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Vitamin B_{12} levels are not affected by radioiodine ablation of the thyroid

[1]Potham SK, [1]Vaikkakara S, [1]Sachan A, [2]Rao S P.V.L.N, [3]Kalawat TC, [1]Ravi P, [1]Sunil E, [1]Rajitha D, [1]Arun M, [1]Sailaja A

[1]Department of Endocrinology and Metabolism, Sri Venkateswara Institute of Medical Sciences, Tirupati; [2]Department of Biochemistry, Sri Venkateswara Institute of Medical Sciences, Tirupati; [3]Department of Nuclear Medicine, Sri Venkateswara Institute of Medical Sciences, Tirupati, India
E-mail: sureshvdrsmailbox@rediffmail.com

Objective. Radioiodine administered for the treatment of hyperthyroidism and thyroid cancer can be taken up by many non-thyroid tissues which express sodium iodide symporter. Though gastric mucosa takes up radioiodine, its impact on parietal cell has not been evaluated. The aim of the present study was to compare vitamin B_{12} and homocysteine concentrations in patients with thyroid disorders treated by radioiodine ablation with those in control population without radioiodine exposure.

Methods. Patients with Graves' disease, toxic multinodular goiter (TMNG), toxic adenoma (TA) or differentiated thyroid cancer (DTC) who had received ^{131}I were included as "patients". Healthy persons and patients having Graves' disease but without exposure to radioiodine were recruited as "controls". A total of 35 patients and 35 controls were included. Patients were divided into Graves' disease and non-Graves' disease (TMNG, TA, DTC) groups. Graves' disease patients were compared with Graves' disease controls while non-Graves' disease patients were compared with healthy controls.

Results. In the Graves' disease group, median vitamin B_{12} concentration was 240 pg/ml (IQR: 148 - 371) in patients (n=23) and 195 pg/ml (IQR: 140 - 291 pg/ml) (p=0.13, ns) in controls (n=24). In the non-Graves' disease group, median serum vitamin B_{12} concentration was 147 pg/ml (IQR: 124 - 325pg/ml) in patients (n=12) and 190 pg/ml (IQR: 157 - 373 pg/ml) (p=0.34, ns) in healthy controls (n=11). Homocysteine concentrations were also similar in compared groups of patients and controls.

Conclusions. Radioiodine ablation does not cause vitamin B_{12} deficiency. However, a prospective study with a larger number of patients is required to confirm this finding.

Key Words: radioiodine ablation, vitamin B_{12}, gastric mucosa, parietal cells

Radioiodine treatment has been an integral part of management of hyperthyroidism and differentiated thyroid cancer for many decades now and has proven to be quite safe. Although few transient side effects like nausea, vomiting, and dysgeusia are reported by a significant proportion of patients receiving radioiodine, long term complications are rare and limited to those patients with metastatic thyroid cancer who received large cumulative doses of radioiodine (Ron et al. 1998; Chow 2005).

Sodium iodide symporter (NIS) is a membrane glycoprotein expressed in the thyroid gland which is responsible for the uptake of iodine, including radioactive iodine, by the thyroid gland (Levy et al. 1997). However,

Corresponding Author: Suresh Vaikkakara, Professor, Department of Endocrinology and Metabolism, Sri Venkateswara Institute of Medical sciences, Tirupati - 517507, India; phone: +91 - 9493547687; e-mail: sureshvdrsmailbox@rediffmail.com.

expression of this iodide transporter is not limited to the thyroid gland and occurs in many other tissues such as salivary glands, lachrymal glands, lactating mammary gland, gastric mucosa, choroid plexus, ciliary body of the eye, skin, placenta, and thymus (Spitzweg et al. 1998). This widespread expression of NIS is considered to be responsible for some of the unwanted side effects of radioiodine ablation of the thyroid.

For example, xerostomia due to damage to the salivary glands, which are known to express NIS and concentrate ^{131}I, is one of the commonest long term complications of radioiodine therapy (Mandel and Mandel 2003). However the long term effects of radioiodine on many of the other tissues such as gastric mucosa, if any, have not received much attention (PubMed search terms for which there were no relevant results were: *radioiodine ablation and vitamin B12, radioiodine ablation and gastric mucosa, radioiodine and B12 deficiency, ^{131}I and B_{12} deficiency*).

It is well known that gastric mucosa expresses NIS and concentrates iodide in its secretions (Spitzweg et al. 1998). This is responsible for the transient upper gastrointestinal symptoms, including nausea that commonly occur following radioiodine treatment. However, whether radioiodine treatment may have long term effects on gastric mucosa remains an unanswered question.

We hypothesized that radioiodine treatment may lead to some degree of permanent impairment of gastric parietal cell function and consecutively defective intrinsic factor secretion. This may then potentially cause malabsorption and deficiency of vitamin B_{12} in patients treated with radioiodine as compared to similar patients treated by other modalities. Severe vitamin B_{12} deficiency leading on to megaloblastic anemia or myeloneuropathy is unlikely to have escaped medical attention over the last several decades of follow-up of patients who have received radioactive iodine. However, more subtle chronic vitamin B_{12} deficiency has been linked to hyperhomocysteinemia (Herrmann et al. 2001), which in turn is a risk factor for atherosclerotic cardiovascular disease (Humphrey et al. 2008). Indeed, a few studies have reported increased mortality due to cardiovascular disease in hyperthyroid patients treated with radioactive iodine (Hall et al. 1993; Ron et al. 1998; Metso et al. 2004). These aspects have not been assessed before and hence the present study has been conducted.

Materials and Methods

Patients. This study was a cross sectional, observational study conducted in the Department of Endocrinology and Metabolism at a tertiary care teaching hospital. The study period was from March 2010 to August 2011. After careful review of the case records of patients who had received therapeutic/ablative dose of ^{131}I, they were selected based on the following inclusion and exclusion criteria and were designated as "patients" (n=35).

1) Patients with Graves' disease, having a diffuse toxic goiter, who had received therapeutic dose of radioiodine at least six months prior to the date of recruitment and had normal serum thyroxine (T_4) levels (55 - 135 ng/ml) and/or normal thyrotropin (TSH) levels (0.5 - 5 mIU/l) with or without medications. They were designated as Graves disease "patients" or Group 1 and included 23 patients.

OR

2) Patients with toxic multinodular goiter (MNG), toxic adenoma (TA) or well differentiated thyroid cancer, either papillary (PTC) or follicular (FTC), who had received ablative dose of radioiodine at least six months prior to the date of recruitment and who either had normal serum T_4 levels and/or TSH levels (for MNG and TA) or were on TSH suppressive doses of T_4 (for FTC or PTC) at the time of the study. They were designated as non-Graves "patients" or Group 2. There were 12 patients selected in this group (7 patients with PTC, 4 with MNG and 1 with TA).

Initial toxicity was diagnosed when patients case records showed serum T_4 > 135 ng/ml in the presence of a suppressed TSH < 0.5 mIU/l among patients presenting to the endocrine outpatient with symptoms suggestive of thyrotoxicosis or coming for evaluation of a goiter. Results of T_4 in the high normal range, but with a suppressed TSH (<0.5 mIU/l) were still considered to be toxic, albeit subclinically. The differential diagnosis of Graves' disease, toxic MNG and toxic adenoma in these patients of toxicosis were made on the basis of the pattern observed on Tc^{99m} thyroid scintigraphy (Bahn et al. 2011). Thyroid scintigraphy was performed in all the patients of toxic goiter using 4-6 m curie of i.v. Tc^{99m} Pertechnitate, with image acquisition on a dual head gamma camera (Symbia E dual head SPECT gamma camera by Siemens AG, Germany) at 20 min in anterior, and in right and left anterior oblique projections. Patients with homogeneous, diffusely increased (>4%) uptake on the radionuclide scan were diagnosed with Graves' disease while patients with foci of increased uptake interspersed with areas of normal or decreased uptake were given a diagnosis of toxic MNG. Toxic ad-

enoma was diagnosed in the presence of solitary focus of increased tracer uptake with decreased or absent uptake in the rest of the gland. Patients with thyroid cancer were selected based on the post operative histopathology report of either papillary or follicular thyroid carcinoma. All patients were required to have undergone near total thyroidectomy followed by radioactive iodine ablation with ^{131}I at least six months prior to their enrollment.

Persons who met the following inclusion criteria were also included in the study and were designated as "controls" (n=35).

1) Patients with Graves' disease (as defined earlier) who had normal serum T_4 levels and/or TSH levels while on antithyroid drugs or following surgery and who had no previous exposure to radioiodine were classified as Graves' disease "controls" or group 3. Twenty four patients were recruited into this group.

2) Apparently healthy euthyroid adults (i.e. having TSH between 0.5-5.0 mIU/l) without a history of any autoimmune disease or any other condition known to be associated with vitamin B_{12} deficiency and without previous exposure to radioiodine were classified as Non-Graves' ("healthy") controls or group 4. Eleven subjects were recruited into group 4. TSH was tested in these patients to confirm their euthyroid status.

The allotment of participants into different groups is summarized below in Fig. 1.

Patients or controls who had total gastrectomy or were on long term proton pump inhibitor therapy or were on treatment with drugs such as metformin or para amino salicylate which might affect the levels of serum B_{12} (Weir and Scott 1999), or those with diseases of terminal ileum, blind loop syndrome or any other condition known to be associated with vitamin B_{12} deficiency (Weir and Scott 1998) were excluded from the study. The study protocol was approved by the institute ethics committee. Informed consent was taken from all the subjects.

A detailed history was taken and complete physical examination was carried out. Complete details of radioiodine therapy such as the dose, timing and number of treatment sessions were obtained. Symptoms suggestive of anemia, myelopathy and neuropathy were enquired into. History regarding any condition or medication

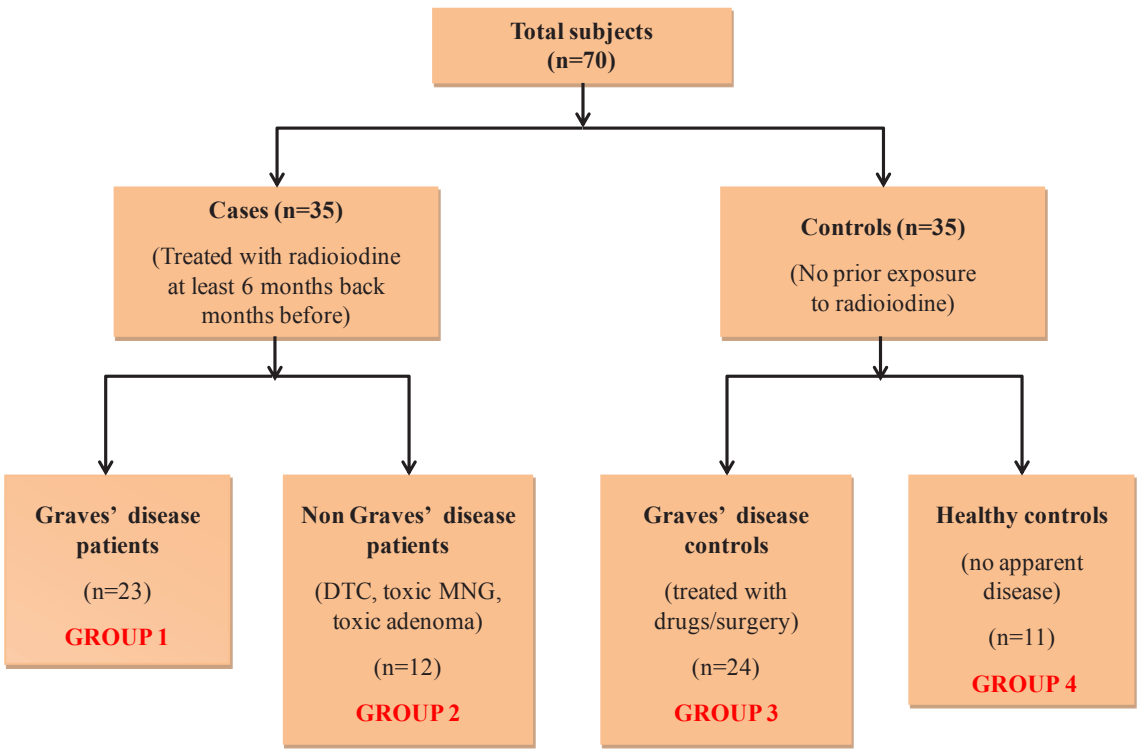

Fig. 1. Distribution of cases and controls into groups.

known to be associated with vitamin B_{12} deficiency was taken.

A complete physical examination was performed, focusing on signs of anemia, myelopathy and peripheral neuropathy. Neck examination for tumor recurrence or cervical lymphadenopathy was done in all patients being followed up for thyroid cancer. Any recent thyroid function tests were noted down and subjects were designated as having normal thyroxine levels if their serum total T_4 was between 55 to 135 ng/ml. Normal TSH was defined as 0.5-5 mIU/l.

Twelve milliliters of venous blood sample was collected from all the patients after an overnight fast between 8:00 a.m. and 9:00 a.m. Approximately 1.8 ml of blood was immediately transferred to an EDTA tube and was mixed thoroughly for the estimation of hemoglobin levels and examination of the peripheral blood smear. The remaining blood sample was immediately ice packed and centrifuged within one hour of collection. Serum sample was stored in two aliquots at -40°C for estimation of vitamin B_{12} and homocysteine concentrations at a later date.

Hemoglobin levels and red cell indices were estimated with the Mindry 5300 autoanalyser. Patients were diagnosed to be anemic if hemoglobin levels were less than 12 g/dl for female subjects and 13 g/dl for male subjects as defined by the World Health Organization (1968). Macrocytic anemia was diagnosed if the mean corpuscular volume was more than 100 femtolitres (Kaferle and Strzoda 2009).

Serum vitamin B_{12} levels were measured by chemiluminescence immunoassay (Beckman Coulter, Access 2). Vitamin B_{12} deficiency was defined by a serum vitamin B_{12} concentration less than 200 pg/ml (Hvas and Nexo 2006).

Serum homocysteine levels were determined by UV 2 point kinetic (fixed time) reaction, enzymatic recycling method using the kit supplied by DIALAB, intended for the quantitative determination of total L-homocysteine in human serum. Hyperhomocysteinemia was defined by serum homocysteine concentration of more than 12 μmol/l (Pandey et al. 2006).

Statistical analysis. Statistical analysis was done using SPSS software version 13.0 for windows. Correlations (Spearman correlation) were derived between serum vitamin B_{12} in patients who received radioiodine ablation and various relevant patient factors. Continuous variables were compared across groups by two independent samples non parametric test (Mann Whitney test). Chi-square test was used for comparison of proportions. Value $p<0.05$ was considered to be significant.

Results

Table 1 and Table 2 show the comparison between groups 1 and 3 and between groups 2 and 4, respectively, for age and sex distribution. Compared groups were matched for all these baseline characteristics ($p>0.05$). Graves´ disease patients groups 1 and 3 were all toxic at diagnosis with T_4 ranging from a minimum of 136 ng/ml up to highest of > 200 ng/ml (the upper limit of detection of the T_4 assay). All of them also had an undetectable TSH (< 0.15 mIU/l), except 5 who had TSH ranging from 0.17 to 0.3 mIU/l. Likewise, four patients with MNG were toxic with undetectable TSH (< 0.15 mIU/l) in all and T_4 values of 133, 230, 233 and 406 ng/ml, respectively. The single patient with TA had T_4 of 142 ng/ml with TSH < 0.15 mIU/l.

Table 1

Comparison of baseline characteristics of patients and controls in Graves' disease groups (groups 1 and 3)

Parameter	Graves' patients (n=23) (group 1)	Graves' controls (n=24) (group 3)	p value
Age in years as median (25-75 IQR)	41 (35 - 49)	36.5 (30 - 44)	0.1 (ns)
Sex ratio (female : male)	18 : 5	20 : 4	0.65 (ns)

Table 2

Comparison of baseline characteristics of patients and controls in Non-Graves' disease groups (groups 2 and 4)

Parameter	Non-Graves' patients (n=12) (group 2)	Healthy controls (n=11) (group 4)	p value
Age (years) as median (25-75 IQR)	41.5 (33 - 47)	33 (21 - 48)	0.2 (ns)
Sex ratio (female : male)	12 : 0	9 : 2	0.12 (ns)

Table 3

Comparison of serum vitamin B_{12} and homocysteine concentrations in patients and controls in Graves' disease group

Parameter	Graves' patients (group 1)	Graves' controls (group 3)	p value
Serum B_{12} (pg/ml) Median (25 – 75 IQR)	240 (148 - 371)	195 (140 - 291)	0.13 (ns)
Serum homocysteine (μmol/l) Median (25 – 75 IQR)	19.5 (13 - 31)	16 (10 - 22)	0.26 (ns)

Table 4

Comparison of serum vitamin B_{12} and homocysteine concentrations in patients and controls in Non-Graves' disease group

Parameter	Non Graves' patients (group 2)	Non Graves' controls (group 4)	p value
Serum B_{12} (pg/ml) Median (25 – 75 IQR)	147 (124 - 325)	190 (157 - 373)	0.34 (ns)
Serum Homocysteine (μmol/l) Median (25 – 75 IQR)	18.5 (10 - 28)	17.8 (13 - 29)	0.90 (ns)

Metabolic status of patients and controls at the time of recruitment. In the Graves' disease patients group (groups 1, n=23) 8 had normal levels of serum T_4 (113.25 ± 13.7 ng/ml) with suppressed TSH (0.13 ± 0.07 mIU/l). The remaining 15 patients were fully euthyroid, 9 having a normal TSH (2.6 ± 1.7 mIU/l) recorded and 6 having both normal T_4 (99.5 ± 25.4 ng/ml) and TSH (2.0 ± 1.3 mIU/l) at the time of recruitment into the study. Group 3 patients (Graves' controls, n=24) included 7 patients having a normal T_4 (82.6 ± 32.3 ng/ml) with suppressed TSH (0.18 ± 0.1 mIU/l). Thirteen other patients were fully euthyroid as they had both normal T4 (86.07 ± 15.05 ng/ml) and TSH (2.3 ± 1.03 mIU/l). Of the remaining 4 patients 3 were recorded to be having a normal T_4 of 76, 126 and 76 ng/ml, respectively, while one other patient had a normal TSH of 1.2 mIU/l. Thus the metabolic state of all the Grave´s patients (group 1) and controls (group 3) was close to the euthyroid state.

All the subjects in group 4 (healthy controls) were fully euthyroid as evidenced by a serum TSH of 2.57 ± 0.96 mIU/l. However, among the patients in group 2 (n=12), patients with toxic MNG and TA had both mean serum T_4 (120.25 ± 21.7 ng/ml) and TSH (1.09 ± 1 mIU/l) in the normal range, while all those with a diagnosis of PTC (n=7) were on suppressive levothyroxine treatment with an average T_4 dose of 3.5μg/kg. Consequently all of them had suppressed serum TSH (<0.15 mIU/l) with T_4 ranging from 138 - 179 ng/ml.

Patients in group 1 had received a median radioiodine dose of 6.7 mCi (IQR: 6-10 mCi) while those in group 2, which included patients with PTC, toxic MNG and TA, received a median radioiodine dose of 30 mCi (IQR:10-75 mCi).

The median duration between radioiodine treatment and inclusion in the study was 36 months (IQR: 14-80 months) in the group 1 and 21 months (IQR: 12-29 months) in group 2. None of the patients had any symptoms of neuropathy or myelopathy. Eight out of 35 patients had microcytic hypochromic anemia but none of the patients had macrocytic anemia.

Table 3 and Table 4 show the comparison between groups 1 and 3 and between groups 2 and 4, respectively for vitamin B_{12} and serum homocysteine. Compared groups had similar levels of both vitamin B_{12} and homocysteine (p>0.05).

Tables 5 and Table 6 show the comparison between groups 1 and 3 and between groups 2 and 4, respectively for the proportion of participants having low vitamin B_{12} (< 200 pg/ml) or elevated serum homocysteine (>12 μmol/l). There were no differences in such proportions between the compared groups.

Among all patients who were treated with radioactive iodine (groups 1 and 2), there was no significant correlation between serum vitamin B_{12} and dose of radioiodine received (p=0.29) or the duration between radioiodine treatment and testing (p=0.94).

Discussion

Radioiodine ablation is commonly used in the management of patients with hyperthyroidism and differentiated thyroid carcinoma. It has been used for several decades now and is considered to be a relatively safe modality of treatment despite both short term and long term side effects being reported after radioiodine treatment (Ron et al. 1998; Chow 2005). It is generally

accepted that the risk of serious long term complications is low and the benefits of treatment far outweigh the associated risks.

Expression of NIS and radioiodine uptake is not limited to the thyroid gland and occurs in many extrathyroidal tissues as well, the significance of which is uncertain (Spitzweg et al. 1998). Xerostomia (Mandel and Mandel 2003) and xerophthalmia have been reported after radioactive iodine ablation and have been linked to the expression of NIS on the salivary glands and the lachrymal glands, with resultant uptake of radioactive iodine leading on to chronic damage and decreased function of these glands. The long term effects of radioiodine on many of the other tissues that express the NIS, however, is not known and has not been studied properly.

Gastric mucosa is one of those extrathyroidal tissues that take up radioiodine (Spitzweg et al. 1998). This is responsible for the acute side effects such as nausea and vomiting, which are quite common. However, whether radioiodine causes permanent damage to the gastric mucosa is not known and there are no studies that have addressed this issue.

The present study was a cross sectional, observational study. All the participants had either a normal T_4 and/or a normal TSH at the time of entry into the study except those patients (n=7) with papillary thyroid carcinoma who were on suppressive doses of thyroxine and were thus thyrotoxic biochemically. Currently available data suggests that hyperthyroidism has no significant impact on serum concentrations of vitamin B_{12} or homocysteine (Nedrebo et al. 2003; Demirbas et al. 2004). Thus the presence of hyperthyroidism in some patients of group 2 does not make them different from the normal healthy controls (group 4) for the purpose of comparing vitamin B_{12} or homocysteine between them.

Vitamin B12 deficiency due to autoimmune atrophic gastritis (i.e. pernicious anemia) is a common cause of anemia in Graves' disease patients, who are at increased risk of developing this condition due to the autoimmune nature of both these conditions (Boelaert et al. 2010). Hence, to avoid the confounding influence of inadvertent co-occurrence of autoimmune pernicious anemia, the study was so designed that Graves' disease patients who had received radioiodine ablation therapy (cases) were compared only with Graves' disease controls (Graves' disease patients who had been adequately managed by either surgery or medical therapy).

In our study, we found that vitamin B_{12} deficiency was very common in all the four groups of subjects. Our data is in accordance with various other studies showing a high prevalence of vitamin B_{12} deficiency in the Indian population (Refsum et al. 2001; Yajnik et al. 2006).

Table 5

Comparison of proportion of participants with abnormal serum vitamin B_{12} and homocysteine concentrations among patients and controls in the Graves' disease groups

Parameter	Graves' patients (group 1)	Graves' controls (group 3)	p value
Proportion of participants with low serum B_{12} (< 200 pmol/l)	48%	50%	0.19 (ns)
Proportion of participants with high serum homocysteine (> 12 µmol/l)	87%	75%	0.29 (ns)

Table 6

Comparison of proportion of participants with abnormal serum vitamin B_{12} and homocysteine concentrations among patients and controls in the Non-Graves' disease groups

Parameter	Non Graves' patients (group 2)	Non Graves' controls (group 4)	p value
Proportion of participants with low serum B_{12} (< 200 pmol/l)	33%	45%	0.29 (ns)
Proportion of participants with high serum homocysteine (> 12 µmol/l)	67%	81%	0.4 (ns)

However, in our study there were no significant differences in serum vitamin B_{12} or homocysteine concentrations between patients treated with radioiodine and those without any exposure to radioiodine. To our best knowledge, there are no previous studies evaluating vitamin B_{12} concentrations in patients treated with radioiodine. As the present study is a pilot study and first of its kind, there are no comparable studies.

The lack of significant difference in vitamin B_{12} levels between patients and controls in our study could be due to many factors. Firstly, the exact cell type that expresses

the NIS in the gastric mucosa is not clear and is still controversial. Initial studies showed that gastric parietal cells actively take up radioiodine or ^{99m}Tc pertechnetate from serum and release the isotopes into the stomach (Williams 1983). Secretion of gastric acid correlated with ^{99m}Tc pertechnetate uptake and studies revealed autoradiographic localization of ^{99m}Tc pertechnetate to the parietal cells. However, gastric ^{99m}Tc pertechnetate uptake still occurred in some patients with paucity or complete lack of parietal cells, as with pernicious anemia, which could not be explained. Williams and Croft (1980) reported that ^{99m}Tc pertechnetate uptake occurs primarily in the gastric mucous cells, because of their finding that ^{99m}Tc pertechnetate uptake in the stomach increased in patients with gastric ulcer after treatment with carbenoxolone to normalize mucous cells. Furthermore, some newer autoradiographic studies localized ^{99m}Tc pertechnetate uptake to the mucous cells (Chaudhuri and Polak 1977). However, others reported that NIS immuno-reactivity is confined to parietal cells (Kotani et al. 1998; Spitzweg et al. 1999). Hence, the issue remains unresolved.

If it is indeed the surface mucous cells that express NIS and not the parietal cells, then intrinsic factor secretion and absorption of vitamin B_{12} will not be affected by radioiodine ablation. This may be responsible for the lack of significant difference in the vitamin B_{12} levels between patients and controls in the present study.

Secondly, the gastric mucosa has the capacity to regenerate itself. Normally the mucosal cells of gastrointestinal tract get entirely replaced every two to three weeks. It is possible that the progenitor cells of parietal cells in the gastric mucosa are unaffected by radioactive iodine, as they may not yet be differentiated enough to express the NIS. Thus in spite of causing acute damage, radioiodine may be unable to inflict any degree of permanent damage to the gastric mucosa.

Thirdly, large amounts of vitamin B_{12} are stored in the liver and even persons who stop consuming vitamin B_{12} in their diet do not become deficient for at least several years (Herrmann et al. 2001). However, vitamin B_{12} is secreted in bile and undergoes entero-hepatic circulation and if this entero-hepatic circulation is interrupted for any reason, including intrinsic factor deficiency, clinical features of vitamin B_{12} deficiency can manifest much earlier, often within few months (Weir and Scott 1998). Hence, an arbitrary time gap of six months between radioiodine treatment and date of inclusion was chosen for the purpose of the present study. Though the median duration between radioiodine treatment and inclusion in the study was 36 months (IQR: 14-80 months) in the Grave´s disease ^{131}I ablated patients and 21 months (IQR: 12-29 months) in the non-Graves disease ^{131}I ablated patients we really do not know if this duration was sufficient for the depletion of the hepatic vitamin B_{12} stores and for the patients to manifest vitamin B_{12} deficiency if their parietal cells were indeed damaged. However, considering the frequent vitamin B12 deficiency in our patients as well as that reported from other Indian studies (Refsum et al. 2001; Yajnik et al. 2006), we do not assume that they had sufficient stores of hepatic vitamin B12. Thus we feel that it may not be necessary to monitor over a longer time interval between ^{131}I treatment and measurement of serum vitamin B_{12} levels.

The present study has certain limitations. The number of patients included in the study was small. As it was a pilot study, the exact sample size needed to give the study sufficient statistical power was not known prior to the study. It was a cross sectional study and ideally these patients who received radioiodine treatment should be followed up prospectively to see if they develop vitamin B_{12} deficiency in the future.

With these limitations in mind, we conclude that radioiodine administered for the purpose of ablation of thyroid gland in hyperthyroidism and thyroid cancer does not appear to cause permanent damage to the gastric mucosa and does not lead to vitamin B_{12} deficiency at least in the initial few years after therapy. Further the increased cardiovascular mortality, previously reported in few studies (Hall et al. 1993; Ron et al. 1998; Metso et al. 2004) in hyperthyroid patients treated with radioiodine cannot be attributed to hyper-homocystenemia in this population. However, a prospective follow up study with a larger number of patients is required to confirm or refute these findings.

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