correlated with the score of FSS. Other hair minerals correlated with the score of FSS. None of hair minerals correlated with the score of BDI-K.

The results of the comparison of the hair mineral content among the three groups showed that the Na, K concentrations, and Na/Mg ratios tended to be decreased with fatigue and depression. The hair K concentrations were significantly different 10.86±17.12 µg/g in the fatigue and depression-free group, 5.02±4.59 µg/g in the group of fatigue without depression, and 5.05±4.44 µg/g in the fatigue with depression group and tended to decrease with increasing fatigue and depression scores (p for trend 0.037). The Na concentration in hair was not significantly different among the three groups (18.07±29.76 µg/g, 11.74±11.56 µg/g, and 8.32±6.37 µg/g for the fatigue and depression free, fatigue without depression, and fatigue with depression groups, respectively; p=0.06) but showed a decreasing trend with increasing fatigue and depression scores (p=0.027 for trend). The Na/Mg ratios also tended to decrease with fatigue and depression at 4.93±1±0.71 µg/g, 1.96±3.20 µg/g, and 1.15±1.78 µg/g in the three groups (p=0.063 and p=0.03 for trend). The concentrations of Ca, Mg, Cu, Zn, and P in hair showed no association with fatigue and depression (Table 2).

DISCUSSION

About 70% of the general population believes that vitamin and mineral supplementation can help to maintain health, and some studies have reported that supplementation improves subjective stress, mild psychiatric symptoms, anxiety, and fatigue [15,16].

In this study, we found that the concentrations of Na and K in hair may be affected by fatigued and depressed women. The hair concentrations of Na and K tended to decrease with fatigue and depression. Na and K are important minerals involved in cell metabolism and blood pressure. The concentration of Na in tissue, not blood, decreased in psychological stress [17]. Increased sympathetic response by stress also leads to neural mediated hypotension as a cause of lightheadedness and chronic fatigue [18]. Both low Na concentrations in tissue and hypotension increase serum aldosterone level, which increased Na reabsorption in kidney and urinary K excretion. A deficiency of Na affects mood and depression in animal study, and low dietary salt intake is associated with depression in women [19,20].

The relationship between the concentration of K in tissue and fatigue and depression was also reported to have an inverse pattern [17]. A decrease in hair K concentration is caused by hyperaldosteronism [21]. Serum aldosterone level increases in the patients with early stage of depression but decreases in severe depression [22,23]. Decreased serum aldosterone concentrations of Na and K in hair may be related to increased aldosterone level and increased Na reabsorption in kidney and urinary K excretion.

Table 1: Partial correlation coefficients between hair minerals and scores of FSS and BDI-K in all subjects (n=97)

| Hair minerals | FSS scores | BDI-K scores |
|---------------|------------|--------------|
|               | R          | R            |
| Ca (µg/g)     | 0.000      | 0.108        |
| Mg (µg/g)     | -0.014     | 0.043        |
| Na (µg/g)     | -0.217*    | -0.089       |
| K (µg/g)      | -0.266*    | 0.006        |
| Cu (µg/g)     | -0.054     | -0.054       |
| Zn (µg/g)     | -0.019     | -0.019       |
| P (µg/g)      | -0.115     | -0.115       |
| Ca/P          | 0.046      | 0.118        |
| Na/K          | -0.021     | -0.076       |
| Ca/K          | 0.056      | 0.092        |
| Zn/Cu         | -0.013     | 0.026        |
| Na/Mg         | -0.216*    | -0.073       |
| Ca/Mg         | 0.021      | 0.071        |

Data expressed as partial correlation coefficient (r). *Significant values, p<0.05, using partial correlation analysis adjusted by age: FSS: Fatigue severity scale, BDI-K: Beck depression inventory-Korean version, Calcium (Ca), Magnesium (Mg), Sodium (Na), Potassium (K), Copper (Cu), Zinc (Zn), Phosphate (P).

Table 2: Comparison of hair mineral concentrations among three patient groups with and without fatigue and depression

| Hair minerals | Fatigue (-) depression (-) | Fatigue (+) depression (+) | Fatigue (+) depression (+) |
|---------------|----------------------------|-----------------------------|-----------------------------|
|               | n=21                       | n=55                        | n=21                        |
| Ca (µg/g)     | 130.24±4.60                | 124.55±78.62                | 165.10±4.59                 |
| Mg (µg/g)     | 9.32±5.96                  | 9.2±4.74                    | 11.4±5.58                   |
| Na (µg/g)     | 20.76±35.27                | 11.1±10.82                  | 8.0±6.34                    |
| K (µg/g)      | 10.86±17.12                | 5.02±4.59                   | 5.0±4.44                    |
| Cu (µg/g)     | 3.41±5.74                  | 2.86±4.21                   | 2.95±2.80                   |
| Zn (µg/g)     | 19.81±9.99                 | 18.6±10.02                  | 18.4±6.38                   |
| P (µg/g)      | 15.67±2.61                 | 14.4±2.28                   | 14.9±4.97                   |
| Ca/P          | 3.87±4.88                  | 8.6±2.55                    | 11.4±6.58                   |
| Ca/K          | 3.07±4.25                  | 3.59±6.93                   | 2.45±1.89                   |
| Zn/Cu         | 4.62±4.96                  | 62.9±83.66                  | 81.5±86.30                  |
| Na/Mg         | 4.9±10.71                  | 1.96±3.20                   | 1.15±1.79                   |
| Ca/Mg         | 14.94±3.94                 | 15.82±6.83                  | 15.6±4.49                   |

Data expressed as mean ± standard deviation, p value was calculated using a general linear model adjusted for age. p for trend was calculated by linear contrast analysis. Ca: Calcium, Mg: Magnesium, Na: Sodium, K: Potassium, Cu: Copper, Zn: Zinc, P: Phosphate.
causes a decrease in Na concentration in the body and reduces K excretion into the kidney.

Mg is the intracellular cation, a necessary cofactor of many enzymes and regulates the Na, K, and Cl cotransport systems [24]. Stress stimulates the adrenal gland to increase cortisol secretion. The increase in cortisol may facilitate cell metabolism, induce hypomagnesemia in the body, causing a decrease of cortisol secretion in the absence of adequate Mg supplements [25,26]. If chronic stress persists, this vicious cycle may result in functional insufficiency of the adrenal gland. In chronic stress or depression, the tissue concentration of cortisol decreases [27,28]. Hair Mg was inversely correlated with tissue cortisol level [29]. Therefore, the accumulation of Mg in tissues including hair may associate with the decline of cortisol. In this study, the hair Mg concentration increased with fatigue and depression, but this increasing tendency was not significant.

In summary, the hair minerals identified in the present study are thought to be associated with hormones of the adrenal gland, and further studies needed to confirm the mechanism of the association adrenal gland with chronic fatigue and depression. In addition, taking herbs such as Passiflora foetida, Bacopa monnieri, Dioscorea oppositifolia, or Alternanthera sessilis which are rich in Na and K can be considered to be an alternative treatment to improve the symptoms of chronic fatigue or depression [30,31].

There are several limitations to this study. First, the mineral state of hair may not reflect that of the whole body and individual information of dietary intake is not reflected in this study. Second, generalization of the results is limited because this was a single-center study and subjects were only the Korean women. Finally, causality cannot be explained by a cross-sectional study design. Nevertheless, the results of this study are meaningful in that fatigue is commonly observed problems in primary care.

CONCLUSION

Chronic fatigue and depression in women affect the concentrations of minerals in the hair, especially Na and K. As fatigue and depression progress, the hair Na and K concentrations tend to decrease.

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AUTHORS’ CONTRIBUTION

Jeong HS contributed to all the work of this article (conceived of this study, collected and analyzed the data, and drafted the manuscript).

CONFLICTS OF INTEREST

The author declare that they have no conflicts of interest.

REFERENCES

1. van’t Leven M, Zielhuis GA, van der Meer JW, Verbeek AL, Bleijenberg G. Fatigue and chronic fatigue syndrome-like complaints in the general population. Eur J Public Health 2010;20:251-7.
2. Manu P, Matthews DA, Lane TJ. The mental health of patients with a chief complaint of chronic fatigue. A prospective evaluation and follow-up. Arch Intern Med 1988;148:2213-7.
3. De Wester JN. Recognizing and treating the patient with somatic manifestations of depression. J Fam Pract 1996;43 Suppl:6-13.
4. Frei M, Born G. Magnesium: Nutrition and metabolism. Mol Aspects Med 2003;24:23-37.
5. Myhill S, Booth NE, McLaren-Howard J. Targeting mitochondrial dysfunction in the treatment of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)-a clinical audit. Int J Clin Exp Med 2013;6:1-15.
6. Manuel y Keenoy B, Moorkens G, Vertommen J, Noe M, Nève J, De Leeuw I, et al. Magnesium status and parameters of the oxidant-antioxidant balance in patients with chronic fatigue: Effects of supplementation with magnesium. J Am Coll Nutr 2000;19:374-82.
7. Kaner G, Soylu M, Yılmaz N, İnanç N, Ongan D, Başınmuşlu E, et al. Evaluation of nutritional status of patients with depression. Biomed Res Int 2015;2015:524818.
8. Klapp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 1989;46:1121-3.
9. Kim S, Bae WK, Kim JY, Jung M, Kim JH, Noh HH, et al. Validation of the Korean version of schedule of fatigue and anergia: General physician questionnaire. J Korean Med Sci 2016;31:159-63.
10. Chung KI, Song CH. Clinical usefulness of fatigue severity scale for patients with fatigue, and anxiety or depression. Korean J Psychosom Med 2001;9:164-73.
11. Lee EJ, Kim JB, Shin IH, Lim KH, Lee SH, Cho GA, et al. Current use of depression rating scales in mental health setting. Psychiatry Investig 2010;7:170-6.
12. Lee MK, Lee YH, Park SH, Sohn CH, Jung YJ, Hong SK, et al. A standardization study of beck depression inventory (I): Korean version (K-BDI): Reliability land factor analysis. Korean J Psychopathol 1995;4:77-95.
13. Trace Elements, Inc. Quality Assurance/Quality Control (QA/QC), Texas; 2018. Available from: http://www.traceelements.com/LabServices/QualityAssurance.aspx.
14. Hong SR, Lee SM, Lim NR, Chung WH, Ahn HS. Association between hair mineral and age, BMI and nutrient intakes among Korean female adults. Nutr Res Pract 2009;3:212-9.
15. Sekhri K, Kaur K. Public knowledge, use and attitude toward multivitamin supplementation: A cross-sectional study among general public. Int J Appl Basic Med Res 2014;4:77-80.
16. Long SJ, Benton D. Effects of vitamin and mineral supplementation on stress, mild psychiatric symptoms, and mood in nonclinical samples: A meta-analysis. Psychosom Med 2013;75:144-53.
17. Burton RF, Hinton JW, Neilson E, Beastall G. Concentrations of sodium, potassium and cortisol in saliva, and self-reported chronic work stress factors. Biol Psychol 1996;42:425-38.
18. Rowe PC, Boui-Holagah I, Kan JS, Calkins H. Is neurally mediated hypotension an unrecognised cause of chronic fatigue? Lancet 1995;345:623-4.
19. Grippo AJ, Moffitt JA, Beltz TG, Johnson AK. Reduced hedonic behavior and altered cardiovascular function induced by mild sodium depletion in rats. Behav Neurosci 2006;120:1133-43.
20. Goldstein P, Leshem M. Dietary sodium, added salt, and serum sodium associations with growth and depression in the U.S. general population. Appetite 2014;79:83-90.
21. Prejzner A, Warchol-Celinska E, Lenders JW, Januszewicz A. Cardiovascular risk in primary hyperaldosteronism. Horm Metab Res 2015;47:973-80.
22. Murck H, Held K, Ziegenbein M, Künzel H, Koch K, Steiger A. The renin-angiotensin-aldosterone system in patients with depression compared to controls—a sleep endocrine study. BMC Psychiatry 2003;3:15.
23. Hallberg L, Westrin A, Isaksso n A, Janelidze S, Träskman-Bendz L, Brundin L. Decreased aldosterone in the plasma of suicide attempters with major depressive disorder. Psychiatry Res 2010;187:135-9.
24. Flatman PW. Mechanism of magnesium transport. Annu Rev Physiol 1991;53:259-71.
25. Kurajoh M, Ohsugi K, Kakutani-Hatayama M, Shoji T, Koyama H. Hypokalemia associated with pseudo-Cushing’s syndrome and magnesium deficiency induced by chronic alcohol abuse. CEN Case Rep 2018;7:148-52.
26. Cinar V, Mogulkoc R, Baltaci AK, Polat Y. Adrenocorticotropic hormone and cortisol levels in athletes and sedentary subjects at rest and exercise: Effects of magnesium supplementation. Biol Trace Elem Res 2006;120:1133-43.
27. Prejzner A, Warchol-Celinska E, Lenders JW, Januszewicz A. Cardiovascular risk in primary hyperaldosteronism. Horm Metab Res 2015;47:973-80.
28. Chromik A, Miszczak RM, Rabinowska J, Górecka-Dolata E, Kowalska K. Changes in the renin-angiotensin-aldosterone system in patients with depression compared to controls—a sleep endocrine study. BMC Psychiatry 2013;74:1-6.
29. Hallberg L, Westrin A, Isakssson A, Janelidze S, Träskman-Bendz L, Brundin L. Decreased aldosterone in the plasma of suicide attempters with major depressive disorder. Psychiatry Res 2010;187:135-9.
30. Flatman PW. Mechanism of magnesium transport. Annu Rev Physiol 1991;53:259-71.
31. Kurajoh M, Ohsugi K, Kakutani-Hatayama M, Shoji T, Koyama H. Hypokalemia associated with pseudo-Cushing’s syndrome and magnesium deficiency induced by chronic alcohol abuse. CEN Case Rep 2018;7:148-52.
concentrations in hair of elementary school girls. Biol Trace Elem Res 2013;153:41-9.
30. Gogoi P, Kalita J.C. Mineral content of some edible medicinally important leafy vegetables of Kamrup district of Assam, India. Int J Pharm Pharm Sci 2014;6:404-6.
31. Prashanth Kumar GM, Chikkapaih L, Nagayya S. Nutritional analysis of edible wild plants used by Hakki Pikki tribes of Hassan district, Karnataka, India. Int J Pharm Pharm Sci 2016;8:390-3.