Assessment of Gonadal Function Following Single Dose of Radioiodine Therapy in Differentiated Thyroid Cancer Patients of Reproductive Age

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ABSTRACT

Objective: **This interventional study has undertaken to assess the gonadal function of differentiated thyroid cancer (DTC) patients within reproductive age group following single dose of radioactive iodine (131-I) therapy/ablation.**

Patients and Methods: **A total of 69 patients (25 male and 44 female) of DTC were included in this study, those were referred for 131-I ablation after total thyroidectomy. Following RAI, these patients were followed-up three times at three months interval. The usual 131-I dose was 75 or 100 mCi for ablation of thyroid residues and 150 mCi for treatment of nodal metastasis. All the patients were interviewed about menstrual (female only) and reproductive history and investigated of the level of follicle stimulating hormone (FSH), luteinizing hormone (LH), testosterone of male patients and FSH, LH, estradiol (E2) of female patients before administration of 131-I and three, six and nine months after therapy.**

Result: **In this study all of the 25 (100.0%) male patients showed high FSH level after three months of therapy. The mean ± SD FSH level of male patients was found significantly (p-0.001) higher (15.59 ± 7.53 IU/L) after three months of therapy than the pretherapy (4.85 ± 2.57 IU/L) level. The mean ± SD of FSH level was significantly declining in six months and nine months of follow up. The mean ± SD of LH hormone level of these patients was found 6.1 ± 3.67 IU/L in pretherapy which was significantly increased to 7.67 ± 4.33 IU/L after three months. The mean LH level was 7.20 ± 3.98 IU/L at six months follow up and 7.3 ± 3.5IU/L after nine months. The differences of LH level between 3 months to 6 months and 6 months to 9 months are not statistically significant. No significant change was observed in testosterone level throughout the study period.**

In female, five patients developed irregular menstruation (changed duration of cycle or lighter amount), three patients developed amenorrhea associated with hot flashes within six months of 131-I administration. Biochemical study of the patients with amenorrhoea showed markedly elevated serum FSH, LH level and declined E2 level. The FSH, LH levels of the two patients with amenorrhea became normal within study period and one patient had persistent amenorrhea at 9 months. E2 level raised slowly.

Conclusion: **A single dose of radioiodine (131-I) therapy causes impairment of gonadal function of male patients within reproductive age group. In case of female patients the effect is insignificant. The effect is usually reversible and gonadal function of the patients restores within the study period.**

Key Words: **Gonadal function, Radioiodine ablation, Differentiated thyroid cancer.**

INTRODUCTION

Thyroid cancer is the most common endocrine malignancy accounting for 90% of all endocrine cancers. Annual incidence of thyroid cancer varies from 0.5 to 10 per 100000 populations throughout the world (1). Age and gender adjusted incidence of thyroid cancer has increased than any other malignancy. Thyroid cancer is commonly diagnosed at a younger age than most other adult cancers. Nearly two out of three cases of thyroid cancer are seen in people younger than 55 years of age (2).

Papillary and follicular thyroid cancers are referred to as differentiated thyroid cancers (DTC) which account for more than 90% of all thyroid cancers (3). The prognosis of differentiated thyroid cancer if appropriately treated is very good in both non-metastatic and local or distant metastatic cases, although the 10-years survival rate in case of distant metastasis is relatively lower (25-40%) than overall cause-specific survival rate as a whole, which is estimated at approximately 85% (4). Since young adults in their reproductive age can be affected by thyroid cancer and have excellent prognosis after treatment, longer survival of the cancer patients gives rise to questions about the quality of survival and complications of cancer therapy.

Radioactive iodine 131-I has been used for treatment of DTC for around 68 years (5). RAI ablation is usually performed 15-40 days after total thyroidectomy and can be repeated at six months interval. The dose of radioactive iodine (RAI) ranges from 1.1 to 5.5 GBq (30 to 150 mCi) or more (6). RAI (an isotope emitting beta and gamma energies during decay) after oral administration goes to the site of thyroid follicular

cells – healthy or cancerous. Excess RAI is cleared from the body through kidneys and gut. Therefore, blood, urinary bladder, gut and pelvic metastases act as primary sources of radiation to male and female gonads. Furthermore, patients are hypothyroid at the time of RAI therapy which slows gut and renal clearance of radioiodine prolonging gonadal exposure to radiation (7). Gonadal damage following chemotherapy and radiotherapy is well established (8). It has been reported that germinal cell got damaged following RAI therapy for DTC in a small group of male patients (9). Similarly, transient ovarian failure and increased incidence of miscarriage has also been reported within one year of RAI therapy (10).

Since a good number of patients with DTC are young and wish to have children, there remains concern whether fertility is impaired because of irradiation of ovaries and testicles or not. It is therefore needed to investigate the gonadal function in our population following RAI therapy for DTC.

Objective of this study was to assess the gonadal function of differentiated thyroid cancer patients within reproductive age group following single dose of radioactive iodine (131-I) therapy/ablation.

PATIENTS AND METHODS

The interventional study was carried out in National Institute of Nuclear Medicine and Allied Sciences (NINMAS), Dhaka, Bangladesh over a period of one year. Study population includes 69 post-surgical diagnosed cases of differentiated thyroid cancer referred for radioiodine ablation. All confounding variables impairing gonadal functions, e.g. previously treated with radiotherapy or chemotherapy, female patients with any gynecological abnormality or history of gynecological operation affecting gonadal function, male patients with testicular diseases or operation, patients having previous history of infertility or impaired fertility, diagnosed cases of panhypopituitarism or hormone secreting pituitary tumors, congenital anomalies like Turner syndrome, Klinefelter syndrome etc, few diseases and drugs affecting gonadal function (as mumps, anabolic streroids etc) were excluded.

Among the 69 patients of DTC, 25 (36.2%) were male and 44 (63.8%) were female with male-female ratio 1:1.8. The age range of male patients was 18 to 53 years (mean ± SD, 37.1 ± 10.8 years) and that of female patients was 15 to 40 years (mean ± SD, 27.5 ± 7.2 years). All the female patients had regular menstrual cycles and no history of any gynecological abnormalities before 131-I administration. After taking proper clinical history, a careful physical examination was carried out. Then blood sample was collected to measure serum level of FSH, LH, testosterone in male patients and FSH, LH, estradiol in female patients. Then all the patients received a single dose of 131-I. Patients without metastasis were given 75-100 mCi of radioactive iodine (131-I) and patients with loco-regional or distant metastases were given 150 mCi of 131-I. Among the 25 male patients, two patients received 75 mCi, 13 patients received 100 mCi and 10 patients received 150 mCi of 131-I with the mean dose of 118.0 ± 27.5 mCi. In case of female patients, 18 patients received 75 mCi, 14 patients received 100 mCi and 12 patients received 150 mCi of 131-I with the mean dose of 103.4 ± 30.8 mCi. The interval between surgery and 131-I administration was 3-5 weeks and all the patients were hypothyroid at the time of 131-I administration. The mean ± SD of TSH level before RAI ablation was 54.38 ± 18.54 mIU/L in male and 67.11 ± 21.03 mIU/L in female patients. After administration of 131-I, levothyroxine therapy was started at suppressive dose of 2.2 mcg/kg/day. All the patients were asked to come after three, six and nine months of RAI ablation for follow-up. In every follow-up, again clinical history was taken, physical examination was performed and dose of levothyroxine was adjusted if needed to achieve targeted level of TSH suppression (< 0.1 mIU/L). Then blood samples were

collected to measure serum level of above mentioned hormones. Normal reference laboratory values of FSH for male - 1.32-7.44 IU/L and for female at follicular phase - 1.82-7.75 IU/L, ovulatory phase - 5.17-29.25 IU/L and luteal phase - 0.75-4.15 IU/L, LH of adult male - 3.11-12.33 IU/L and in female at follicular phase - 2.84-13.74 IU/L, ovulatory phase - 15.05-72.20 IU/L and in luteal phase - 1.72-13.26 IU/L, Serum testosterone (male): 3.2-14.6 ng/ml and estradiol (female) : 31-417 pg/ml

Statistical analysis was performed using SPSS package 16.0 (SPSS Inc, Chicago, Illinois, USA). Statistical analysis was evaluated by paired't' test and 'Z' test of proportion. A p-value ≤ 0.05 was taken as significant.

RESULTS

Among 69 patients all 25 (100%) male patients had PTC and 43 (97.73%) female patients had PTC and only one (2.27%) female study subject had FTC. Among 44 female patients 34 (77.3%) were married and 10 (22.7%) patients were unmarried and it was observed that majority (85.3%) of the married patients took oral contraceptive pills (OCP). were married and 10 (22.7%) patients were unmarried and it was observed that majority (85.3%) of the married patients took OCP. Table 1 shows changes of mean ± SD of serum FSH, LH and testosterone level in male patients from pretherapy to three months after radioiodine therapy. The mean ± SD of FSH of male patients was found 4.85 ± 2.57 IU/L in pretherapy which was significantly ($p<0.05$) increased to 15.59 ± 7.53IU/L after three months. The mean ± S D of LH was found 6.1 ± 3.67 IU/L in pretherapy and 7.67 ± 4.33IU/L after three months, the change in mean level was also statistically significant ($p<0.05$). The mean ± SD of testosterone was found 4.88 ± 2.9 ng/ml in pretherapy and 4.95 ± 2.15 ng/ml after 3 months, which was not statistically significant.

The mean ± SD of FSH level of male patients was significantly decreased from 3 months (15.59 ± 7.53 IU/L) to six months (9.58 ± 4.45 IU/L) after therapy ($p < 0.05$). The difference between mean ± SD of LH level between three months (7.67 ± 4.33 IU/L) and six months (7.20 ± 3.98IU/L) was not statistically significant ($p > 0.05$).The mean ± SD of testosterone level was found 4.95 ± 2.15 ng/ml after three months and 5.46 ± 2.73 ng/ml after six months following therapy which was not statistically significant (Table 2).

The changes of mean ± SD of serum FSH, LH and testosterone level in male patients from six months to nine months after radioiodine therapy were shown in table III. The mean ± SD of FSH level of male patients decreased significantly from six months to nine months. Changes in mean ± SD of LH and testosterone from six months to nine months were not statistically significant ($p = 0.849$ and 0.091 respectively).

Regarding the menstrual history, all 44 (100%) patients had history of regular menstruation before therapy (pretherapy). After three months four (9.1%) patients developed irregular menstruation which increased to five (11.4%) after six months and decreased to two patients (4.55%) after nine months. At three months follow up no patient was found with history of amenorrhea. Whereas, three (6.8%) patients developed amenorrhea after six months and in one of them (2.27%) amenorrhea persisted till nine months of follow up (Table 4).

It was also observed that the period of amenorrhea was brief (lasting less than five months) in two patients and persisted throughout the study period in one patient. Biochemical study of the three patients with amenorrhea showed marked elevated serum FSH, LH level and declined E2 level. The FSH, LH levels of the two patients having transient amenorrhea associated with hot flash became normal within study period and E2 level was elevated slowly. Again three out of five patients with history of menstrual irregularity had temporary slightly elevated FSH, LH level which returned to normal within six months. Their serum E2 levels were unchanged after radioiodine therapy.

Table 1: Different hormone levels in male patients in pretherapy and 3 months of follow up

Hormones	Pretherapy Mean ± SD	After 3 months Mean ± SD	P value
FSH (IU/L)	4.85 ± 2.57	15.59 ± 7.53	0.001^{s}
LH (IU/L)	6.1 ± 3.67	7.67 ± 4.33	0.041^{s}
Testosterone (ng/ml)	4.88 ± 2.90	4.95 ± 2.15	0.897^{ns}

P value reached from paired "t" test ns- not significant s- significant

Table 2: Different hormone levels in male patients in 3 months and 6 months of follow up

Hormones	After 3 months Mean ± SD	After 6 months Mean ± SD	P value
FSH (IU/L)	15.59 ± 7.53	9.58 ± 4.45	0.001^{s}
LH (IU/L)	7.67 ± 4.33	7.20 ± 3.98	0.306^{ns}
Testosterone (ng/ml)	4.95 ± 2.15	5.46 ± 2.73	1.153^{ns}

P value reached from paired "t" test ns- non significant s- significant

Table 3: Different hormone levels in male patients in 6 months and 9 months of follow up

Hormones	After 6 months Mean ± SD	After 9 months Mean ± SD	P value
FSH (IU/L)	9.58 ± 4.45	6.91 ± 3.06	0.001^{s}
LH (IU/L)	7.20 ± 3.98	7.30 ± 3.50	0.849^{ns}
Testosterone (ng/ml)	5.46 ± 2.73	6.25 ± 2.93	0.091^{ns}

P value reached from paired "t" test ns- non significant s- significant

Table 4: Distribution of the female study patients according to menstrual history (n = 44)

Menstrual history	Pretherapy	After 3 months	After 6 months	After 9 months
	N (%)	N (%)	N (%)	N (%)
Regular	44 (100)	40 (90.9)	36 (81.8)	41 (93.18)
Irregular	0	4 (9.1)	5 (11.4)	2 (4.55)
Amenorrhea	0	0	3 (6.8)	1 (2.27)

DISCUSSION

Radioactive iodine exerts both beta and gamma radiation which are ionizing radiation that can result in tissue damage and disruption of cellular function at the molecular level. In males, the spermatogonia are the cells most sensitive to the effects of ionizing radiation and in females, the mature oocyte is less sensitive than male spermatogonia cells, but it is the most radiosensitive female reproductive cell (11).

After oral administration of 131-I, it goes to the site of thyroid follicular cells – healthy or cancerous and excess RAI is cleared from the body through kidneys and gut. Therefore, blood, urinary bladder, gut act as the sources of radiation to the surrounding tissues. Besides these, pelvic metastasis also concentrates 131-I. Furthermore, patients are hypothyroid at the time of RAI therapy which causes slow gut and renal clearance resulting more prolonged exposure of male and female gonads to radiation (7, 12). In this condition, the estimated radiation dose to the testis is higher (0.5-1.5 rad/mCi) than that (0.085 rad/mCi) of a euthyroid adult. Thus the cumulative radiation to the testes after a standard dose of 100 mCi is roughly 50-150 rad per treatment (12). It is reported that, transient suppression with subsequent recovery of spermatogenesis occurs with doses as low as 0.5 Gy (50 rad). Following 2–3 Gy (200-300 rad) there is a period of azoospermia after which full recovery is expected within three years. The Leydig cell is more resistant to irradiation. Nevertheless, a dose of irradiation in excess of 15 Gy (1500 rad) may be sufficient to affect Leydig cell function and production of testosterone (13).

Handelsman et al. first reported about the complication of testicular damage of male patients treated by radioiodine for thyroid carcinoma. They found azoospermia, oligospermia, elevated serum FSH and LH level and subnormal testosterone level within one to 42 months after radioiodine therapy (9). Another report showed a 13 years old boy with an elevated FSH, normal LH and testosterone level suffering from gonadal damage following two doses of 131-I. One years after therapy he developed azoospermia (8).

In this study all of the 25 (100.0%) male patients showed high FSH level three month after therapy which

gradually decreased in six months and nine months follow-up. Similarly serum LH level increased significantly from pre therapy to three months follow up and decreased slightly in six months and nine months follow-up which was not statistically significant.

The Leydig cell is more resistant to irradiation. A dose of irradiation in excess of 15 Gy may be sufficient to affect Leydig cell function and production of testosterone (13). In this study, it was observed that the mean ± SD of testosterone level showed no significant change from pretherapy to three, six and nine months follow-up. This indicates that the therapy dose of RAI was not adequate enough to significantly affect the Leydig cells to hamper the production of testosterone.

Based on these data, the finding of an increased serum FSH level after 131-I therapy is one of the markers of germinal cell failure. Each single treatment was frequently associated with elevation of FSH level with respect to the pre-treatment value. The declining level of FSH indicated possible recovery of gonadal function. Two different groups of researchers reported about azoospermia and oligospermia following radioiodine therapy (8, 9), which could not be tested in this current study.

In case of female patients ovarian dose estimations that are roughly three fold higher than the MIRD estimation of 0.14 cGy (0.14 rad)/37 MBq (1mCi) (7). Irradiation produces severe dose-related gonadal damage to both the germ cell and endocrine components of ovarian tissue. It may cause immediate permanent sterility, temporary cessation of menses or lead to a premature menopause. Immediate ovarian failure will be produced by 16.5 Gy in females of 20 years, while 14 Gy is sufficient in 30-year-olds (13).

Female patients came at different phases of ovarian cycle (follicular, ovulation and luteal phase) at different follow-up. As the FSH and LH levels differ in different phases of ovarian cycle, so quantitative data (FSH and LH hormone level) could not be analyzed in case of female patients. Only analysis of qualitative data (number of patients who experienced ovarian dysfunction or failure) was done in case of female patients.

Raymond et al. studied on ovarian function of a group of non-menopausal women after total thyroidectomy followed by radioiodine ablation due to DTC. They found that approximately 30% of the non-menopausal women had temporary ovarian failure within the first year after thyroidectomy and 131-I remnant ablation. The period of amenorrhea was brief. The high serum FSH, LH values in the women with temporary amenorrhea clearly indicate the presence of ovarian failure (10). Vini et al. reported in another study that temporary amenorrhea lasting for up to 10 months occurred in about 8% of patients after ablative radioiodine. In patients with amenorrhea there was a temporary marked increase of FSH and LH level indicating transient ovarian failure. Patients who developed amenorrhea were relatively older aged. Permanent ovarian failure was rare after therapy and fertility do not appear to be reduced. Menstrual disturbance was related to higher cumulative doses of RAI and older ages (14).

In this study, all the 44 (100%) patients showed regular menstrual history in pretherapy. Three (6.8%) patients developed amenorrhea associated with hot flash after six months of therapy which was statistically non-significant ($p>0.05$). The period of amenorrhea was brief in two patients and persisted throughout the study period in one patient. Amenorrhea never developed immediately after therapy. The average age of the three patients who experienced amenorrhea was higher (40 years) than those who had no menstrual abnormality. Even though all women were biochemically hypothyroid at the time of 131-I administration, a relationship between hypothyroidism and amenorrhea was eliminated because the ovarian failure that occurred in these patients always arose after the start of levothyroxine replacement therapy.

From the biochemical examinations of the patients with amenorrhea associated with hot flash, high FSH and LH level and low estradiol (E2) level were observed at six months follow-up. The FSH and LH level of the two patients returned to normal after restoration ovarian function at nine months follow-up. Two of the three patients who developed amenorrhea, received 150 mCi dose of 131-I and one received 100 mCi of 131-I . The likely explanation for the occurrence of temporary amenorrhea in only a few women is variable ovarian sensitivity to irradiation. Beside this, 34 (77.3%) out of total 44 female patients were married and 10 (22.7%) patients were unmarried and it was observed that majority (85.3%) of the married patients took OCP. Raymond et al. showed there was an inverse relationship between the use of an estrogen/ progesterone contraceptive and the likelihood of temporary amenorrhea, indicating a small protective role on ovarian function for the hormone therapy (10). In addition at three months follow-up, four (9.1%) patients showed irregularity of menstruation, at six months follow-up, the number of the patients increased to five (11.4%) and at nine months follow-up only two (4.55%) patients persist irregular menstruation.

CONCLUSION

Differentiated thyroid carcinoma when treated with high doses of radioiodine has an excellent long-term prognosis. But radiation therapy is always associated with some fear. Incidence of DTC is increasing among the young generation and as life expectancy is increasing following RAI therapy, people became concern about the adverse effect of radioiodine on their reproductive life. This current study showed that single high doses of radioiodine therapy is associated with transient gonadal dysfunction in the form of raised FSH and LH levels in males and menstrual irregularity and amenorrhea in only a few female patients. The effect is usually reversible and gonadal function restores within a year.

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