Effect of selenium supplementation for protection of salivary glands from iodine-131 radiation damage in patients with differentiated thyroid cancer

Haiyoung Son[1,2,3] **MD,**
Sang Mi Lee[4] **MD, PhD,**
Ra Gyoung Yoon[5] **Md,**
Hakmin Lee[1] **MD,**
Ilkyun Lee[1] **Md,**
Soon Kim[5] **MD, PhD,**
Woong Youn Chung[6] **MD, PhD,**
Jeong Won Lee[3,7] **MD**

1. Department of Surgery, Catholic Kwandong University International St. Mary's Hospital, Catholic Kwandong University College of Medicine, Incheon, Korea
2. Department of Surgery, Graduate School, Yonsei University College of Medicine, Seoul, Korea
3. Institute for Integrative Medicine, Catholic Kwandong University International St. Mary's Hospital, Catholic Kwandong University College of Medicine, Incheon, Korea
4. Department of Nuclear Medicine, Soonchunhyang University Hospital, Cheonan, Korea
5. Department of Radiology, Catholic Kwandong University International St. Mary's Hospital, Catholic Kwandong University College of Medicine,Incheon, Korea
6. Department of Surgery, Yonsei University Health System, Seoul,Korea
7. Department of Nuclear Medicine, Catholic Kwandong University International St. Mary's Hospital, Catholic Kwandong University College of Medicine, Incheon, Korea

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Corresponding author:
Jeong Won Lee, M.D.
Catholic Kwandong University International St. Mary's Hospital, 25, Simgok-ro 100 beon-gil, Seo-gu, Incheon, 404-834, Korea
82-32-290-2975 +82-32-290-3128,
jwlee223@ish.or.kr

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Abstract

Objective: In the current study, we examined whether selenium supplementation during iodine-131 (^{131}I) treatment had a radio-protective effect on salivary glands. **Subjects and Methods:** Sixteen patients with differentiated thyroid cancer were prospectively enrolled in the study. Patients after total thyroidectomy, before ^{131}I treatment, were divided into two groups; 8 patients in the selenium group and 8 patients in the control group. Patients in the selenium group received 300μg of selenium orally for 10 days, from 3 days before to 6 days after ^{131}I treatment. The control group received a placebo over the same period. To assess salivary gland function, salivary gland scintigraphy was performed before and 6 months after ^{131}I treatment. Serum amylase and whole blood selenium levels were measured before and 2 days and 6 months after ^{131}I treatment. Using salivary gland scintigraphy, maximum uptake ratio (MUR), maximum secretion percentage (MSP), and ejection fraction (EF) of each salivary gland were calculated. **Results:** Baseline clinical characteristics, baseline amylase and selenium levels, and parameters of baseline salivary gland scintigraphy were not significantly different between selenium and control groups (P>0.05). On a blood test performed 2 days after ^{131}I treatment, the selenium group showed a significantly higher whole blood selenium level (P=0.008) and significantly lower serum amylase level (P=0.009) than the control group. On follow-up salivary gland scintigraphy, the control group showed significantly decreased, MUR of the bilateral parotid and left submandibular glands, MSP of the bilateral parotid and submandibular glands, and EF of the left submandibular glands (P<0.05), while the selenium group only had a significant decrease in MSP of the right submandibular gland and EF of the left submandibular gland (P<0.05). **Conclusion:** Selenium supplementation during ^{131}I treatment was effective to reduce salivary glands damage by ^{131}I radiation in patients with differentiated thyroid cancer.

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Introduction

Radioiodine treatment with iodine-131 (^{131}I) is used to ablate the thyroid remnants or to treat cancer lesions after total thyroidectomy in patients with differentiated thyroid cancer [1, 2]. Besides thyroid tissue uptake, radioiodine can also accumulate in the salivary glands through the $Na^+/K^+/Cl^-$ co-transport system, and the concentration of radioiodine in the saliva is 30-40 times higher than in the plasma [3, 4]. In patients with differentiated thyroid cancer who undergo high-dose ^{131}I treatment, significant salivary gland dysfunction can occur, often accompanied by symptomatic sialadenitis [5-7]. Because salivary gland damage by ^{131}I radiation can permanently impair quality of life, prevention and reduction of salivary glands damage is important during ^{131}I treatment [5, 8, 9]. Currently, to reduce radiation damage to the salivary glands, hydration with the use of sialogogues such as lemon candy, sour candy, or chewing gum in the 24 hours after ^{131}I treatment is recommended by the European Association of Nuclear Medicine guideline [10]. However, there is no established protocol for the use of sialogogues and several studies showed contradictory results for the effects of sialogogues [11-13]. Moreover, a recent study showed that 41% of patients with high-dose ^{131}I treatment still experienced symptomatic sialadenitis even after hydration and use of sialogogues [8].

Selenium is an essential trace element that is a key constituent of metalloenzymes and has fundamental importance in human biology [14]. In addition to its role in thyroid function regulation, DNA synthesis, and functioning of the immune system, selenium has a key role in cell protection from oxidative stress such as reactive oxygen species induced by ionizing radiation [15, 16]. In several clinical studies, selenium supplementation has been shown to alleviate side effects of external beam radiotherapy in patients with vari-

ous cancers [17-19]. Furthermore, in animal studies, selenium showed a radio-protective action in the parotid glands against gamma radiation and in the blood cells against ^{131}I radiation [20, 21]. However, the radio-protective effect of a selenium supplement on the salivary glands from ^{131}I treatment of patients with differentiated thyroid cancer has not been evaluated yet.

In the present study, by using salivary gland scintigraphy, we examined whether selenium supplementation during ^{131}I treatment could reduce ^{131}I radiation damage of the salivary glands in patients with differentiated thyroid cancer.

Subjects and Methods

Patients

This single-blind randomized prospective study was approved by the Institutional Review Board of our university (IRB No. IS14OISI0029) and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study. We prospectively enrolled 16 patients with differentiated thyroid cancer (6 men and 10 women) who were scheduled to undergo high-dose ^{131}I treatment to ablate the remnant thyroid and/or to treat metastatic lesions after total thyroidectomy between April 2015 and May 2016. Patients with a history of malignant tumors other than differentiated thyroid cancer; previous radiation therapy to the neck area including ^{131}I treatment; salivary gland disorders such as a salivary stone, tumor, or sialadenitis; autoimmune disease; or collagen tissue disease were excluded from study enrollment. All patients underwent ^{131}I treatment for the first time after total thyroidectomy.

Before the preparation for ^{131}I treatment, all patients were randomly allocated to one of two patient groups: a selenium supplement group with 8 patients and a control group with 8 patients. The 8 patients in the selenium supplement group received 300μg of selenium (as inorganic sodium selenite; selenase®) orally for 10 days, from 3 days before to 6 days after ^{131}I treatment. The 8 patients in the control group received an oral placebo for the same duration. Before the beginning of administration of selenium and placebo, a blood test was performed for all patients to measure baseline levels of serum amylase and whole blood selenium. All 16 patients had discontinued replacement of L-thyroxine for 4 weeks before the ^{131}I treatment and received L-triiodothyronine for the first 2 weeks. Furthermore, all patients consumed a low iodine diet for 2 weeks before ^{131}I treatment. The dose of ^{131}I for enrolled patients was 3.7GBq for 8 patients or 5.6GBq for 8 patients. Because the dose of ^{131}I is related to salivary gland dysfunction [8, 22], the same proportion of patients with 3.7GBq or 5.6GBq were assigned to the selenium and control groups (4 patients with 3.7GBq and 5.6GBq for each group).

On the day of high-dose ^{131}I treatment, baseline salivary gland scintigraphy was performed and serum levels of thyroid stimulating hormone (TSH), thyroglobulin, and anti-thyroglobulin antibody were measured before the administration of ^{131}I. Serum TSH levels were higher than 30IU/mL in all patients. During admission, patients were instructed to take fluids and sialagogues such as a lemon candy or chewing gum after ^{131}I treatment to promote ^{131}I secretion from the salivary glands. Two days after ^{131}I treatment, blood tests were performed before discharge from the hospital to measure serum amylase and whole blood selenium levels. A post-therapeutic ^{131}I scan was performed 5-6 days after ^{131}I treatment. To assess subjective symptoms of sialadenitis, patients answered 14 questions on a symptoms questionnaire before ^{131}I therapy (baseline) and at 1 week and 6 months after ^{131}I therapy. In all patients, follow-up blood tests for serum amylase and whole blood selenium levels and follow-up salivary gland scintigraphy were performed 6 months after ^{131}I therapy.

Symptoms questionnaire

The symptoms questionnaire was composed of 14 questions that were used to assess the symptoms of sialadenitis (Table 1) [23]. Patients were asked to score each question using a 4-point score system as follows: score 1, not at all; score 2, a few times; score 3, fairly often; and score 4, almost always. The total score of the symptoms questionnaire ranged from 14 points to 56 points.

Table 1. *Symptoms questionnaire used in the study to evaluate symptoms of sialadenitis, for scores 1, 2, 3 and 4*

Questions
I have my chin and cheek swelling
I have pain in my chin and cheek
I have dryness in my mouth
I feel dryness in my mouth when I eat
I have trouble in eating dry food without water
I wake up while sleeping for dryness in my mouth
I drink water and eat sweets to reduce dryness
I feel dryness in my mouth when I speak and chew
I feel pain or burning sense in my tongue
I have ulcers around my lips more often than before
I have bad breath
I have throat discomfort or hoarseness
I have trouble with taste
I visited dentist for dental caries or gingivitis

Salivary glands scintigraphy

Baseline and follow-up salivary glands scintigraphy in all patients was performed with a gamma camera system (Symbia E, Siemens Healthcare, US) equipped with a low-energy general-purpose collimator. Patients were instructed to fast for 2 hours before the scintigraphy. Patients were positioned supine with the neck hyperextended and 370MBq of ^{99m}Tc pertechnetate was intravenously administered. Immediately after the injection, dynamic images were sequentially taken at 1min per frame for 30min on a 128×128 matrix. Twenty minutes after ^{99m}Tc pertechnetate injection, lemon juice was administered to stimulate salivary glands emptying.

Quantitative analysis of salivary gland function was performed by two nuclear medicine physicians. For quantification of salivary gland uptake, circular-shaped regions-of-interest (ROI) were manually drawn on the bilateral parotid and submandibular glands (Figure 1). For measurement of background activity, a circular ROI was drawn in the right shoulder area (Figure 1). The highest mean count of ROI of each salivary gland (SG) and the mean count of ROI of the background (BH) synchronized with the highest mean count of ROI of the salivary glands were measured [24]. Furthermore, the lowest mean count of ROI of each salivary gland (SL) after lemon juice stimulation and the mean count of ROI of the background (BL) synchronized with the lowest mean count of ROI of the salivary glands were calculated [24]. From these mean counts of ROI, 3 parameters of salivary gland scintigraphy, maximum uptake ratio (MUR), maximum secretion percentage (MSP), and ejection fraction (EF), were calculated for each salivary gland as follows: MUR=SH/BH; MSP=MUR–SL/BL; EF=(SH–BH–SL+BL)/(SH–BH)×100 [24].

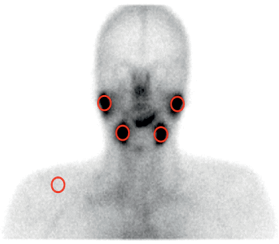

Figure 1. An example of circular regions-of-interest drawn to measure the uptake of bilateral parotid and submandibular glands and background activity on the right shoulder area on salivary gland scintigraphy.

Statistical analysis

With the serum amylase and whole blood selenium levels at baseline and 2 days post-therapy blood tests, the changes of amylase (Δamylase=post-treatment serum amylase–pre-treatment serum amylase) and selenium (Δselenium=post-treatment whole blood selenium–pre-treatment whole blood selenium) levels were calculated. Additionally, using the values of MUR, MSP, and EF of each salivary gland on baseline and follow-up salivary gland scintigraphy, the changes of MUR (ΔMUR=post-treatment MUR–pre-treatment MUR), MSP (ΔMSP=post-treatment MSP–pre-treatment MSP), and EF (ΔEF=post-treatment EF–pre-treatment EF) of salivary gland scintigraphy were calculated. For comparison of clinical factors of salivary gland scintigraphy parameters between the selenium and control groups, the Mann-Whitney test was used for continuous variables and Fisher's exact test was performed for categorical variables. For comparison of salivary gland scintigraphy parameters between baseline and follow-up scans within the same group, the Wilcoxon signed-rank test was performed. All statistical analyses were performed by using MedCalc Statistical Software version 16.8.4 (MedCalc Software, Ostend, Belgium) and a P-value less than 0.05 was defined to be statistically significant.

Results

Patient characteristics

The demographic data and results of baseline blood tests and salivary gland scintigraphy of the enrolled 16 patients are summarized in Table 2. All 16 patients were histopathologically diagnosed with papillary thyroid cancer. There were no significant differences in baseline age, sex, pathological stage, serum TSH, thyroglobulin, and amylase levels, whole blood selenium, and MUR, MSP, and EF for baseline salivary gland scintigraphy between the selenium and control groups (P>0.05), indicating that baseline characteristics of the two patient groups were comparable. Only 3 patients (37.5%) for each group had a serum selenium level within the normal range on the baseline test.

Comparison of subjective symptoms and blood tests

The results of scores of symptoms questionnaires and serum amylase and whole blood selenium levels before and after ^{131}I treatment in both patient groups are shown in Table 3. In contrast to baseline selenium levels, the selenium group had significantly higher levels of whole blood selenium 2 days after ^{131}I treatment (P=0.008) and Δselenium (P=0.001) than the control group. In the selenium group, 7 patients (87.5%) had a selenium level within the normal range on blood tests performed 2 days after ^{131}I treatment, while only 2 patients (25.0%) in the control group were within the normal range of selenium level. For serum amylase, although both groups showed an increase of amylase levels, the control group had a significantly higher level 2 days after ^{131}I treatment (P= 0.009) and Δamylase (P=0.018) than the selenium group. Among all patients, 15 patients had a serum amylase level exceeding the normal range except one patient in the selenium group who had a serum level of 100IU/L. In contrast to the serum levels 2 days after ^{131}I treatment, there were no significant differences of serum amylase and whole blood selenium levels between the two groups 6 months after ^{131}I treatment (P>0.05). For symptom questionnaires, there was no significant difference in symptom scores 1week after ^{131}I therapy (P=0.685). However, symptom scores 6 months after ^{131}I therapy in the control group tended to be higher than those in the selenium group with borderline significance (P=0.051).

Comparison of parameters of salivary glands scintigraphy

The values of 3 parameters at baseline and 6 months follow-up salivary glands scintigraphy are summarized in Table 4.

Table 3. *Comparison of questionnaire score and levels of serum amylase and whole blood selenium in selenium and control groups*

Variables	Selenium group	Control group	P-value
Baseline whole blood selenium (μg/dL)	10.3 (4.3-11.8)	10.2 (8.6-12.6)	0.529
Whole blood selenium 2 days after ^{131}I therapy (μg/dL)	13.6 (10.2-16.5)	9.8 (7.6-12.1)	0.008
Δselenium (μg/dL)	2.2 (0.60-10.2)	-0.95 (-2.30-0.60)	0.001
Whole blood selenium 6 months after ^{131}I therapy (μg/dL)	10.0 (8.6-12.2)	10.5 (8.2-11.1)	0.465
Baseline serum amylase (IU/L)	53 (43-61)	54 (24-84)	0.753
Serum amylase 2 days after ^{131}I therapy (IU/L)	139 (100-178)	296 (126-371)	0.009
Δamylase (IU/L)	88 (45-121)	234 (77-337)	0.018
Serum amylase 6 months after ^{131}I therapy (IU/L)	66 (49-80)	54 (45-84)	0.121
Baseline questionnaire score	14.5 (14-16)	15.0 (14-16)	0.784
Questionnaire score 1 week after ^{131}I therapy	19 (14-23)	20 (16-28)	0.685
Questionnaire score 6 months after ^{131}I therapy	18.5 (14-24)	23 (15-28)	0.051

Normal range for serum amylase, 20-100 IU/L. Normal range for whole blood selenium, 10.6-15.4 μg/dL.

In the selenium group (Figure 2), only MSP of the right submandibular gland (P=0.039) and EF of the left submandibular glands (P=0.039) significantly decreased on follow-up salivary gland scintigraphy. No statistically significant differences were found in other parameters of salivary gland scintigraphy between baseline and follow-up scans. In contrast, in the control group (Figure 3), MUR of the bilateral parotid glands and left submandibular gland, MSP of the bilateral parotid and submandibular glands, and EF of the left submandibular glands significantly decreased on follow-up scans as compared with baseline salivary glands scintigraphy (P<0.05 for all), indicating more significant deterioration of salivary gland function in the control group.

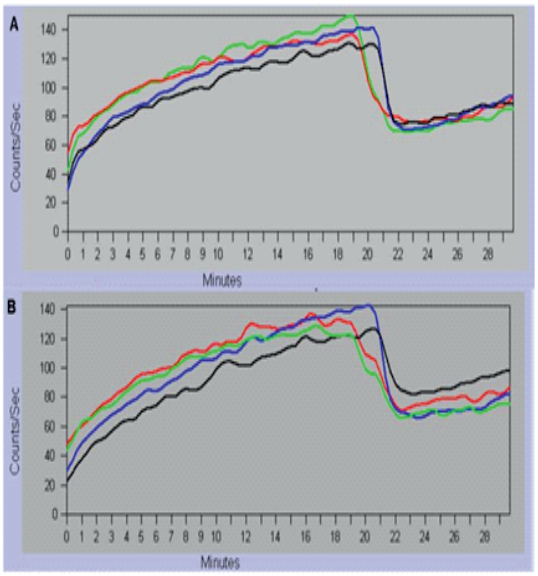

Figure 2. Baseline (A) and 6 months follow-up (B) dynamic salivary gland scintigraphy in a 27 years old man who underwent ^{131}I treatment with 5,550MBq and selenium supplementation. There was no significant deterioration of function in bilateral salivary glands (black line, right parotid gland; blue line, left parotid gland; red line, right submandibular gland; green line, left submandibular gland).

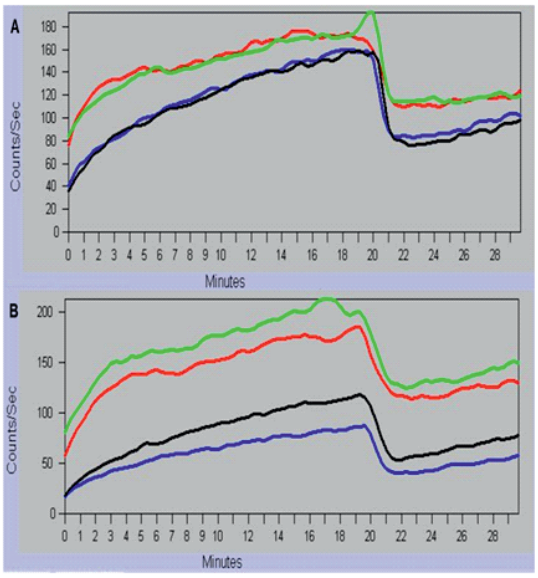

Figure 3. Baseline (A) and 6 months follow-up (B) dynamic salivary gland scintigraphy in a 40 years old woman in a control group who underwent ^{131}I treatment with 5,550MBq. Bilateral parotid glands showed significant decrease of uptake on follow-up scintigraphy (black line, right parotid gland; blue line, left parotid gland; red line, right submandibular gland; green line, left submandibular gland).

Table 2. *Baseline characteristics of the enrolled patients*

Characteristics		Selenium group (n=8)	Control group (n=8)	P-value
Age (year)*		40 (20-67)	50 (36-65)	0.093
Sex (M:F)		3:5	3:5	>0.999
Stage	T1N1	0 (0%)	1 (12.5%)	>0.999
	T2N1	1 (12.5%)	0 (0%)	
	T3N0	1 (12.5%)	0 (0%)	
	T3N1	6 (75.0%)	7 (87.5%)	
^{131}I dose	3.7 GBq	4 (50.0%)	4 (50.0%)	>0.999
	5.6 GBq	4 (50.0%)	4 (50.0%)	
Serum TSHIU/mL level at ^{131}I treatment*		86.0 (73.7-100.0)	80.0 (49.7-100.0)	0.679
Serum Tgng/mL at ^{131}I treatment*		2.5 (0.1-39.6)	3.5 (0.2-32.6)	>0.999
Baseline serum amylase (IU/L)*		53 (43-61)	54 (24-84)	0.753
Baseline whole blood selenium (μg/dL)*		10.3 (4.3-11.8)	10.2 (8.6-12.6)	0.529
Baseline questionnaire score*		14.5 (14-16)	15.0 (14-16)	0.784
Baseline MUR*	Right parotid	4.7 (2.6-8.3)	4.1 (2.6-6.0)	0.462
	Left parotid	4.9 (3.0-5.7)	4.9 (2.9-5.4)	0.708
	Right submandibular	4.9 (2.7-6.0)	4.4 (3.2-7.4)	0.753
	Left submandibular	4.8 (2.2-6.2)	4.8 (3.1-8.1)	0.600
Baseline MSP*	Right parotid	51.3 (22.0-79.6)	51.0 (30.0-66.3)	0.834
	Left parotid	46.4 (26.8-66.5)	47.8 (28.7-62.9)	0.916
	Right submandibular	56.1 (32.5-67.3)	42.9 (13.1-60.9)	0.115
	Left submandibular	48.7 (15.4-62.0)	43.3 (7.1-61.1)	0.529
Baseline EF*	Right parotid	68.2 (35.4-90.5)	70.3 (56.4-89.4)	0.753
	Left parotid	66.6 (47.7-82.7)	70.4 (52.7-89.1)	0.600
	Right submandibular	64.8 (41.5-80.6)	59.5 (39.3-68.3)	0.124
	Left submandibular	66.8 (28.1-77.6)	61.1 (33.0-70.5)	0.529

**Expressed in median (range). Normal range for serum amylase, 20-100 IU/L. Normal range for whole blood selenium, 10.6-15.4 μg/dL*

Table 4. *Comparison of parameters of baseline and follow-up salivary glands scintigraphy*

Parameters		Baseline	Follow-up	P-value
Selenium group				
MUR	Right parotid	4.7 (2.6-8.3)	4.6 (2.3-7.2)	0.742
	Left parotid	4.9 (3.0-5.7)	4.4 (2.8-5.9)	0.843
	Right submandibular	4.9 (2.7-6.0)	3.9 (2.3-6.3)	0.843
	Left submandibular	4.8 (2.2-6.2)	4.5 (2.4-6.2)	>0.999
MSP	Right parotid	51.3 (22.0-79.6)	59.5 (29.5-67.4)	0.383
	Left parotid	46.4 (26.8-66.5)	49.6 (32.4-63.6)	0.945
	Right submandibular	56.1 (32.5-67.3)	45.4 (20.1-58.3)	0.039
	Left submandibular	48.7 (15.4-62.0)	43.3 (21.7-65.3)	0.461
EF	Right parotid	68.2 (35.4-90.5)	76.5 (41.8-82.6)	0.641
	Left parotid	66.6 (47.7-82.7)	67.3 (40.5-79.0)	>0.999
	Right submandibular	64.8 (41.5-80.6)	59.1 (37.3-77.1)	0.078
	Left submandibular	66.8 (28.1-77.6)	58.9 (36.4-74.7)	0.039
Control group				
MUR	Right parotid	4.1 (2.6-6.0)	2.9 (2.7-4.2)	0.016
	Left parotid	4.9 (2.9-5.4)	2.9 (2.5-4.3)	0.016
	Right submandibular	4.4 (3.2-7.4)	3.8 (2.7-5.8)	0.195
	Left submandibular	4.8 (3.1-8.1)	3.9 (2.6-5.2)	0.023
MSP	Right parotid	51.0 (30.0-66.3)	30.7 (15.1-46.2)	0.016
	Left parotid	47.8 (28.7-62.9)	32.4 (14.4-53.3)	0.016
	Right submandibular	42.9 (13.1-60.9)	25.1 (15.0-45.8)	0.023
	Left submandibular	43.3 (7.1-61.1)	23.9 (5.1-55.1)	0.023
EF	Right parotid	70.3 (56.4-89.4)	51.0 (30.1-83.6)	0.078
	Left parotid	70.4 (52.7-89.1)	59.1 (46.7-84.1)	0.078
	Right submandibular	59.5 (39.3-68.3)	49.5 (23.7-68.4)	0.383
	Left submandibular	61.1 (33.0-70.5)	42.6 (25.7-70.6)	0.008

All data are expressed in median (range)

Table 5. Changes of parameters of salivary glands scintigraphy between selenium supplementation group and control group

Parameters		Selenium group	Control group	P-value
ΔMUR	Right parotid	0.1 (-1.6-0.9)	-1.0 (-2.6-0.2)	0.208
	Left parotid	-0.2 (-2.6-0.8)	-1.3 (-1.9-0.5)	0.074
	Right submandibular	0.1 (-2.8-1.2)	-0.6 (-3.0-0.6)	0.462
	Left submandibular	0.2 (-2.7-1.7)	-0.8 (-4.1-0.6)	0.115
ΔMSP	Right parotid	3.6 (-12.2-21.7)	-20.2 (-32.4-0.8)	0.003
	Left parotid	-0.1 (-14.7-22.2)	-12.6 (-50.5-6.0)	0.016
	Right submandibular	-7.9 (-3.3-6.1)	-9.2 (-35.9-4.9)	0.599
	Left submandibular	-9.2 (-23.6-23.1)	-14.6 (-37.7-2.3)	0.141
ΔEF	Right parotid	0.1 (-8.4-20.7)	-19.4 (-38.1-13.3)	0.059
	Left parotid	-1.2 (-25.8-22.3)	-5.7 (-42.4-5.6)	0.172
	Right submandibular	-12.3(-38.1-1.6)	-8.3 (-37.5-18.3)	0.462
	Left submandibular	-11.9 (-20.1-31.4)	-15.9 (-26.7-13.0)	0.834

All data are expressed in median (range): ΔMUR; ΔEF; ΔMSP;

In comparison with changes of salivary glands scintigraphy parameters after ^{131}I treatment, there were significant differences in ΔMSP of the bilateral parotid glands between the two groups (Table 5; P<0.05), indicating a significant decrease in MSP of the bilateral parotid glands after ^{131}I treatment in the control group compared with the selenium group.

Discussion

Radioiodine can cause direct damage to the epithelium of the intralobular ducts of the salivary glands and significant histopathological changes of salivary gland parenchyma such as periacinoductal inflammation and fibrosis [25]. Radiation sialadenitis is the most common longterm complication of ^{131}I treatment, resulting in xerostomia, taste alterations, infections, and dental caries [23, 26]. A single ^{131}I dose of 6GBq can induce more than 30% loss of salivary glands function and a cumulative ^{131}I dose of 24GBq can cause 90% loss of function [27]. Many researchers have attempted to develop methods of preventing salivary gland damage from ^{131}I radiation. However, sialogogues, vitamin C and chewing gum, failed to significantly reduce the absorbed radiation dose to the salivary glands [12, 13]. Pilocarpine, a parasympathomimetic agent, was shown to alleviate subjective symptoms of sialadenitis, but, it did not reduce the occurrence of sialadenitis and showed severe side effects [23, 28, 29]. Amifostine, a cytoprotective agent, significantly reduces salivary glands damage; however, limited availability, high cost, and side effects restrict its use [30]. Interestingly, a recent study using vitamin E, an antioxidant, demonstrated a significant protective effect of vitamin E supplements against ^{131}I radiation damage without any side effects [24].

Selenium is another well-known antioxidant. Selenium incorporated into selenoproteins, such as glutathione peroxidase and thioredoxin reductase, is crucially involved in the protective process against oxidative stress damage [15, 16]. Several previous studies have already evaluated the effects of selenium supplements in patients undergoing external beam radiotherapy. Because sodium selenite has high biological activity and primarily enhances selenoprotein expression, most of the previous studies with cancer patients used sodium selenite for supplementation, which was also used in the present study [16]. In previous studies, sodium selenite has been administered with a dose ranging from 200-500μg/day and showed that the supplement increased the blood selenium level and was well-tolerated by the patients without any toxicity [16, 18, 19, 31]. Furthermore, in patients with autoimmune thyroid disease, a dose of sodium selenite of more than 200μg/day is needed to be effective in modifying disease activity [32]. In the current study, we administered 300μg/day and there was no toxicity to report. Previous studies demonstrated that selenium supplements enhanced cell-mediated immune responsiveness and reduced the dysphagia and lymphedema caused by radiotherapy in patients with head and neck cancer [19, 31, 33]. In patients with lung cancer, selenium supplements reduced the rate of myelosup-

pression after concurrent chemoradiotherapy [17]. Moreover, in a multicenter phase III clinical trial of patients with cervical and uterine cancer, selenium supplements significantly reduced the frequency of episodes and severity of diarrhea caused by radiotherapy without any negative influence on the effectiveness of radiotherapy and on survival [18, 34].

Hyperamylasemia after irradiation is mainly correlated with the severity of salivary glands damage and can be used as a biomarker for estimating absorbed radiation dose [35]. In addition, patients with ^{131}I treatment also showed an increased serum amylase level 1 day after treatment and the change in serum amylase was correlated with the administered dose of ^{131}I [36]. Considering that we equally distributed patients with administered doses of 3.7GBq and 5.6GBq, the changes of serum amylase level in the present study suggested that selenium supplementation could reduce radiation damage to the salivary glands. The results of salivary glands scintig-raphy also supported this suggestion. In contrast to the sig-nificant deterioration of bilateral parotid glands in the con-trol group, the selenium group showed no significant chan-ge of bilateral parotid gland function. The previous study with vitamin E supplements also showed significant decre-ase of EF of left parotid gland in the control group when compared to the patients with vitamin E supplementation [24]. Because the parotid glands have a higher concentration of radio-sensitive serous acinar cells, parotid glands are more adversely affected by ^{131}I treatment [5, 37, 38]. Therefore, a ra-dio-protective effect of selenium might be more prominent in the parotid glands. The results of the present study sug-gested that antioxidant supplementation such as selenium supplements could also be effective for protection against internal exposure of beta-emitting radioiodine [21, 24].

There are several limitations to the current study. First, although the study was performed in a prospective manner, the number of enrolled patients was too small to justify the results. Second, we only assessed the radio-protective effect of a selenium supplement on a certain institution. The influence of a specific dose of a selenium supplement on the effectiveness of ^{131}I treatment for thyroid remnants ablation and thyroid cancer-free survival should be further studied. Finally, further study for the optimal administered dose and duration of selenium supplementation is needed in order to standardize the protocol of selenium supplementation.

In conclusion, our prospective study demonstrated a radioprotective effect of selenium supplementation for the salivary glands from ^{131}I treatment based on blood tests and salivary gland, scintigraphy in patients with differentiated thyroid cancer. The control group in our study showed increased serum amylase levels and significant deterioration of the bilateral parotid glands compared with the selenium group. However, further study with a larger number of patients is needed to confirm the results of our study.

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The authors declare that they have no conflicts of interest.

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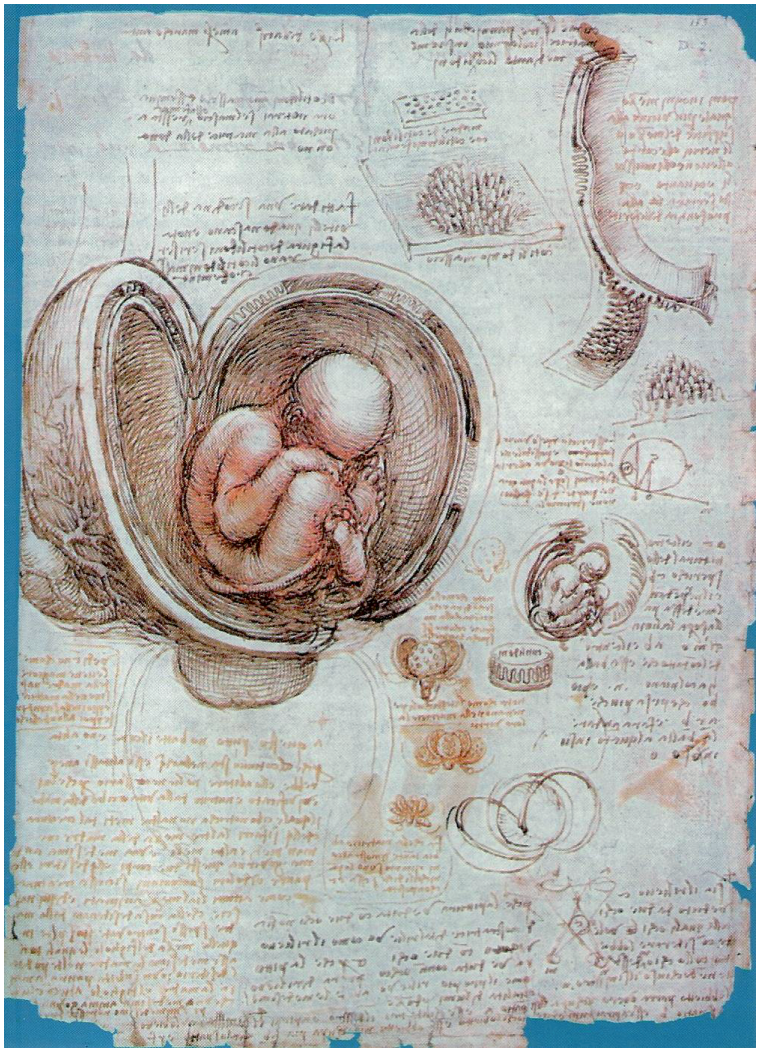

Leonardo da Vinci, "Embryo in uterus", 1510, Basic collection.