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Does vitamin E protect salivary glands from I-131 radiation damage in patients with thyroid cancer?

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Objectives Salivary gland impairment after high-dose radioiodine (^{131}I) treatment is well recognized. The aim of this study was to determine the protective effect of vitamin E on radiation-induced salivary gland dysfunction in patients undergoing ^{131}I treatment for differentiated thyroid cancer.

Methods Thirty-six patients with differentiated thyroid carcinoma were enrolled in this study. They were randomly divided into two groups before postsurgical ablation therapy with 3700–5550 MBq ^{131}I: the control group, comprising 17 patients, and the vitamin E group, comprising 19 patients. All 19 patients in the experimental group received vitamin E at a dose of 800 IU/day for a duration of 1 week before to 4 weeks after ^{131}I therapy and the 17 patients in the control group received a placebo for the same duration. Salivary gland function was assessed using salivary gland scintigraphy with intravenous injection of 370 MBq ^{99m}Tc-pertechnetate in two phases, one immediately before and the other 6 months after ^{131}I ablative therapy. First-minute uptake ratio, maximum uptake ratio, maximum secretion percentage, and excretion fraction (EF) of each salivary gland were measured and compared between the study phases for the two groups.

Results There was no significant difference between preablative and postablative salivary scintigraphic indices in the experimental vitamin E group, whereas maximum secretion percentage and EF of the right submandibular gland and EF of the left parotid gland were significantly decreased in the control group. There was also a higher significant decrease in the EF of the left parotid gland in the control group compared with the vitamin E group.

Conclusion Vitamin E consumption may be associated with a significant protective effect against radiation-induced dysfunction in salivary glands following single-dose ^{131}I therapy in patients with differentiated thyroid cancer. *Nucl Med Commun* 34:777–786

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Introduction

Standard treatment in differentiated thyroid carcinoma requires total or near-total thyroidectomy and high-dose radioiodine (^{131}I) therapy to completely ablate the thyroid remnants [1,2].

Over time, the extensive therapeutic effects of oral β-emitting ^{131}I for the treatment of well-differentiated thyroid carcinoma have been well established [1,2]. Apart from specific uptake by thyroid tissue, ^{131}I actively also accumulates in the acinar cells of salivary glands through an adenosine triphosphate-dependent $Na^+/K^+/2Cl^-$ cotransport mechanism [3]. The concentration of iodide in the saliva is about 30–40 times higher than that in the plasma. Accordingly, when the salivary glands are exposed to high concentrations of ^{131}I after therapy, the radiation dose is sufficient to cause an injury and rapidly affect the salivary gland function [4–6]. As a result, salivary gland dysfunction is the most common side effect and is associated with dry mouth, swelling difficulties, dental diseases, and loss of taste, impairing the quality of life of thyroid cancer patients for the duration of their life after ^{131}I therapy [7–10].

Salivation-inducing snacks, such as lemon candy, have been presumed to be helpful in the prevention of side effects in salivary glands accruing from ^{131}I therapy. However, despite its frequent use, there is no established evidence indicating that lemon candy, with any specific dosage or timing of administration, actually decreases the extent of injury to the salivary glands after ^{131}I therapy [4]. In contrast, even under salivary gland stimulation, parenchymal damage and functional impairment could be seen after high-dose ^{131}I therapy using quantitative or semiquantitative salivary gland scintigraphy (SGS) [4,11,12].

The damaging effects of ionizing radiation are mediated by the formation of free radicals, which are highly reactive in removing hydrogen atoms from fatty acids, causing lipid peroxidation and consequently cell death [5]. Vitamin E is a natural component of cell membranes

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and is the strongest antioxidant of the tocopherols, reacting quickly with peroxyl radicals and forming a tocopheroxyl radical, which interrupts the free radical chain reaction [5]. Some radioprotective effects of vitamin E have already been recognized in experimental animals [5,13,14]. The administration of vitamin E before external γ irradiation may protect salivary gland function in rats [5]. In addition, presupplementation with vitamin E seems to offer a significant radioprotection for salivary glands against ^{131}I-induced radiation injury in mice [14]. However, the radioprotective effect of vitamin E on human salivary glands exposed to therapeutic doses of ^{131}I has not been evaluated so far.

The aim of this study was to evaluate whether supplementation with vitamin E could diminish the radiation-induced damage to major salivary glands, using a semiquantitative scintigraphic method for measuring the secretory and excretory salivary function.

Methods

Patients

This double-blind randomized clinical trial study was approved by the ethics committee of Tehran University of Medical Sciences. From June 2006 to February 2007, 36 postsurgical differentiated thyroid cancer patients aged less than 55 years, who were referred to our institute for ^{131}I therapy to ablate the remnant thyroid tissue or to treat metastatic tumor, were enrolled in this study. All patients were in a hypothyroid state with serum thyroid stimulating hormone levels higher than 25 mIU/l. Patients with xerostomia, previous salivary gland dysfunction, salivary stone or tumor, those who had undergone head and neck radiotherapy previously, who had known rheumatological diseases such as Sjögren's disease, who had been administered ^{131}I earlier, who had known liver disease, had taken drugs influencing salivary gland function, such as antihistaminic agents, β-blockers, atropine, benzodiazepines, tricyclic antidepressants, and antipsychotic drugs in the past 2 weeks, and pregnant women were excluded from the study.

After signing the written informed consent form, all patients were allocated to one of two groups using a permuted block randomization method: the vitamin E group, comprising 19 patients, and the control group, comprising 17 patients. The 19 patients in the vitamin E group received vitamin E orally at a dose of 800 IU/day for 5 weeks, from 1 week before to 4 weeks after ^{131}I therapy. The 17 patients in the control group received a placebo in the same order and for the same duration.

Salivary gland scintigraphy

On the day of admission, SGS was performed for all patients. The patients were positioned supine with hyperextended neck and the images were obtained on a large field of view using a single-head gamma camera equipped with a low-energy, all-purpose collimator. Each patient received an intravenous injection of 370 MBq of ^{99m}Tc-pertechnetate. Immediately after administration, sequential dynamic images were taken at 1 min/frame on a 128×128 matrix with a zoom factor of 1.55 for 30 min. The energy window was 20% around the 140 keV photopeak of ^{99m}Tc. Twenty minutes after the injection, 5 ml of lemon juice (50% concentrated) was administered through a syringe into the patient's mouth to stimulate salivary secretion.

Salivary gland function was evaluated semiquantitatively by two expert nuclear medicine physicians. Circular regions of interest (ROIs) were drawn manually around both the parotid and submandibular glands. To detect the background activity, ROIs of equal sizes were also drawn in the temporal region.

From these ROIs the following parameters were calculated: (a) the first-minute uptake ratio (FUR), which is C_1/C_2, where C_1 is the mean counts in ROIs of the salivary glands and C_2 is the mean counts in ROIs of the background during the first minute of injection; (b) the maximum uptake ratio (MUR), which is C_3/C_4, where C_3 is the highest mean count in ROIs of the salivary glands after injection and C_4 is the mean counts in ROIs of the background synchronized with the highest mean count in ROIs of the glands; (c) the maximum secretion percentage (MSP), which is $(\text{MUR} - C_5/C_6) \times 100/\text{MUR}$, where C_5 is the lowest mean count in ROIs of the salivary glands after stimulation with lemon juice and C_6 is the mean counts in ROIs of background synchronized with the lowest mean count in ROIs of the glands; and (d) the excretion fraction (EF), which is $(C_3 - C_4 - C_5 + C_6) \times 100)/C_3 - C_4)$.

Follow-up assessments

All patients underwent a second SGS 6 months after ^{131}I therapy in an off-levothyroxine hypothyroid state with thyroid stimulating hormone levels higher than 25 mIU/l, similar to the values obtained in the baseline scan. All of the above-mentioned parameters were also calculated for the recent scintigraphies in the same way, and consequently the markers of functional changes were calculated as follows: (a) ΔFUR: pretreatment FUR minus post-treatment FUR; (b) ΔMUR: pretreatment MUR minus post-treatment MUR; (c) ΔMSP: pretreatment MSP minus post-treatment MSP; (d) ΔEF: pretreatment EF minus post-treatment EF. A positive value for each of the above-mentioned markers means a decrease in the corresponding functional parameter after ^{131}I treatment. In contrast, a negative value affirms an increase in functional parameter.

Statistical analysis

The Mann–Whitney *U*-test was used to assess the differences in the quantitative variables (e.g. age, dose of ^{131}I, and measured scintigraphic parameters) between the two groups. The categorical variables were compared between the groups using Fisher's exact test. Statistical comparisons between the two phases within the same group were made using the Wilcoxon signed-rank test. Statistical significance was set at *P*-values less than 0.10.

Results

The baseline demographic and scintigraphic data of patients are shown in Table 1. There was no statistically significant difference between the two groups with respect to age, sex, histology of tumor, type of surgery, ^{131}I dose, and baseline scintigraphic parameters, that is FUR, MUR, MSP, and EF, pointing to the fact that the two groups were comparable with respect to their baseline characteristics (Table 1).

There was no statistically significant difference in scintigraphic findings between the two phases (i.e. before and after treatment) in the vitamin E group (Table 2). As a result, no evidence of function deterioration was noted in this group.

The scintigraphic data of the control group before and after ^{131}I treatment are summarized in Table 3. As noted, MSP and EF of the right submandibular gland and EF of the left parotid gland are significantly decreased following ^{131}I treatment in this group, compared with baseline values (Table 3).

Table 4 shows a comparison between the vitamin E and control groups regarding scintigraphic markers of functional changes after treatment. As shown in this table, ΔFUR for the right parotid and ΔEF for the left parotid glands differ significantly between the two groups in support of less functional deterioration in the patients receiving vitamin E. Figures 1 and 2 show the pretherapy and post-therapy salivary gland scintigraphies of a patient pretreated with vitamin E. The corresponding scintigraphies of a control patient have also been shown in Figs 3 and 4.

Three out of 38 parotid glands (7.9%) in the vitamin E group versus nine out of 34 parotid glands (26.5%) in the control group revealed more than 15% decline in EF ($P = 0.035$).

Discussion

As differentiated thyroid cancer has a good prognosis, the long-term side effects of high-dose ^{131}I therapy have important implications for the patient's quality of life. Radiation-induced xerostomia or hyposalivation in ^{131}I-treated patients results in oral discomfort and compromised oral health,

Table 1 Comparison of baseline variables in the vitamin E and control groups before treatment

Baseline variables	Vitamin E group (*n*=19)	Control group (*n*=17)	*P*-value
Patient's age (years)			
Mean±SD (range)	32.47±10 (17–48)	29.59±6.59 (19–41)	0.45
Sex [*N* (%)]			
Male	4 (21.1)	4 (23.5)	0.86
Female	15 (78.9)	13 (76.5)	
Histopathology of DTC [*N* (%)]			
Papillary	19 (100)	15 (88.2)	0.22
Follicular	0 (0)	2 (11.8)	
Type of surgery [*N* (%)]			
TT or NTT	17 (89.5)	17 (100)	0.49
STT	2 (10.5)	0 (0)	
Administered I-131 activity (MBq)			
Mean±SD (range)	4138±778 (3700–5550)	4679±832 (3700–5550)	0.10
Scintigraphic parameters [mean±SD (range)]			
Right parotid			
FUR	2.28±0.518 (1.18–3.22)	2.60±0.72 (1.93–4.72)	0.238
MUR	4.65±0.96 (2.84–6.03)	5.18±2.13 (2.94–11.88)	0.640
MSP	35.69±13.68 (13.39–49.75)	43.48±11.48 (24.87–66.22)	0.107
EF	51.94±7.55 (40.32–66.58)	55.68±11.90 (35.51–74.04)	0.358
Right submandibular			
FUR	1.93±0.41 (1.21–2.85)	2.10±0.43 (1.41–2.92)	0.306
MUR	2.66±0.68 (1.64–4.18)	2.62±0.48 (1.56–3.33)	0.822
MSP	28.73±14.59 (0.4–67.11)	28.60±10.04 (12.29–47.96)	0.903
EF	47.73±16.65 (7.60–81.50)	49.42±15.31 (21.97–78.14)	0.931
Left parotid			
FUR	2.16±0.54 (1.13–3.17)	2.34±0.77 (1.78–4.89)	0.931
MUR	4.44±1.11 (2.43–6.33)	4.66±1.86 (2.93–10.76)	0.876
MSP	40.42±13.92 (8.23–55.30)	46.41±10.12 (30.23–64.79)	0.306
EF	58.14±7.85 (44–73.67)	61.08±9.17 (45.45–78.30)	0.415
Left submandibular			
FUR	1.89±0.42 (1.17–2.78)	1.87±0.40 (1.22–2.58)	0.876
MUR	2.55±0.56 (1.62–3.94)	2.33±0.50 (1.28–3.05)	0.358
MSP	29.50±13.47 (4.07–59.35)	28.81±9.34 (10.65–42.57)	0.903
EF	50.03±15.81 (12.70–69.30)	56.22±19.03 (23.29–89.87)	0.640

DTC, differentiated thyroid carcinoma; EF, excretion fraction; FUR, first-minute uptake ratio; MSP, maximum secretion percentage; MUR, maximum uptake ratio; NTT, near-total thyroidectomy; STT, subtotal thyroidectomy; TT, total thyroidectomy.

Table 2 Comparison of scintigraphic findings before and after radioiodine treatment in the vitamin E group

	Scintigraphic parameters [mean±SD (range)]		
Type of salivary gland	Before treatment	After treatment	*P*-value
Right parotid			
FUR	2.28±0.518 (1.18–3.22)	2.68±0.84 (1.7–5.05)	0.17
MUR	4.65±0.96 (2.84–6.03)	5.46±1.88 (3.22–12.18)	0.06
MSP	35.69±13.68 (13.39–49.75)	40.36±18.50 (−17.25 to 67.17)	0.18
EF	51.94±7.55 (40.32–66.58)	55.62±10.30 (36.67–74.34)	0.31
Right submandibular			
FUR	1.93±0.41 (1.21–2.85)	2.03±0.58 (1.2–3.78)	0.93
MUR	2.66±0.68 (1.64–4.18)	2.60±0.79 (1.68–5.31)	0.74
MSP	28.73±14.59 (0.4–67.11)	23.86±13.33 (3.02–48.44)	0.13
EF	47.73±16.65 (7.60–81.50)	42.76±18.60 (9.3–78.15)	0.27
Left parotid			
FUR	2.16±0.54 (1.13–3.17)	2.57±0.82 (1.63–5.08)	0.17
MUR	4.44±1.11 (2.43–6.33)	5.26±1.68 (3.33–10.99)	0.09
MSP	40.42±13.92 (8.23–55.30)	42.07±17.71 (−11.72 to 65.67)	0.31
EF	58.14±7.85 (44–73.67)	57.70±10.07 (36.51–73.45)	0.74
Left submandibular			
FUR	1.89±0.42 (1.17–2.78)	2.05±0.61 (1.16–3.81)	0.33
MUR	2.55±0.56 (1.62–3.94)	2.55±0.88 (1.45–5.61)	0.74
MSP	29.50±13.47 (4.07–59.35)	25.09±13.72 (−3.44 to 54.54)	0.12
EF	50.03±15.81 (12.70–69.30)	45.07±18.21 (−3.98 to 68.47)	0.20

EF, excretion fraction; FUR, first-minute uptake ratio; MSP, maximum secretion percentage; MUR, maximum uptake ratio.

causing great difficulty that is life-long and impairing the patient's quality of life. Unfortunately, many treatment modalities, such as use of salivary stimulants and saliva substitutes, are palliative and generally offer only short-term relief from symptoms [15,16]. The prevention of salivary damage is therefore an important task in these patients.

A single activity of 6 GBq is thought to result in absorbed radiation doses of about 1 Gy to the parotid and 3 Gy to the submandibular salivary glands, inducing more than 30% loss of parenchymal function as measured by salivary scintigraphy [17]. Correspondingly, a cumulative administered dose of about 24 GBq may result in 4 Gy for the parotid gland and 12 Gy for the submandibular gland, leading to a 90% loss of function in these glands [17]. Meanwhile, serous cells, which are found almost exclusively in the acini of the parotid glands, are assumed to be more radiosensitive than mucous cells, which predominantly exist in submandibular glands, because serous secretory granules are rich in transition metals such as Zn^{2+}, Fe^{2+}, and Mn^{2+}, which may leak into the cytoplasm, causing autolysis and inducing cell death. Further, it is clinically accepted that the most sensitive glands affected by ^{131}I are the parotid glands, whereas the submandibular and sublingual glands are somewhat more resistant to radiation [12,18].

SGS with ^{99m}Tc-pertechnetate is an easy, safe, and noninvasive method for evaluating the major functions of salivary glands [3]. Although the reduction in salivary gland function based on the findings specified on scintigraphy does not necessarily reflect the incidence of the corresponding clinical complications, such as dry mouth, the rate of incidence of these complications may subsequently increase in patients with scintigraphically impaired salivary function [4,19]. In semiquantitative SGS studies, the calculation of three functions (perfusion, uptake, and secretion) has been often carried out and its values widely used. The correlation between ^{99m}Tc uptake into the salivary glands and saliva secretion has also been established [20]. Helman *et al.* [20], using semiquantitative methods, revealed that ^{99m}Tc substitutes for Cl^- in the $Na^+/K^+/Cl^-$ salivary cotransport system and therefore may serve as a measure of saliva secretion.

It is well documented that there is a positive correlation between the cumulative activity of ^{131}I and the rate of scintigraphically impaired function of the salivary glands. In the study by Albrecht *et al.* [21], the researchers showed that after a dose of 0.3 Ci there was a change in T_{max} values and maximal excretion capacity in 30% of patients, whereas after a dose of 0.5–1 Ci the corresponding changes were detected in 60 and 80% of patients; consistently, after very high doses of 1.1–3.2 Ci, two-thirds of patients showed evidence of abnormal T_{max}, and reduced or absent salivary excretion capacity was seen in all patients.

The damaging effects of ionizing radiation are induced by free radicals through a cytotoxic process caused by lipid peroxidation that finally leads to cell death [5]. A potentially successful strategy to prevent salivary gland damage after ^{131}I therapy is the prophylactic use of amifostine [11]. However, amifostine as a prophylactic drug is currently underutilized because of limited availability, high cost, severe side effects, and lack of sufficient evidence favoring its radioprotective impact on humans [11,22].

Another possible method of reducing salivary gland radiation during radioactive iodine treatment is by

Table 3 **Comparison of scintigraphic findings before and after radioiodine treatment in the control group**

	Scintigraphic parameters [mean±SD (range)]		
Type of salivary gland	Before treatment	After treatment	*P*-value
Right parotid			
FUR	2.28±0.518 (1.18–3.22)	2.53±0.47 (1.96–3.66)	0.256
MUR	4.65±0.96 (2.84–6.03)	5.40±1.83 (2.88–10.57)	0.463
MSP	35.69±13.68 (13.39–49.75)	44.55±15.54 (2.68–69.18)	0.653
EF	51.94±7.55 (40.32–66.58)	54.64±17.31 (7.46–78.62)	0.407
Right submandibular			
FUR	1.93±0.41 (1.21–2.85)	2.04±0.47 (1.44–3.01)	0.435
MUR	2.66±0.68 (1.64–4.18)	2.48±0.42 (1.84–3.21)	0.381
MSP	28.73±14.59 (0.4–67.11)	24.53±10.91 (4.46–45.05)	0.039*
EF	47.73±16.65 (7.60–81.50)	43.02±16.69 (15.18–76.32)	0.015*
Left parotid			
FUR	2.16±0.54 (1.13–3.17)	2.37±0.61 (1.79–4.01)	0.831
MUR	4.44±1.11 (2.43–6.33)	5.05±2.04 (2.91–10.45)	0.554
MSP	40.42±13.92 (8.23–55.30)	41.09±18.25 (0.00–67.75)	0.619
EF	58.14±7.85 (44–73.67)	51.99±21.12 (4.23–76.82)	0.035*
Left submandibular			
FUR	1.89±0.42 (1.17–2.78)	1.88±0.45 (1.27–2.94)	0.619
MUR	2.55±0.56 (1.62–3.94)	2.32±0.39 (1.73–3.16)	0.868
MSP	29.50±13.47 (4.07–59.35)	27.36±9.30 (4.98–40.14)	0.210
EF	50.03±15.81 (12.70–69.30)	52.04±20.47 (14.65–89.46)	0.193

EF, excretion fraction; FUR, first-minute uptake ratio; MSP, maximum secretion percentage; MUR, maximum uptake ratio.
*Significant difference.

Table 4 **Comparison between the vitamin E and control groups after treatment**

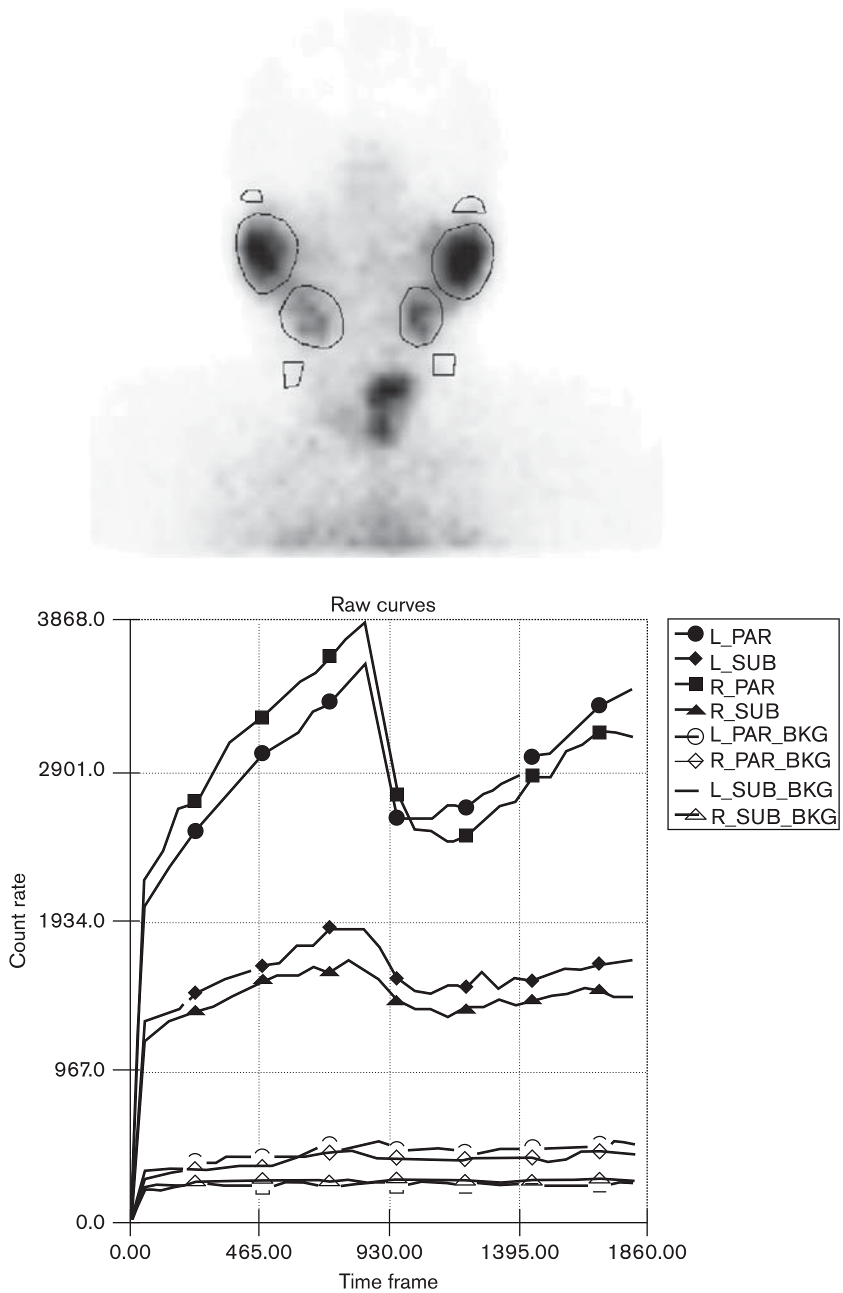
		Before and after values [mean±SD (range)]		
Type of salivary gland	Scintigraphic marker of functional changes[a]	Vitamin E group (n=19)	Control group (n=17)	*P*-value
Right parotid	ΔFUR	−0.39±0.97 (−2.88 to 0.97)	0.09±0.47 (−0.84 to 1.06)	0.04†
	ΔMUR	−0.80±2.11 (−8.08 to 2.75)	−0.21±0.84 (−2.26 to 1.31)	0.45
	ΔMSP	−4.67±12.43 (−25.88 to 23.53)	−2.05±10.48 (−24.48 to 22.19)	0.71
	ΔEF	−3.68±9.23 (−23.22 to 981)	−0.94±11.78 (−20.64 to 28.05)	0.60
Right submandibular	ΔFUR	−0.10±0.62 (−2.38 to 0.62)	−0.05±0.48 (−1.10 to 1.16)	0.98
	ΔMUR	0.5±0.77 (−1.93 to 1.72)	0.05±0.47 (−0.99 to 1.24)	0.88
	ΔMSP	4.86±14.39 (−27.94 to 42.13)	3.42±6.65 (−4.63 to 19.18)	0.96
	ΔEF	4.97±19.16 (−40.74 to 51.26)	5.97±12.97 (−3.94 to 51.49)	0.64
Left parotid	ΔFUR	−0.41±1.04 (−3.04 to 1.21)	−0.04±0.37 (−0.98 to 0.88)	0.38
	ΔMUR	−0.81±1.94 (−6.71 to 2.63)	−0.33±0.95 (−2.57 to 0.62)	0.23
	ΔMSP	−1.64±11.19 (−23.29 to 27.16)	7.25±17.78 (−13.82 to 48.83)	0.15
	ΔEF	0.43±9.48 (−15.16 to 23.57)	11.15±22.49 (−13.7 to 60.9)	0.04†
Left submandibular	ΔFUR	−0.16±0.57 (−2.24 to 0.71)	−0.11±0.50 (−1.01 to 1.02)	0.98
	ΔMUR	0.002±0.79 (−2.52 to 1.45)	−0.72±0.47 (−1.08 to 0.96)	0.43
	ΔMSP	4.40±13.15 (−25.53 to 33.31)	1.10±4.53 (−5.94 to 10.48)	0.28
	ΔEF	4.96±17.76 (−34.27 to 56.01)	4.76±14.49 (−9.96 to 56.08)	0.78

EF, excretion fraction; FUR, first-minute uptake ratio; MSP, maximum secretion percentage; MUR, maximum uptake ratio.
[a]For all scintigraphic parameters, the changes (Δ) after radioiodine treatment corresponding to the values before treatment were calculated as pretreatment minus post-treatment values.
†Significant difference.

increasing salivation using sour candy, lemon juice, or vitamin C tablets. However, the sour prescription has been shown to have little effect on the absorbed dose of the salivary glands [23]. Similarly, current evidence suggests that, despite the use of salivation-inducing snacks, functional impairment of salivary glands may occur after high-dose ^{131}I therapy in thyroid cancer patients [4,12,24]. Some researchers even reported that the use of lemon candy in close temporal proximity to ^{131}I administration leads to increased salivation and therefore to increased salivary gland blood flow, which in turn results in more ^{131}I uptake and subsequently more radiation and more damage to the salivary gland function [4]. However, no well-controlled clinical trial has been conducted so far to test this assumption.

Although it is generally accepted that the use of antioxidants may provide some degree of protection against ionizing radiation especially on the basis of animal experiments, known antioxidant radioprotectors have not been extensively prescribed to patients exposed to different levels of radiation [13]. Some nutrients such as vitamin E not only have the advantage of low toxicity but also exert a natural radioprotective effect when administered at pharmacological doses. The protective effects of vitamin E against radiation-induced chromoso-

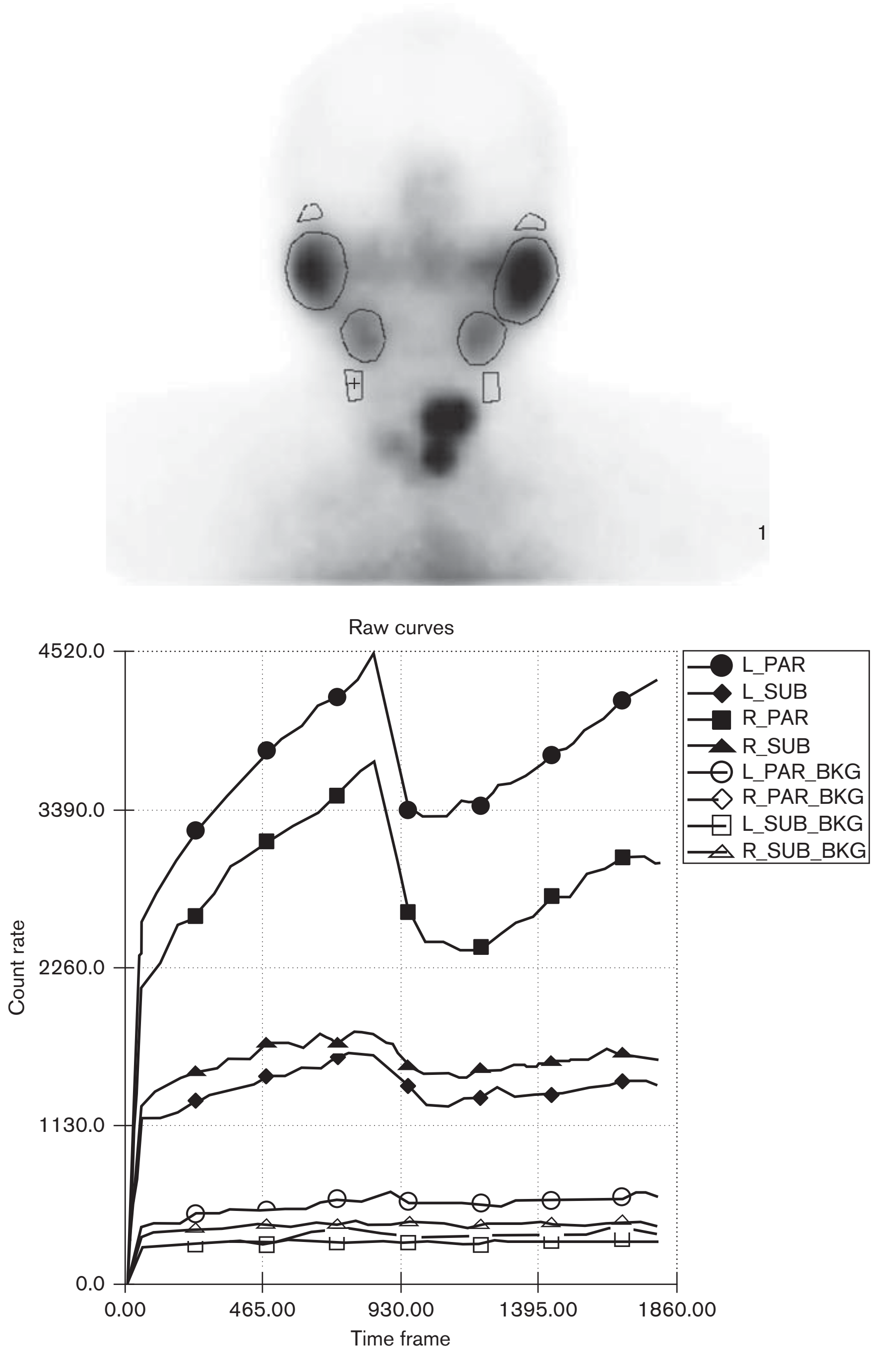
Fig. 1



Dynamic salivary gland scintigraphy in a patient pretreated with vitamin E before radioiodine ablative therapy (L_PAR, left parotid; L_SUB, left submandibular; R_PAR, right parotid; R_SUB, right submandibular).

mal aberrations and micronuclei have been established in rodents [13]. Previous studies on rats have shown that vitamin E and other antioxidant vitamins, by decreasing oxidative stress, exert some degree of protective effect against radiation-induced injuries such as oral mucositis, myelosuppression [25], intestinal injuries [26], lipid and DNA damage to the liver [27], and cataract [28]. Protection against radiation-induced damage in small bowel crypts of rats [29], modification of micronucleus induction by γ rays in mice [30], and in-vitro reduction in the number of micronuclei in human lymphocytes before and after γ-ray irradiation have also been reported by others [31]. More relevantly, in a study conducted on the radioprotective effect of vitamin E on the salivary gland function of irradiated rats, it was demonstrated that significant protection of salivary flow and volume could be achieved 30 days after irradiation in the group pretreated with vitamin E in relation to the control group [5].

Fig. 2

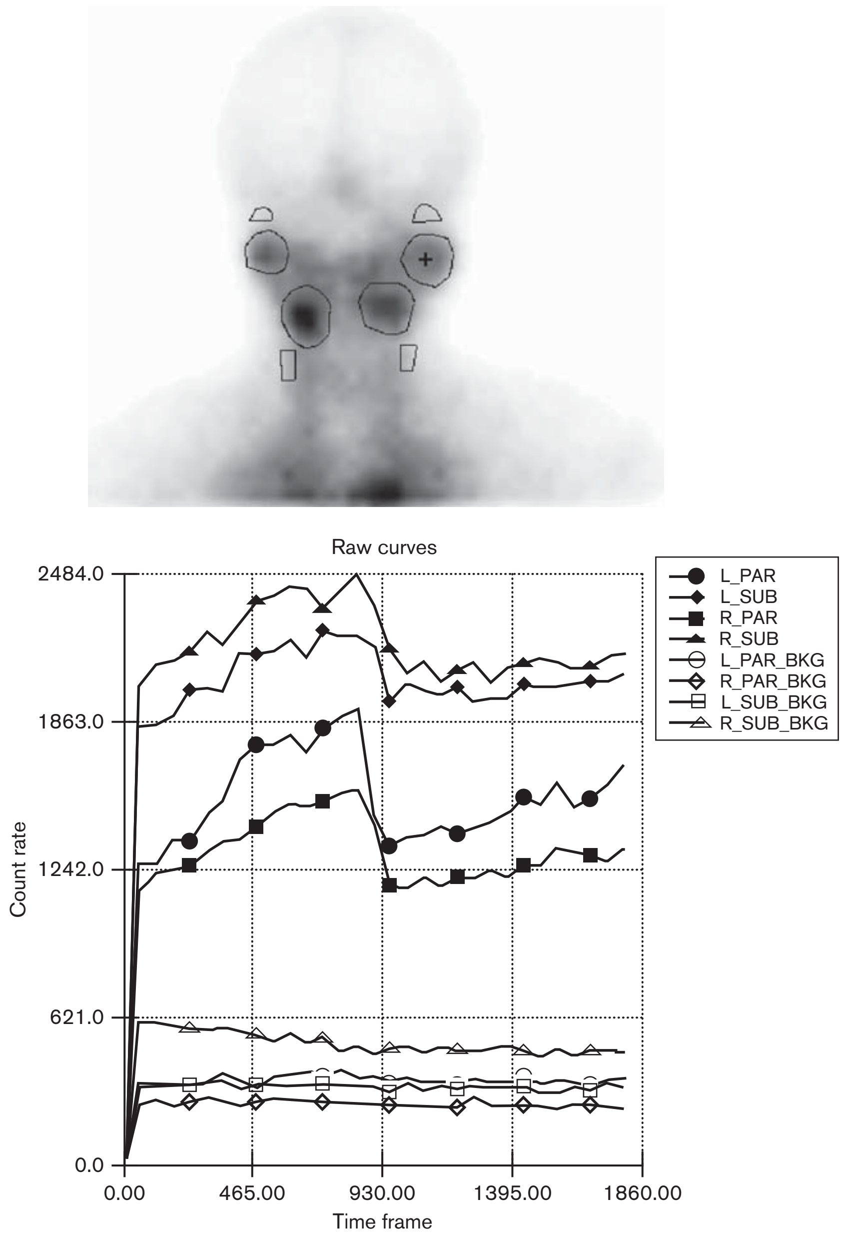


Post-therapy scintigraphy in the same patient 6 months after treatment with 5550 MBq ^{131}I without significant deterioration in salivary function (^{131}I, radioiodine; L_PAR, left parotid; L_SUB, left submandibular; R_PAR, right parotid; R_SUB, right submandibular).

In all of the above-mentioned studies the rodents were externally irradiated. The available data on the use of antioxidants for radioprotection of salivary glands against internal exposure to β-emitting radioactive iodine are limited. In a recent study, it was shown that presupplementation with vitamin E against a single dose of 3.7 MBq ^{131}I in mice may be associated with a marked beneficial antioxidant effect on salivary glands [32].

In contrast to the numerous studies performed on animals, only a few reports are available on the effect of vitamin E supplementation against radiation-induced

Fig. 3



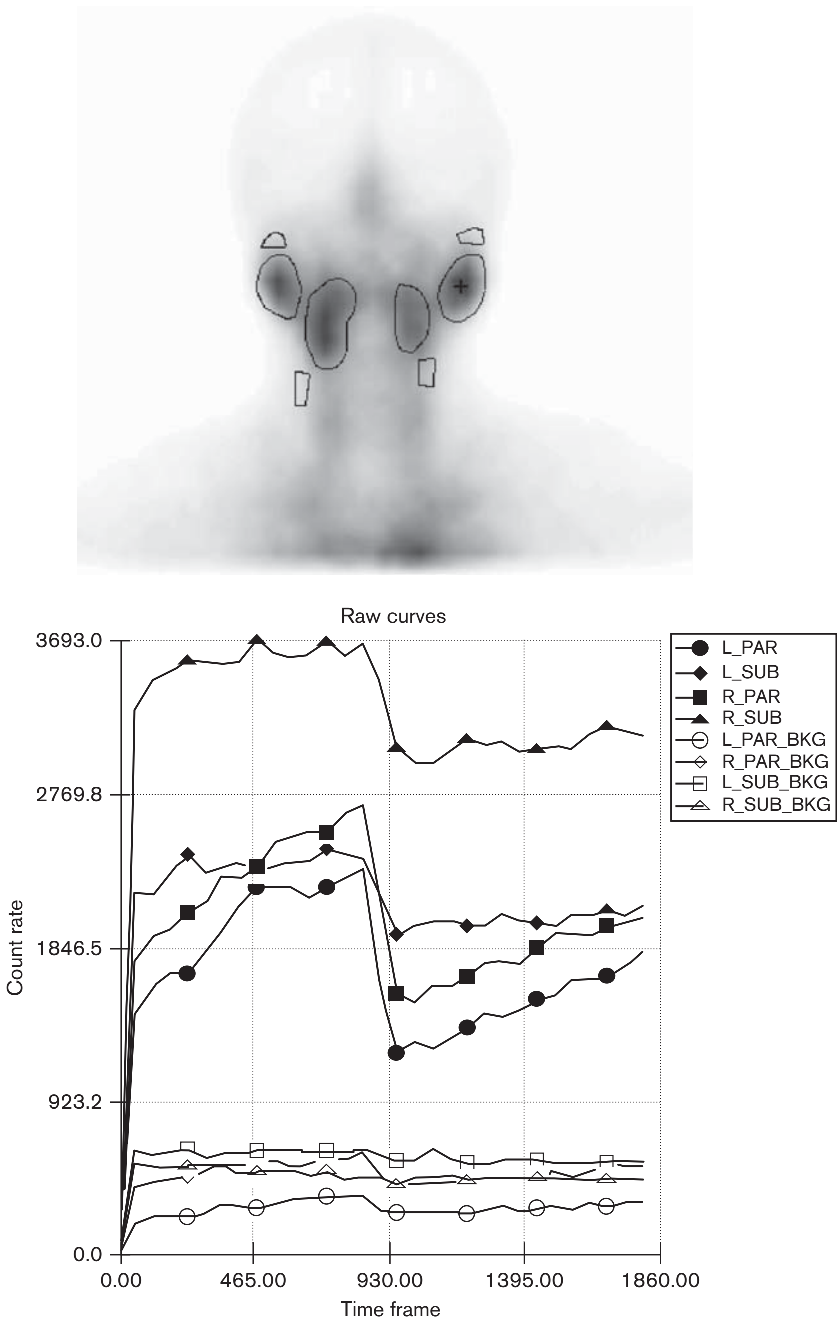
Scintigraphy of a control patient before radioiodine ablation therapy (L_PAR, left parotid; L_SUB; left submandibular; R_PAR, right parotid; R_SUB, right submandibular).

injuries to the salivary gland of humans after external or internal irradiation. In a study on patients who had undergone external radiation therapy against oral cancer, a considerable preservation of salivary flow rate and significant maintenance of some other salivary parameters such as pH, protein, amylase, sodium, and potassium contents were observed in the group with vitamin E supplementation as compared with the control group [33].

On the basis of the above-mentioned studies, vitamin E seems to have an important radioprotective effect on salivary gland function; however, no investigation has been performed so far with regard to the corresponding effects against ^{131}I therapy in humans [5].

To the best of our knowledge, our study is the first to investigate the radioprotective effect of vitamin E against radiation-induced damage to the salivary glands after a single-dose of ^{131}I therapy in thyroid cancer patients. In our study there was no significant decrease in salivary gland function after ^{131}I therapy in patients pretreated with vitamin E, whereas a significant decline was noted in the MSP and EF of the right submandibular and EF of the

Fig. 4



Scintigraphy in the same control patient showing significant drop in the first-minute uptake ratio (FUR) and maximum uptake ratio (MUR) of the left submandibular gland (L_PAR, left parotid; L_SUB, left submandibular; R_PAR, right parotid; R_SUB, right submandibular).

left parotid gland in the control group (Tables 2 and 3). Notably, there was no difference between the two groups at the beginning of the study, which in turn suggests that both groups were selected from a population with the same characteristics. In addition, the ΔEF of the left parotid glands in the control group differed significantly from that of the vitamin E group (Table 4). Significant deterioration of parotid gland excretion (more than 15% decrease in EF) was less frequent in patients pretreated with vitamin E when compared with the control group (7.9 vs. 26.5%).

Conclusion

Our study demonstrated a significant benefit from vitamin E consumption for the protection of salivary glands against radiation-induced dysfunctions during single-dose ^{131}I therapy among patients with differentiated thyroid cancer. However, we recommend further studies with larger sample sizes and different cumulative doses of ^{131}I to reach a more comprehensive conclusion with respect to these patients.

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Conflicts of interest

There are no conflicts of interest.

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