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Blood and Urine Iodine Levels in Patients with Gastric Cancer

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ABSTRACT

In this study, we aimed to investigate whether there is any relationship between gastric cancer and iodine concentrations in blood and urine in the northeast Anatolia region, where iodine deficiency is common. A total of 56 patients, diagnosed as gastric cancer and 25 healthy volunteers were included in the study. The methods used were based on the Sandell–Kolthoff reaction. The urine iodine concentration (UIC) and serum protein-bound iodine (PBI) levels were higher in patients with gastric cancer compared with healthy control subjects. The UIC in stage IV was higher than all other stages and the control group. The UIC was higher in stages III and IV compared with stages I and II. However, serum PBI levels in stage III were higher compared with stages I and II and also control group. The serum PBI level in stage IV was higher than stage II and the control group. In the patient and control groups, there were no significant differences in serum PBI and UIC with regard to age or sex. Our results suggested that urinary and blood iodine concentration might be a useful marker for following the disease.

Index Entries: Gastric cancer; iodine; serum protein-bound iodine; urine iodine.

INTRODUCTION

Iodine is an essential nutrient for the normal growth and development of humans and animals and it is necessary for normal metabolism

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and regulation of thyroid hormones *(1).* The body contains about 25 mg of iodine. A small percentage of this is in the muscles, 20% is in the thyroid gland, and the rest is in the skin and bones. Only 1% is present in the blood. Iodine is well absorbed from the stomach into the blood. About 30% goes to the thyroid gland depending on the need. Iodine is eliminated rapidly. Most of the remaining iodine (70%) is filtered by the kidneys into the urine *(2).* Recommendations by the International Council for the Control of Iodine Deficiency Disorders, WHO, and UNICEF *(3)* set the minimal urinary iodine concentration (UIC) for iodine sufficiency as 100 μg/L; this figure corresponds roughly to a daily intake of 150 μg iodine.

Gastric cancer, the second most common cancer in the world, kills about 1 million people every year *(4).*

The human stomach, breast and thyroid share an important iodide-concentrating ability *(5).* Venturi et al. *(6)* have hypothesized that in relation to the functional role of inorganic iodine in the metabolism of algal and animal cells, iodide might have a phylogenetic and evolutionary ancient antioxidant role in extrathyroidal iodine-concentrating cells. This hypothesis of the antioxidant role of iodine is experimentally confirmed in algae *(7).* Iodide might act as an electron donor in the presence of H_2O_2 and peroxidase, and the remaining iodine readily iodinates the tyrosine (and, more slowly, the histidine or proteins and lipids), and so, it neutralizes its own high oxidant power in algae *(8).* Iodide can also act as antioxidant in vitro. Winkler et al. *(9)* have shown that the addition of NaI (15 μ*M*) increased the human serum total antioxidant status.

In early studies, Spencer *(10)* and Eskin *(11,12)* have found a correlation among goiter, iodine, and cancer. Venturi et al. *(6)* have recently found such a correlation with gastric cancer. Kandemir et al. *(13)* have shown that there is a significant association between gastric cancer and thyroid disorders. They hypothesized that iodine deficiency or, in some cases, iodine excess is associated with the development of gastric cancer *(6).* The fact that ^{131}I can cause gastric cancer in the first generation of exposed pregnant rats confirms indirectly its action at the stomach level *(14).* In gastric cancer, Wang et al. *(15)* recently reported alterations of the thyroid hormone receptor-α (TH-R-α) gene and an association with Nm23 protein expression. Li et al. *(16)* reported that the observation of frequent mechanisms of TH-R-β-1 inactivation suggests a potential role for this gene in the suppression of nonthyroidal primary tumors in early-stage cancer and that TH-R genes (c-erbA, or TR) have been implicated as tumor-suppressor genes of gastric cancer. Two subtypes of TR genes (TR-α and TR-β) are altered in human gastric cancer *(16).*

Endemic goiter has been shown to have a prevalence in Turkey *(17).* The prevalence of goiter has been reported to be 5.6% in Erzurum, a city in northeastern Anatolia. The frequency of people with urinary iodine concentration lower than 5 μg/dL was 37.6% *(18),* which shows that this region is an endemic region in terms of iodine deficiency. In our region, where goiter is common *(18),* deaths as a result of gastric cancer are high

Table 1
Age, Height, and Body Weight of Patients
with Gastric Cancer and Subjects in the Control Group

	n	Age (year)	Height (cm)	Body weight (kg)
Patients with	56	59.4 ± 10.9	165.2 ± 8.3	60.9 ± 9.9
gastric cancer		(23-77)	(150.0 –1 83.0)	(43-85)
Control group	25	50.7 ± 9.8	163.9 ± 9.8	64.2 ± 10.4
		(25-62)	(152.0-178.0)	(50-90)

Note: Values are given as means ± SD, min.–max.

(19). Iodine deficiency, which is common in Erzurum *(20),* leads to goiter *(18).* In endemic goiter nations, the gastric cancer mortality is generally higher than in nonendemic countries *(21).*

In our previous study, we have found lower tissue iodine levels in gastric cancer tissue compared with surrounding normal tissue *(22).* Because there is no study reporting iodine levels in urine and blood in patients with gastric cancer, we report the iodine levels in urine and blood of these patients to search for a possible relationship with gastric cancer in this study.

PATIENTS AND METHODS

Patients

A total of 56 patients (34 males and 22 females ranging in age between 23 and 77 yr: average: 59.4 yr) were diagnosed as gastric cancer in the Surgery Clinics of Medical Faculty of Atatürk University and 25 healthy volunteers (10 males and 15 females, ranging in age between 25 and 62 yr; average: 50.7 yr) were included in the study after giving their informed consent. The study was performed in accordance with the ethical standards in the Declaration of Helsinki. Pathological diagnosis of gastric cancer was adenocarcinoma. All patients were studied prior to treatment. The patients were classified according to the TNM (tumor, node, metastasis) staging *(23).* The age, height, and body weight of patients with gastric cancer and subjects in the control group are given in Table 1. The localizations of the gastric cancers were as follows: 18 in the antral region, 16 on small and large curvatures, 14 in the fundus, and 8 in the pyloric region of the stomach. Of these patients with gastric cancer, 13 had a nodular goiter. All of them were euthyroid: T_3: 1.19 ± 0.38 μg/dL; T_4: 9.57 ± 2.76 μg/dL; TSH:

0.64 ± 0.35 μIU/mL; FT_3: 2.61 ± 0.56 pg/mL; FT_4: 1.55 ± 0.37 ng/dL. The others were also euthyroid (T_3: 0.66 ± 0.49 μg/dL; T_4: 7.14 ± 0.32 μg/dL; TSH: 1.38 ± 0.15 μIU/mL; FT_3: 1.74 ± 0.96 pg/mL; FT_4: 0.9 ± 0.02). Normal ranges of the laboratory were as follows: T_3: 0.8–2 μg/dL; T_4: 5.1–14.1 μg/dL; TSH: 0.27–4.2 μIU/mL; FT_3: 1.8–4.6 pg/mL; FT_4: 0.93–1.7 ng/dL. The control group had normal thyroid fonctions (data not shown).

Urinary Iodine

It is reported that there was no significant difference in the concentration between the 24-h urine sample and the morning spot urine sample *(24).* Therefore, morning spot urine samples were used to determine UIC. Urine samples, collected as 5 mL urine plus 2 drops of glacial HCl acid, were stored at 4°C and studied once a week. The UIC was determined using the Sandell–Kolthoff reaction *(25).* Urine was first digested with chloric acid in a heating block and iodine was determined from its catalytic reduction of ceric ammonium sulfate in the presence of arsenious acid *(25).*

Serum Iodine

Blood samples were collected after an overnight fast (12–24 h) into tubes before any treatment modality such as chemotherapy and surgery was applied to the patients. The blood samples were centrifuged, and serum samples were obtained and stored at –80°C until analysis. The alkaline incineration procedure consists of precipitating the serum proteins and determining the iodine in the precipitate after incineration of the latter with alkali hydroxide or carbonate *(26).* Iodine was determined in blood samples using the Sandell–Kolthoff reaction *(26).*

Statistical Analysis

The unpaired *t*-test was used to compare the group means of the patients with the control group. One-way analysis of variance (ANOVA) with post hoc least significant difference (LSD) test was used to compare the group means of patients with different stages of gastric cancer.

RESULTS

The UIC was signifantly increased in patients with gastric cancer compared with healthy control subjects (Fig. 1). In addition, serum protein-bound iodine (PBI) levels were also higher in patients with gastric cancer compared with healthy control subjects (Fig. 1).

The patients with gastric cancer were divided into stages according to the TNM classification, and their UIC and serum PBI levels were also presented according to this classification (Table 2). As seen from Table 2, the

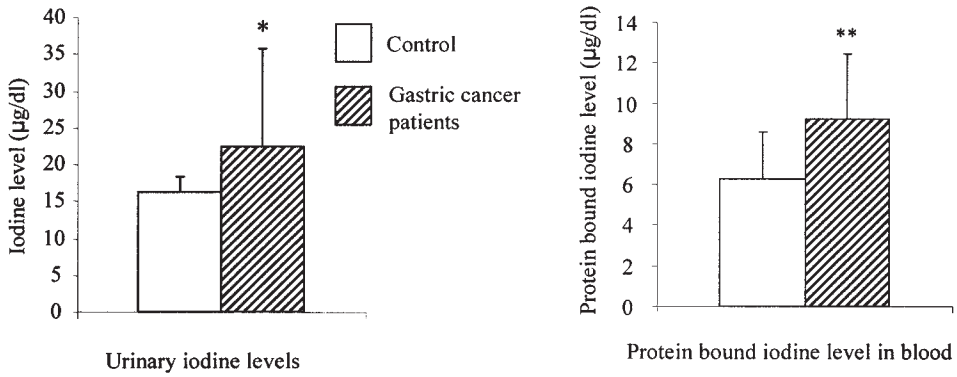

Fig. 1. Iodine levels in urine and blood of patients with gastric cancer (n = 56) and the control group (n = 25). The bars indicate the means ± SD. *$p < 0.05$, **$p < 0.001$

Table 2
Urine and Serum PBI Levels in Patients with Gastric Cancer in Various Stages and in the Control Group

	n	UIC (µg/dL)	Serum PBI (µg/dL)
Stage I	9	12.1 ± 3.6 [a,b]	7. 8 ± 2.8 [f]
Stage II	10	13.0 ± 7.3 [a,b]	7.5 ± 2.5 [g]
Stage III	17	21.9 ± 14.2 [c]	10.3 ± 3,1
Stage IV	20	31.8 ± 11.4 [d,e]	9.9 ± 3.3
Control group	25	16.3 ± 2.1	6.3 ± 2.3 [h]

Note: Values are given as means ± SD.
[a] Versus stage IV ($p < 0.001$).
[b] Versus stage III ($p < 0.05$).
[c] Versus stage IV ($p < 0.01$).
[d] Versus stage III ($p < 0.01$).
[e] Versus stage I and II and the control ($p < 0.001$).
[f] Versus stage III ($p < 0.05$).
[g] Versus stage III and IV ($p < 0.05$).
[h] Versus stage III and IV ($p < 0.001$)

UIC in stage IV was higher than all other stages and control group. The UIC was higher in stages III and IV compared with stages I and II.

On the other hand, serum PBI levels in stage III were higher compared with stages I and II also the control group. The serum PBI level in stage IV was higher than stage II and the control group, but not higher than stage 1 (Table 2).

There was no difference between females and males in the control group in terms of UIC and serum PBI levels. The UIC of females and males were 16.4 ± 2.5 and 16.1 ± 1.7 μg/dL, respectively and the serum PBI levels of females and males were 6.4 ± 2.6 and 6.0 ± 1.9 μg/dL, respectively.

When we compared the control subjects who were older than 60 yr old and the ones who were younger than 60 yr old, there was no statistically significant difference in the UIC and serum PBI levels. The UIC of control subjects who are older than and younger than 60 yr old were 16.0 ± 2.4 and 16.3 ± 2.1 μg/dL, respectively, and the serum PBI levels who are older than and younger than 60 yr old were 5.9 ± 2.1 and 6.3 ± 2.3 μg/dL, respectively.

There was no difference between female and male patients in terms of the UIC and serum PBI levels. The UIC of females and males were 21.3 ± 11.5 and 22.9 ± 14.6 μg/dL, respectively, and the serum PBI levels of females and males were 8.9 ± 3.0 and 9.4 ± 3.3 μg/dL, respectively.

Similarly, when we compared the patients who were older than 60 yr old and the ones who were younger than 60 yr old, there was no statistically significant difference in the UIC and serum PBI levels. The UIC of control subjects who are older than and younger than 60 yr old were 23.5 ± 12.5 and 22.5 ± 13.4 μg/dL, respectively, and the serum PBI levels who were older than and younger than 60 yr old were 9.6 ± 3.0 and 8.4 ± 2.8 μg/dL, respectively.

DISCUSSION

Although there are epidemiological studies showing an inverse relationship between iodine and gastric cancer *(6,15),* to our knowledge this is the first study investigating the iodine levels in blood and urine in patients with gastric cancer and looking for a possible relationship between these iodine levels and the stages of the gastric cancer.

The finding of higher UIC in stages III and IV compared with stages I and II suggests that the UIC increases by the level of gastric cancer: The higher the stage of the gastric cancer, the higher the level of the UIC. Similarly, blood PBI level was high in stages III and IV; however, it was highest in stage III.

The World Cancer Research Fund and the American Institute for Cancer Research *(27)* reported that dietary iodine deficiency and excess are tumor promoters and carcinogens in the thyroid gland. Significantly elevated levels of iodine–131 (^{131}I) in plasma and depressed thyroid uptake of ^{131}I have been reported in cancer patients *(28).* Loss of iodide uptake is frequently observed in metastasized thyroid cancer, which is explained by diminished expression of the human sodium-iodide symporter (hNIS) *(29).* Reduced NIS expression might be an important factor in the impairment of iodine-concentrating ability of *neoplasia* thyroid tissues *(30).*

The possibility of an autoimmune-mediated mechanism being responsible for inhibition of iodine uptake in the thyroid has been previ-

ously reported *(31).* Other groups *(32)* have demonstrated an increased prevalence of circulating thyroid antibodies in breast cancer, thus emphasizing a possible link with thyroid autoimmunity. Whether this is a consequence of the disease or part of its pathogenesis is unclear.

Eskin *(11)* reported that iodine deficiency causes breast dysplasia and cancer in rats and probably in humans and showed a mammary tumor reduction in rats after iodine treatment. Tissue iodide content of breast carcinomas was found to be significantly lower than that in remote normal tissue from the tumor-bearing breast or in fibroadenoma *(33).* Therefore, it is proposed that a disorder of iodide uptake might be involved in the development of breast cancer, which might be the result of NIS-inhibiting antibodies. In fact, in various extrathyroidal tissues, such as gastric mucosa, salivary glands, and lacrimal gland, hNIS might act as a target antigen for T-cells and cross-reacting autoantibodies, thus perhaps providing a link between autoimmune thyroid diseases and associated autoimmune diseases of other organs systems, such as autoimmune gastritis *(34).*

Previous studies have demonstrated the frequent association between atrophic gastritis and goiter-dysthyroidisms, well known as thyro-gastric syndrome, and between gastric antimucosa and antithyroid antibodies, which might be attributed to common organospecific antigens resulting from the same embryogenetic derivation. In fact, injected antithyroid serum can cause experimental gastritis in the stomach *(6).* Venturi et al. *(6)* have shown the atrophic regulating action of iodine on gastric mucosa similar to the action on the thyroid and have found relationships among iodine deficiency, goiter, and atrophic gastritis. The prevalence of atrophic gastritis was correlated to the degree of iodine deficiency and goiter. In addition, Venturi et al. have found that a normal gastric mucosa contains more iodine than that affected by atrophic gastritis *(6).*

The thyroid gland shares its capacity to actively accumulate iodide (I^-) with several other tissues, including gastric mucosa, and the lactating mammary gland. The authors have hypothesized that dietary iodine (deficiency or excess) is associated with the development of some gastric and mammary cancer, as it is well known for thyroid cancer *(5).*

It has recently been hypothesized that iodide might have an ancestral antioxidant function in all iodide-concentrating cells. In these cells, iodide acts as an electron donor in the presence of H_2O_2 and peroxidase, and the remaining iodine atom readily iodinates tyrosine or certain specific lipids *(8).* Iodine can add to double bonds of some polyunsaturated fatty acids of cellular membranes, making them less reactive to free oxygen radicals *(35,36).* Iodolipids have been shown to be regulators of cellular metabolism. This antioxidant action can be exerted through oxidized iodine species obtained from the diet or from local deiodination *(36).* In particular, δ-iodolactone (6-iodo-5-hydroxy-eicosatrienoic acid) has been found to be a potent inhibitor of the proliferation of the thyroid and probably of some nonthyroidal cells *(37).* Berking et al. *(38)* have recently reported that iodide and tyrosine form an efficient antioxidant defense system in some

marine invertebrates (polyps of the cnidaria *Aurelia aurita*), which shields the tissue against damage by reactive oxygen species.

Iodine is a regulator of gastric trophism. This trophism-regulating action on the gastric mucosa could provide a new interpretation (by impairing iodine intracellular concentration) of the pathogenetic mechanism of previously studied risk factors for gastric cancer *(6).*

Iodine might trigger apoptosis in abnormal cells in the body. In the stomach, iodine protects against abnormal growth of bacteria, in which *Helicobacter pylori* is the most clinically significant. Iodine in the stomach can also deactivate all biological and most chemical poisons *(39).* Failure to trigger the apoptosis in gastric cancer cells resulting from decreased iodine might be harmful.

Upadhyay et al. *(40)* reported that excess iodine has been observed to induce apoptosis in thyrocytes and mammary cells. The mechanism of iodine-induced apoptosis is poorly understood. Mitochondria are the main executioners of apoptosis and therefore might play an important role in carcinogenesis. Upadhyay et al. *(40)* observed that mitochondria isolated from the tumor and extratumoral tissue of the human breast display a significant uptake of iodine. Mitochondrial proteins were observed to be predominantly iodinated in extratumoral tissue but not in tumor mitochondria. In their study, treatment with iodine increased mitochondrial permeability transition in the tumor, but decreasing it in extratumoral tissue. Iodine-induced released factors other than cytochrome-*c* from tumor mitochondria initiate apoptosis in vitro, whereas those from extratumoral tissue mitochondria were nonapoptogenic in nature. Upadhyay et al. *(40)* have shown that iodine acts differentially on mitochondria of tumor and extratumoral origin to release apoptogenic proteins from the tumor and has a protective effect on extratumoral tissue.

In line with our finding in cancer patients, serum total iodine concentration was found to be higher in rats with 7,12-dimethylbenz*(a)*-anthacene-induced mammary tumor *(41).* These authors assume that iodine is transported from the serum into the tumor tissue inducing apoptosis through the expression of transforming growth factor-β.

In contrast, an excess of dietary iodine impairs the iodide pump and the functions of some concentrating tissues (thyroid, stomach, and salivary gland). This might lead to degenerative, necrotic, and neoplastic lesions, which are well known in the thyroid gland *(42).* The fact that iodine excess is also able to damage the stomach should be examined carefully if we consider that the coastal populations of Japan *(43)* and China *(44),* who have the highest rate of gastric cancer mortality in the word, frequently eat an excessive and harmful quantity of marina algae (seaweeds), which are very rich in iodine.

Although iodine deficiency is common in the region according to a previous study *(19)* carried out in our region, the UICs were within the normal range reported in the literature *(25).* This, of course, does not mean that the iodine-deficiency problem of the region has been solved. The use

of salt with iodine in the city centers and the higher socioeconomic status of the subjects in the control group might have affected the results of this study.

The ranges of the UIC in patients with gastric cancer and control group were 3–50 μg/dL and 10–20 μg/dL, respectively. As these results did not provide much information about the prognosis of the disease, we have also compared the urinary and serum iodine levels according the level of gastric cancer.

No difference has been found in urinary iodine excretions between patients with breast disease and age-matched controls *(45).* In another study, it was reported that the mean levels of serum PBI in the group of patients with advanced metastatic carcinoma of the breast were significantly higher than those in the control group. No conclusions could be drawn at present as to the significance of this change or the mechanism by which the alteration in circulating thyroid hormone takes place *(46).* Eskin et al. *(47)* measured the 24-h radioiodide uptake in 57 clinically normal breasts and in 8 clinically abnormal breasts. They found a higher uptake in the abnormal breasts, suggesting that the abnormal breasts were more iodine deficient than normal breasts.

Both the UIC and serum PBI in patients with gastric cancer were found to be higher compared with the control group. The increase in urine iodine concentration does not mean that patients with gastric cancer receive enough iodine. In the previous work *(22),* we have shown decreased tissue iodine levels in gastric cancer tissue compared with surrounding normal tissue. Significantly elevated levels of iodine in the blood and urine might result from depressed stomach uptake of iodine occurring in cancer patients. Levels of iodine in blood and urinary were proportional to the stage of the gastric cancer.

To conclude, although our results suggested that iodine concentration in blood and urine might increase by the stages of the gastric cancer, it remains to be seen whether it can be used to follow the severity of the disease.

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