*Acta Pharm.* 54 (2004) 79–89

Original research paper

# Supplementation with antioxidants in the treatment of Graves' disease: the effect on the extracellular antioxidative parameters

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In this study, the effect of supplementation with a fixed combination of antioxidants (vitamins C and E, β-carotene and selenium) on concentrations of antioxidative parameters in serum was monitored. Measurements were performed prior to the commencement of therapy and after 30 and 60 days in patients with Graves' disease treated with methimazole. Patients who received extra supplementation with antioxidants (group A, $n$ = 29) attained euthyroidism faster than the patients treated only with methimazole (group B, $n$ = 28). Statistically significant differences were achieved after supplementation with antioxidants for all investigated parameters (uric acid, transferrin, ferritin), except TAS and glucose. Nevertheless, due to the fact that all measured parameters remained within the range of referent values, they may not be proposed as reliable indicators of the level of oxidative stress in Graves' disease.

*Keywords*: Graves' disease, antioxidants, ferritin, TAS, transferrin, urates

Received February 20, 2004
Accepted May 14, 2004

Graves' disease is a hypermetabolic state accompanied with an increase in the total consumption of oxygen, which results in increased formation of reactive oxygen species and other free radicals, or the occurrence of oxidative stress (1–4). Namely, in a small number of experimental clinical studies, the existence of oxidative stress in hyperthyroidism was confirmed by determining different parameters. Some investigators have studied changes in the parameters of oxidative defence in the thyroid gland tissue of patients with hyperthyroidism (5, 6). Treatment with propylthiouracil (PTU) for three months only partially resulted in balanced antioxidative activity, as compared to the

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control group (7). Komosinska-Vassev and coworkers (8) carried out an investigation into the activity of free radicals and antioxidative defence in patients with Graves' disease, during methimazole therapy. In untreated patients, an increase in lipid peroxidation and the activity of cellular antioxidative enzymes was detected in comparison with the control group, with simultaneous lowering of extracellular antioxidative parameters and total antioxidant status (TAS). Disturbed antioxidative defence indicates the possible usefulness of supplementation with antioxidants, aimed at preventing the occurrence of oxidatively damaged tissues in patients with Graves' disease.

An investigation on an experimental model of hyperthyroidism in animals demonstrated the useful effect of supplementation with vitamin E (9).

Clinical investigations of the effect of particular antioxidants in the treatment of Graves' disease are scarce and the results are partially contradictory. Seven and coworkers (10) examined the effect of supplementation with vitamin C on oxidative stress in hyperthyroid patients treated with PTU. The results show that additional application of vitamin C strengthens the antioxidative defence and consequently lowers the degree of oxidative stress. On the other hand, a study by Adali and coworkers (11) on the effect of PTU, propranolol and vitamin E on lipid peroxidation and antioxidative status in patients with hyperthyroidism failed to show any additional positive effect of vitamin E.

Investigations published to date on the effect of applying a combination of antioxidants in the treatment of Graves' disease provide encouraging results (12, 13). Results of these studies indicate the effectiveness of supplementation with antioxidants in the treatment of Graves' disease.

In the present study, we have attempted to evaluate the effect of supplementation with a fixed combination of antioxidants, available on the market, on some extracellular antioxidative parameters such as urates, transferrin, ferritin, glucose, and TAS, as an indicator of the total strengthening of the antioxidative defence of the organism. These antioxidants are supposed to have the ability to neutralise free radical action.

## EXPERIMENTAL

### *Subjects*

The study consisted of a group of 57 patients with newly detected Graves' disease from the Department of Nuclear Medicine and the Department of Endocrinology of the Dubrava University Hospital (Zagreb, Croatia).

The patients were randomly divided into two groups. Group A ($n$ = 29, 25 women and 4 men) took methimazole (Athyrazol, Jadran Galenski Laboratorij), 120 mg daily for the first weeks, 80 mg daily the second week, 60 mg daily the third and fourth week, 40 mg daily for the following four weeks, plus an additional daily capsule of a fixed combination of pharmacological antioxidants: 6 mg β-carotene, 200 mg C vitamin, 36 mg E vitamin and 60 μg Se (Symbion, Merck, Germany). Group B ($n$ = 28, 27 women and 1 man) took only methimazole, at the same doses as group A. More than 60% of the patients were aged 30 to 45 years.

The patients were examined prior to the commencement of therapy, after 30 and 60 days. Apart from a clinical examination of the patient, ultrasound of the thyroid gland was performed and a blood sample was taken. Graves' disease was diagnosed on the basis of the clinical status, ultrasound findings, reduced activity of the thyroid stimulating hormone (TSH) and increased concentration of the free fraction of $T_3$ and $T_4$ hormones, compared to referent values. Criteria for exclusion of patients from the study were the presence of other chronic and acute diseases, or conditions requiring application of other drugs or additional vitamins and minerals.

Questionnaires were completed with data on patients' age, sex, body mass and height, nutritive habits, smoking and previous health status.

None of the patients in either group had special nutritive habits such as avoidance of certain types of food for religious or other reasons, and none of the patients were vegetarians. None of the patients had previously suffered from any serious infections or other diseases.

Informed consent was obtained from all the participants in the study. The study protocol was approved by the Ethics Committee of the Dubrava University Hospital (Zagreb, Croatia) and was carried out in accordance with the ethical guidelines of the Helsinki Declaration.

### *Laboratory analysis*

Fasting samples of venous blood were collected between 8.00 and 10.00 A.M. for analyses of the free fraction of thyroid hormones ($FT_4$, $FT_3$), TSH, ferritin, transferrin, glucose, uric acid and TAS. Serum samples were stored in polyethylene Eppendorff test tubes at –20 °C until analysis.

Concentrations of $FT_4$ and $FT_3$ and TSH activity were determined by the chemiluminescence method on a Vitros Eci analyser (Ortho-Clinical Diagnostic, UK) using the test package (C1387000 for $FT_4$, C1315589 for $FT_3$, C1912997 for TSH) of the same manufacturer.

TAS was determined with Randox test kits (Randox, UK; TAS NX2332). The procedure precision and accuracy were controlled using the respective control specimens of the same manufacturer: Randox Total Antioxidant Control (Cat.No.NX 2331). All parameters were determined on an Olympus AU500 analyser (Olympus Co., Japan), with test kits of the same manufacturer.

### *Statistical analysis*

Significance of the changes in the selected parameters was tested within each group: prior to the commencement and on the 30th and 60th day after the commencement of therapy, and between each measurement of both examined groups. Significance of the difference between the results was determined by means of the Friedman ANOVA nonparametric analysis of variance for independent samples, Wilcoxon's nonparametric test for dependent samples (within groups A and B), and Mann-Whitney's nonparametric test for independent samples (between groups A and B).

## RESULTS AND DISCUSSION

The degree of cell damage in Graves' disease is in direct correlation with the level of oxidative stress, which depends on the efficacy of the applied therapy and the capacity of the antioxidant defence of the organism. A speedy recovery is important for all patients, particularly in some categories, such as pregnancy and cardiomyopathy. In this context, the role of the free radical scavengers can be extremely important.

### *Uric acid*

The concentration of uric acid in serum was within the wide range of referent values (90–420 μmol $L^{-1}$) during the treatment, but it decreased significantly in both groups of patients (group A: $p < 0.05$, group B: $p < 0.01$). A statistically significant difference was found between the groups 60 days after the commencement of therapy ($p < 0.05$) (Fig. 1).

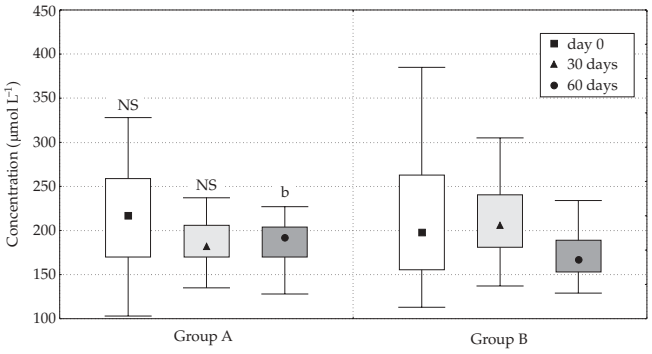


Fig. 1. Concentration of uric acid in serum (median box: 25–75%, bars: min – max). Statistical significance of the difference between the groups at the same time points: NS – not significant, b – $p < 0.05$.

Uric acid acts as an extracellular antioxidant because of its ability to remove singlet oxygen, hydroxyl and peroxyl radical. Sato *et al.* (14) registered this phenomenon of an increased level of uric acid in the serum of patients with untreated Graves' disease. In a group of 92 patients with Graves' disease, an increased concentration of uric acid in serum was determined, which correlated well with the concentration of thyroid hormones. The concentration of uric acid decreased with treatment and was in positive correlation with the clearance of uric acid and increased blood flow through the kidneys. The ratio of uric acid clearance and glomerular filtration was within the range of referent values and similar to the ratio in the control group of healthy subjects. The concentration of uric acid in the serum of patients with hypothyroidism was lower compared to the control group and increased with treatment, within the same study. Raised concentration of uric acid may be a consequence (if nutritional factor is ruled out) of increased purine synthesis, on the one hand, or increased degradation of puric nucleotides or decreased secretion on the other.

In our study, we were able to rule out decreased secretion as the reason for the increased concentration of uric acid in the serum prior to the commencement of therapy. Thus, we considered the effect of the state of intensified metabolism and catabolism,

such as in Graves' disease, on the concentration of uric acid. However, the question can also be raised as to whether the increased concentration of uric acid in hyperthyroidism is a consequence of the response of the organism to oxidation stress and mobilisation of protective antioxidative mechanisms, or not. It is interesting to note that the oxidation activity of uric acid, with respect to function, is identical to the activity of ascorbic acid. The biosynthesis of ascorbic acid is extinguished in man and higher primates, parallel with gene expression for uricase. This evolutionary phenomenon has been explained by the following provocative hypothesis. Effective synthesis and maintenance of a high concentration of uric acid, which is energetically more rational than ascorbate biosynthesis, is an essential precondition for successful protection from the harmful action of free radicals of several types. Humans and higher primates are cumulatively most exposed, not only because of the aerobic metabolism but also because of the life span (15). According to this hypothesis, an increased concentration of uric acid in serum would be the response of the organism to oxidation stress. Thus, this would explain the significant decrease in the concentration of uric acid during treatment of patients in both groups in the present study. After 60 days of therapy, the concentration of uric acid in group B was significantly lower compared to group A, which points to the effect of supplementation with antioxidants. This phenomenon may perhaps be explained by the effect of the rate of »consumption« of uric acid on neutralisation of free radicals in the serum of patients in whom there were no free radical scavengers. We consider that further study is necessary to better understand the above complex phenomenon.

## *Transferrin and ferritin*

During the treatment, the concentration of transferrin in serum was within the range of the referent values (2.0–3.8 g $L^{-1}$) but increased significantly in both groups of patients ($p < 0.01$). A statistically significant difference was also found between groups A and B 60 days after the commencement of therapy ($p < 0.05$) (Fig. 2).

In contrast, concentration of ferritin in serum (referent values 10–300 ng $mL^{-1}$) decreased significantly in both groups ($p < 0.001$) during the treatment, and a statistically significant difference between the groups was observed 60 days after the commencement of therapy ($p < 0.001$) (Fig. 3).

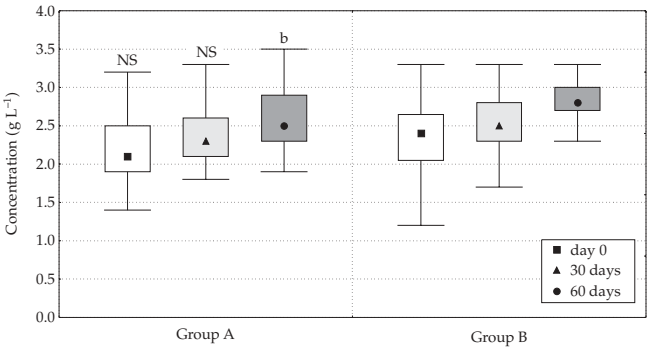


Fig. 2. Concentration of transferrin in serum (median box: 25–75%, bars: min – max). Statistical significance of the difference between the groups at the same time points: NS – not significant, b – $p < 0.05$.

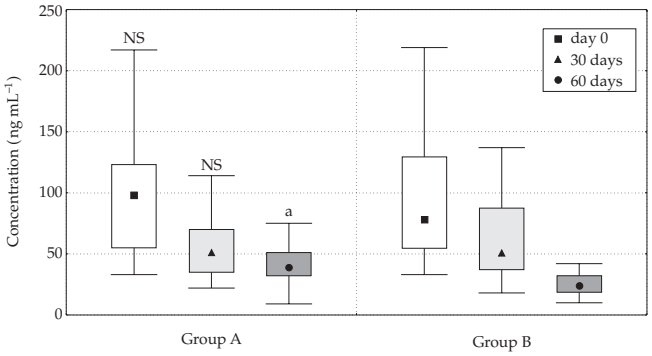


Fig. 3. Concentration of ferritin in serum (median box: 25–75%, bars: min – max). Statistical significance of the difference between the groups at the same time points: NS – not significant, a – $p < 0.001$.

Transferrin and ferritin have antioxidative characteristics due to their ability to bind iron. Iron, along with copper, is the most important transfer metal, which participates in the reactions between oxidants and antioxidants. In Fenton's reaction, $Fe^{2+}$ and $Cu^{+}$ change to a higher oxidative state, when the exceptionally reactive hydroxyl radical develops from hydrogen peroxide. Hydroxyl radical also develops from superoxide radical and hydrogen peroxide, with free ions of $Fe^{2+}$ and $Cu^{+}$ in the Haber-Weiss reaction. Hydroxyl radicals can further induce lipid peroxidation and thus cause changes in the nucleal and cytoplasmic membrane. Consequently, the mechanisms that control and reduce the catalytic ability of these metals are important. The amounts of free ions of iron and copper are minimal, while the remainder is bound to proteins, transferrin, ferritin and ceruloplasmin.

Transferrin is the most important protein for the transfer of iron in the organism. In normal human plasma, only 20–30% of transferrin is saturated with iron, and consequently plasma almost completely lacks free iron. Bound iron cannot take part in the reactions during the formation of the highly reactive hydroxyl radical. Ferritin is a protein for the storage of iron in cytosol. It can bind up to 4500 iron ions per molecule. Iron enters ferritin as $Fe^{2+}$ and deposits as $Fe^{3+}$ and hence it has a protective role in cytosol.

The raised concentration of ferritin in serum, which decreases with treatment, has been described in several studies concerning hyperthyroidism (16, 17). This increase in the level of ferritin in serum can be explained by the response of the organism to oxidative stress. As the level of oxidative stress decreases with the treatment, the level of ferritin also drops. In this respect, it should not be forgotten that ferritin in serum has no longer an antioxidative effect. Some authors suggest that the raised level of ferritin in the serum of patients with hyperthyroidism is a result of the direct action of the thyroid hormones themselves on its synthesis (16, 17). This mechanism may also explain the raised level of ferritin in serum before treatment and its decrease during treatment, as recorded in our patients. The significant difference in the ferritin concentration between groups A and B, 60 days after the commencement of therapy, indicates the possible additional effect of antioxidants. The lower level of ferritin in the serum of patients in group B, who did not receive antioxidants, can be explained by the faster »consumption« of ferritin in the cells. Possibly, the lack of supplementation with pharmacological antioxidants was one of the reasons for the significant increase in the level of transferrin

in the serum of patients in group B, as a result of a compensatory mechanism. We are inclined to believe that the described changes in transferrin and ferritin cannot be explained merely in the context of oxidative stress and antioxidative defence, but rather in terms of the general development of hyperthyroidism and its consequence on the organism.

## *Glucose*

In both groups of patients, the concentration of glucose in serum was within the range of referent values (3.6–5.5 mmol $L^{-1}$). It did not change significantly either within each group or between the groups during the therapy (Fig. 4).

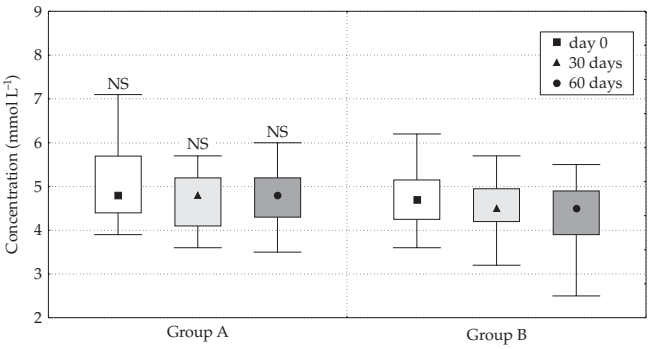


Fig. 4. Concentration of glucose in serum (median box: 25–75%, bars: min – max). NS – not significant differences between the groups at the same time points.

Theoretically, glucose can act as an antioxidant because of its ability to bind free ions of iron and copper and remove the hydroxyl radical (18). However, the results of our study did not show any significant changes. We can therefore conclude that the concentration of glucose cannot be used as a sufficiently sensitive indicator of antioxidative defence in a clinical examination of this type.

## *TAS*

During the treatment, the concentration of TAS in serum (referent value 1.5 mmol $L^{-1}$) increased significantly in both groups (group A: $p < 0.05$, group B: $p < 0.01$); no statistically significant difference was found between the groups (Fig. 5). Similar results were obtained in a few studies that investigated this indicator in Graves' disease. In the investigation done by Komosinske-Vassev (8), a higher concentration of TAS was found in the serum of patients with Graves' disease after therapy with methimazol and attainment of euthyreosis, compared to the state prior to the commencement of treatment. However, the concentration of TAS in euthyreotic patients under therapy, compared to the values of TAS in subjects in the control (healthy) group, was still lower. This lower level of extra-cellular total antioxidation potential in untreated patients indicated the level of oxidation stress, which was higher prior to the commencement of therapy. The existence of differences in the level of TAS in the serum of euthyreotic patients compared to healthy subjects may indicate the relative slowness in the rate of the change of this in-

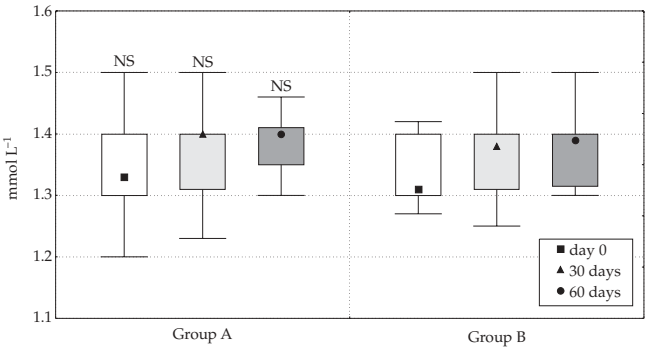


Fig. 5. Concentration of TAS in serum (median box: 25–75%, bars: min – max). NS – not significant difference between the groups at the same time points.

dicator. A certain slowness and also the fact that thiol groups of albumins contribute most to TAS may be the reason for the non-existence of significant differences in the TAS values between our groups of patients.

## *Thyroid hormones and TSH*

Concentration of $FT_4$ in serum, which was above the upper limit of referent values (10.0–28.2 pmol $L^{-1}$) prior to commencement of treatment, gradually decreased in both groups of subjects. In both groups, we observed, a statistically significant decrease in the concentration of hormone $FT_4$ in serum during the study ($p < 0.001$). A statistically significant difference between the groups was observed 30 ($p < 0.001$) and 60 days ($p < 0.005$) after the commencement of therapy (Table I).

During the treatment, the concentration of $FT_3$ hormone in serum, which was above the upper limit of referent values (4.7–8.0 pmol $L^{-1}$) prior to the commencement of treatment, decreased in both groups. Statistically significant differences ($p < 0.001$) were found within each group. However, a statistically significant difference between the groups was evaluated only after 30 days ($p < 0.001$) (Table I).

*Table I. Concentrations of $FT_4$, $FT_3$ and activity of TSH in serum*[a]

| Parameter | $FT_4$ (pmol $L^{-1}$) | | $FT_3$ (pmol $L^{-1}$) | | TSH (mU $L^{-1}$) | |
|---|---|---|---|---|---|---|
| Group | A | B | A | B | A | B |
| 0 day | 41.4 (16.6–90.0)$^{NS}$ | 46.8 (31.4–82.3) | 21.0 (8.0–47.8)$^{NS}$ | 24.8 (11.3–37.0) | 0.00 (0.00–0.04)$^{NS}$ | 0.00 (0.00–0.00) |
| 30 days | 15.9 (8.4–27.4)$^{b}$ | 25.25 (8.6–41.7) | 7.9 (3.1–14.9)$^{b}$ | 11.5 (4.0–20.7) | 0.00 (0.00–0.45)$^{NS}$ | 0.00 (0.00–1.56) |
| 60 days | 9.6 (4.0–18.3)$^{c}$ | 13.6 (6.0–40.8) | 6.3 (3.6–13.5)$^{NS}$ | 6.4 (4.0–12.3) | 0.00 (0.00–4.10)$^{d}$ | 0.00 (0.00–1.20) |

Absolute values are expressed as the median (min–max). Statistical significance of the difference between the groups at the same time point: $^{b}$ $p < 0.001$; $^{c}$ $p < 0.01$; $^{d}$ $p < 0.05$; $^{NS}$ not significant.
[a] For more information see reference 13.

During the study, a statistically significant increase in TSH activity (referent values 0.47–4.68 mU $L^{-1}$) was determined only in group A ($p < 0.001$). Comparison of the groups shows that a statistically significant difference was observed only 60 days after the commencement of therapy ($p < 0.05$) (Table I).

Based on the results obtained it can be concluded that patients in group A, who received additional therapy with pharmacological antioxidants, exhibited a significantly different decrease of $FT_4$ and $FT_3$ concentration and a significant increase of TSH activity in serum, and thus attained euthyroidism more rapidly, compared to patients in group B. The statistically significant difference between groups A and B with regard to the speed of attaining euthyroidism indicates the favourable effect of additional therapy with pharmacological antioxidants, vitamin E, vitamin C, β-carotene and selenium.

Pharmacological antioxidants may affect the peripheral conversion of thyroid hormones by way of deiodination and/or mechanism of cell membrane defence, the integrity of which can have an effect on the activity of deiodinases (19, 20).

## CONCLUSIONS

Application of the fixed combination of antioxidants accelerated normalisation of the thyroid hormone values and thus shortened the period of exposure of the organism to oxidation stress. There was no significant change in the concentration of glucose in serum in either group during the treatment, although theoretically glucose could be a useful natural antioxidant. The concentration of TAS in serum significantly increased during the treatment, though there was no significant difference between the groups, and thus it cannot be considered a sufficiently sensitive indicator of the level of oxidative stress. Although the concentrations of uric acid, transferrin and ferritin significantly differed between the groups during the treatment, they cannot be considered sufficiently reliable indicators of extracellular non-enzymatic antioxidative defence of the organism, either for several reasons: the wide range of referent values (uric acid), the fact that the measured values, though significantly changed during treatment, were within the physiological ranges, and the fact that their primary role in the organism is not antioxidative defence. Further targeted investigations in this respect are needed in order to clarify the nature of the described changes.

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*S A Ž E T A K*

## Suplementacija s antioksidansima u terapiji Graves-ove bolesti: učinak na ekstracelularne antioksidativne parametre

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U ovom istraživanju promatran je učinak suplementacije fiksnom kombinacijom antioksidansa (vitamini C i E, β-karoten i selen) na koncentracije pokazatelja antioksidacijske obrane u serumu. Mjerenja su obavljena u bolesnika s Graves-ovom bolešću liječenih metimazolom (tiamazolom) prije početka terapije, te nakon 30 i 60 dana. Bolesnici, koji su uz metimazol imali i dodatnu terapiju s antioksidansima (skupina A, $n$ = 29), postizali su eutireozu brže od bolesnika koji su bili samo na terapiji metimazolom (skupina B, $n$ = 28). Koncentracije svih mjerenih parametara (urata, feritina i transferina), (osim koncentracije TAS-a i glukoze), značajno su se razlikovale među skupinama. Unatoč tomu, rezultati ove studije ukazuju na to kako se određivani parametri ne mogu smatrati dovoljno pouzdanim pokazateljima razine oksidacijskog stresa u Graves-ovoj bolesti, radi činjenice da su njihove koncentracije tijekom ispitivanja ostale unutar granica referentnih vrijednosti.

*Ključne riječi*: Graves-ova bolest, antioksidansi, feritin, TAS, transferin, urati

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