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ORIGINAL ARTICLE

Thyroid, Parathyroid and Gonadal Function, and Glucose Tolerance After Bone Marrow Transplantation and Chemotherapy

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Following bone marrow transplantation (BMT), life expectancy of many patients increases, necessitating medical follow up, especially function of the endocrine gland. Previous studies have shown that endocrine dysfunctions are caused not only by total body irradiation, but also by cytotoxic conditioning regimens.

Materials and Methods: 46 patients (12 F, 34 M), aged 1.5-49 years were evaluated for thyroid (T3, T4, TSH, T3RU, FTI, Anti Tg-Ab, Anti TPO-Ab), parathyroid (Ca, Alkp, PTH), gonad function (LH, FSH, E2, progesterone in females and semen analysis in males) and function of β-cells of pancreas by O.G.T.T (in 12 major thalassemic patients) before and 3, 6, 12, 24 months after BMT, by the "Little" Busulfan-Cyclophosphamide conditioning regimen.

Results: There are no differences between results of clinical examinations and laboratory tests of pre and post BMT function of thyroid or parathyroid and calcium metabolism. The function of leydig cells was normal in 11 adult men (G5P5) before and 3, 6, 12 months after BMT, but injury of germinal cells (oligo- or azospermia) before and 12 months after BMT was seen. There is no relation between FSH and injury of germinal cells. Development of puberty was normal in 5 boys (G2P2 or G3P3) before and one year after BMT Primary hypogonadism was induced in 4 females (B5P5) after BMT In one 14 year-old female, regular menstruation continued 2 years after BMT In one girl (P1B1 before BMT) ovarian failure developed 12 months after BMT. Function of β-cells in thalassemic patients (Ferritin>1000 before BMT) before and after BMT was normal.

Conclusion: One year after B.M.T, the chemotherapy-conditioning regimen per se did not affect function of thyroid or parathyroid gland, but ovarian failure and germinal cells injuries developed (without effect on leydig cells). BMT had no effect on the function of β-cells of the pancreas.

Key Words: Bone marrow transplantation, thalassemia major, thyroid, parathyroid, puberty, gonad, glucose.

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Introduction

Bone marrow transplantation (BMT) is defined as intravenous infusion of hematopoietic precursor cells to restore the function of bone marrow, which may be immature or have been destroyed due to various factors. The procedure is used to treat a wide range of benign and malignant hematologic or non-hematologic diseases.[1]

Increasing usage of bone marrow transfusion has increased the number of children and adults who can now survive longer

despite their benign or malignant diseases. Therefore, increased attention is being paid to enhancing the quality of life of these patients.[2]

Bone marrow transplantation was begun in March 1991 in Shariati hospital. Like other procedures, BMT affects different organs of body, leading to acute and chronic complications,[3] including neuroendocrine disorders.[2]

The extent and severity of post transplant complications on the neuroendocrine system are influenced by the conditioning protocol performed prior to transplant,[2] that includes either total-body irradiation accompanied by chemotherapy, or chemotherapy alone.[2] Previous studies have shown that gonadal and thyroid dysfunctions have been seen in the patients during their growth stages resulting from radiotherapy or chemotherapy protocols performed before transplant, especially in those with major thalassemia.[4-9]

The aim of this study was to investigate, thyroid, and gonadal fuction, as well as carbohydrate metabolism following bone marrow transplantation. The conditioning protocol consisted of only chemotherapy. Bone marrow transplantation was performed using autologous and allogenic transplants. The maximum chemotherapy regimen administered (without total body irradiation - TBI) before allogenic bone marrow transplantation included the use of Busulphan-Cyclophosphamide (B4-Cy).[10]

Cyclophosphamide may be administered in high doses (200 mg/kg) with busulfan (16 mg/kg), known as "Big Bu-Cy". Currently, in most cases, low doses of cyclophosphamide known as "little Bu-Cy, are used (120 mg/kg). In this study, patients taking conditioning protocol of low-dose chemo-therapy, underwent bone marrow transplant.

Materials and Methods

In this analytic descriptive study, 46 subjects (12 females – 34 males) aged 1.5 - 49 years (mean age of 15.1 years) were enrolled for investigation of their thyroid, parathyroid and gonadal function. The functioning of pancreatic β cells was studied in 12 patients with thalassemia major. The grouping of patients according to illness, and chemotherapy regimen given are shown in Table 1. A questionnaire, completed by two physicians, was used to obtain details including personal information, medical history, the BMT characteristics, symptoms and signs of thyroid and parathyroid diseases, and stage of puberty determined according to Marshall-Tanner scale with respect to sex.

Table 1. Conditioning regimen in 46 patients studied

Disease	Number of patients		Type of transplant		Chemotherapy regimen
	Male	Female	Allogenic	Autologous	
Thalassemia	11	7	18	-	BU-Cy
ALL	5	-	3	2	BU-Cy
CML	4	1	5	-	BU-Cy
AML	5	1	3	3	BU-Cy
MM	2	-	-	2	Cy+Vp16+AL
Breast Cancer	-	1	-	1	Car+Cy+VP16
Aplastic anemia	4	1	5	-	CY
Fanconi Syndrome	1	1	2	-	-
Lymphosarcoma	1	-	-	1	-
Chediak-Higashi	1	-	1	-	-

ALL= Acute lymphoblastic leukemia, CML= Chronic myeloblastic leukemia
AML= Acute myeloblastic leukemia, MM=Multiple myeloma
Bu= Busulfan, Cy=cyclophosphamide, Al=
Car= Carboplatin, VP=Vinplastin

Physical examination and history taking were repeated at 3,6,12 and 24 months following BMT.

To study glucose metabolism in thalassemic patients, oral glucose tolerance tests (1.75 gr/kg of anhydrous glucose, max. 75 gr) were performed, measuring blood glucose levels before the test and 120 minutes thereafter. Serum FT4I, RT3U, TSH, T3 and T4, thyroglobulin and thyroid peroxidase antibodies were determined to evaluate thyroid function, as were serum calcium, phosphorous, alkaline phosphatase and PTH to evaluate parathyroid axis. To evaluate gonads, females of B2P2 stage (according to Tanner scale) and above, males with G2P2 stage (Tanner scale) and above were studied as were as those who had not reached puberty by 12 years of age. Serum PRL, FSH, LH (of all cases), testosterone (males), esteradiol and progesterone (females), semen indices (married males) were determined. The specifications of the laboratory kits used are given in Table 2.

Table 2. Specifications of laboratory kits

No	Test	Normal range	Manufacturer	Country of origin	Unit	Technique
1	T3	80-230	Kavoshyar	Iran	ng/dL	RIA
2	T4	4.5-12.8	Kavoshyar	Iran	µg/dL	RIA
3	TSH	0.2-5	Kavoshyar	Iran	µIU/mL	RIA
4	T3RU	25-37	Kavoshyar	Iran	%	RIA
5	FTI	1.12-4.7	Kavoshyar	Iran	-	RIA
6	Antig-Ab	Positive >150	IBL-GmbH	Germany	IU/mL	Elisa
7	AntiTPO-Ab	Positive >150	IBL-GmbH	Germany	U/mL	Elisa
8	PTH (N-terminal)	9-65	Diasorin	Germany	Pg/mL	RIA
9	Cortisol (Am)	5.6-26	Spectra	Finland	µg/dL	RIA
10	GH (basal)	>10	Immunotech	Czeck Republic	ng/mL	RIA
11	PRL	m 1.3-18 f: 2.9-8.8	Kavoshyar	Iran	ng/mL	RIA
12	Testosterone	m:2.8-8.8 f: 0.1-0.8	Spectra	Finland	ng/mL	RIA
13	FSH	m: 1-10 f: 8-25	Kavoshyar	Iran	mIU/mL	RIA
14	LH	m: 1.5-10 f: 15-80	Kavoshyar	Iran	mIU/mL	RIA
15	Progesterone	m: 0.1-0.88 f: 1.67-27.9	Spectra	Italy	ng/mL	RIA
16	Esteradiol	m: 10-40 f: 30-50	Spectra	Finland	pg/mL	RIA
17	Glucose	70-110	Pars-Azmoon	Iran	mg/dL	Colorometery

Table 3. Mean T_4, T_3, TSH and T_3RU before and after BMT

Thyroid function tests	Before BMT	3 months after BMT*	6 months after BMT*	1 year after BMT*	2 years after BMT*
T3 (mg/d/L)	148±45†	138.5±41	161±83	163±55	145±65
T4 (µg/dL)	10±12.5	8±1	8±2	8±2	7.8±2
TSH (µIU/mL)	1.5±1	2±1.5	2±1	2.5±2	3.5±2
T3RU (%)	28.5±5	28±6	27±6	28±3	28±3.5
Antig-tg	-	27±20	38±19	32±15	-
Anti-TPO	-	27±14	13±10	22±21	-

* No significant difference was observed. † Numbers represent Mean ± SD.

Table 4. Mean serum Ca, P, alkaline phosphotase and PTH before and after BMT

Parathyroid function tests	Before BMT	3 months after BMT*	6 months after BMT*	1 year after BMT*
Ca (mg/dL)	9±1†	9±3	8±3	10±0.5
P (mg/dL)	5±1	5±1	6±2	5±0.5
Alk phos (mg/dL)	309±197	498±541	564±402	502±176
PTH (pg/mL)	25±15	56±26	52±21	27±14

* No significant difference was observed. † Numbers represent Mean ± SD.

All patients gave oral consent. The Medical Ethics Committee of the Ministry of Health and Medical Education approved the study.

Four patients died within two years of transplantation. Repeated measure ANOVA was performed to analyze the data of thyroid and parathyroid axes while non-parametric Wilcoxon's rank were used to study fetal axis and glucose metabolism. $P<0.05$ was considered significant.

Results

Thyroid axis: No signs or symptoms of hypo- or hyperthyroidism were observed in the population studied, at any of the earlier specified intervals of BMT. Thyroid axis hormones did not differ significantly before or 3, 6, 12 and 24 months after BMT (Table 3).

Parathyroid axis: None of the patients studied showed signs of hypo- or hypercalcemia. Serum calcium, phosphorous, alkaline phosphatase and PTH were normal before and 3, 6 and 12 months after BMT with no significant differences (Table 4).

Gonads, males: In 11 adults (G5P5), 16-50 years of age (mean 32±11), serum FSH, LH, testosterone and prolactin were normal before and at 3, 6 and 12 months after BMT. No primary or secondary hypogonadism were observed. In 3 patients in whom semen analysis was performed, azospermia was observed before and up to one year after BMT. In one patient sperm count decreased from 12 million/mL preceding BMT to 6 million/1mL one year following BMT. In all four patients mentioned, except for one, serum FSH did not increase either before or after BMT, despite oligo and azospermia. In 5 boys, 12-16 years of age (mean 14±2), at G2P2 and G3P3 stages before BMT, serum LH, FSH, testosterone and prolactin were normal throughout the first year following BMT and puberty developed normally.

Mean serum levels of sex hormones are given in Tables 5 and 6. No significant difference was observed.

Gonads, females: 5 female adults (B5P5), 15-40 years of age (mean 25±11) were studied. In 4 females, primary hypogonadism (increase in FSH and LH) began at 3 months after BMT, and continued for 2 years. In two of these cases, oral contraceptive pills were used for treatment.

Table 5. Mean serum LH, FSH, Prolactin and Testosterone profiles in males at G5P5 stages before and after BMT

Variable	Before BMT	3 months after BMT*	6 months after BMT*	1 year after BMT*
LH (mIU/mL)	7±3†	15±19.5	39±51	12±8
FSH (mIU/mL)	9±6	17±11	42±59	15±10
PRL (ng/mL)	10±6	5±0.2	10±2	16±4
Testosterone (ng/mL)	6±2	5±2	4±1	3±1

* No significant difference was observed. † Numbers represent Mean ± SD.

Table 6. Mean serum gonadal profiles in males at G2P2 or G3P3 stages of puberty

Variable	Before BMT	3 months after BMT*	6 months After BMT*
LH (mIU/mL)	2±1†	7.5±4	6±2
FSH (mIU/mL)	2±1	10±11	11±9
PRL (ng/mL)	10±9	8±6	15±9
Testosterone (ng/mL)	5±3	3±1	5±1

* No significant difference was observed. † Numbers represent Mean ± SD.

Table 7. Mean serum glucose level in oral glucose tolerance test in 12 patients with thalassemia *

Variable	Before BMT	3 months After BMT	6 months After BMT	1 year after BMT*
FBS (mg/dL)	84±10	78±8	76±16	81±8
BS2hp (mg/dL)	95±17	87±16	79±16	94±18

* No significant difference was observed. † Numbers represent Mean ± SD.

In one 14-year-old female (B5P5), with regular menstruation prior to BMT, menses remained regular for 2 years following BMT with normal serum levels of FSH, LH, PRL, estradiol and progesterone. In another 11-year-old female (P1B1) with low serum FSH and LH before BMT, gonadotropins increased at 6 and 12 months after BMT (FSH 6m, 53 and 12m, 60; LH 6m, 11.8. and 12m, 22.5) indicating primary hypo- gonadism.

Glucose metabolism: Table 7 shows the mean values obtained from oral glucose tolerance tests (OGTT) of 12 patients with thalassemia (5 females-7 males) with a mean age of 4.8± 1.95 who had serum ferritin levels above 1000 ng/mL before BMT.

Discussion

Our findings indicate that thyroid and parathyroid function and calcium metabolism suffer no impairment during the 2 years following BMT in those who have received low dose cyslophosphamide (120 mg/kg) in a chemotherapy conditioning regimen. Moreover, puberty is not hindered or delayed in males, and leydig cell function is preserved, while detoriation of testicular germinal cells is observed for one year following BMT. Primary hypogonadism and ovarian damage are seen in females. In thalassemic patients no malfunctioning was observed for pancreatic β-cells.

Various disorders of thyroid function have been reported in patients receiving BMT. These include hypothyroidism, autoimmune thyroiditis, thyroid tumors, graft-versus-host disease and transient thyrotoxicosis post transplantation.

The prevalence of the disorders is believed to be up to 40% that seems to increase with prolonged follow-up.[11] Although hypothyroidism is attributed to total body irradiation (to prepare for transplant), it is also been reported following chemotherapy conditioning regimens.[11] Most thyroid disorders occur 1- 4.2 years. One study showed early changes in thyroid function (within the 6 months of BMT) which appeared as non-thyroidal illness syndrome (NTIS) in 44% and transient thyrotoxicosis in 16% of patients.[12] In this study, conditioning regimens included total body irradiation or chemotherapy using busulfan-cyclophos-phamide whereas the patients were not categorized according to the type of conditioning regimen. Hypothyroidism developed in all cases of thyrotoxicosis, indicating thyroiditis in the patients. No thyroid dysfunction was seen for 2 years after BMT in those who had no thyroid dysfunction before BMT. As patients were not evaluated in first 3 months of BMT, transient changes such as euthyroid syndrome

may have occurred during this period.

As mentioned earlier, busulfan-cyclophosphamide (Bu-Cy) is the most common chemotherapy regimen used to prepare patients for BMT. The effects of the regimen used on gonads have been reported by the Seattle team.[13] They administered busulfan (16 mg/kg) and cyclophosphamide (200 mg/kg) known as "Big Bu-Cy". In their report, only one of 73 females regained her sexual axis function following BMT, although the mean age (38 years) of females was relatively high (range: 14-57 years) and the mean of duration of follow-up was 2 years. Improvement of testicular function (defined as normal serum LH, FSH and testosterone along with evidence of sperm production) was observed in 8 patients out of 46 (17%), with a mean age of 34 years (13-56) and a mean follow-up of 2 years.[14]

Currently, cyclophosphamide at 120 mg/kg is used, known as "Bu-Cy little". Grigg et al. investigated ovarian function in19 females and testicular function in 47 males, who were using this regimen, for 2-5 years following transplant. In 84% of males, spermatogenesis improved to varying degrees. The researchers pointed out that chronic graft-versus-host disease may have deleterious effects on sperm count. Ovarian function did not improve in any of the females studied.[15]

Continuous infusion of VP16 to the "Little Bu-Cy" regimen had no adverse effects on gonads. Given time the improve-ment of spermatogenesis is more likely. Grigg et al. showed that serum FSH and LH values are not reliable indices for improvement of spermatogenesis or sperm count, while inhibin B has a good correlation with sperm count, but cannot clearly distinguish azospermia from non-azospermia. Although in one study, combination of FSH and Inhibin B was found to be more helpful in this regard, it was not so in the study conducted by Grigg et al. Grigg suggest sperm counts as the most reliable test for evaluation of spermatogenesis. Inhibin B, a hormone secreted by the Sertoli cells, suppresses FSH secretion. Compared to germinal epithelium, Leydig cells are less susceptible to chemotherapy.

In Grigg's study, 12% of males had testosterone levels less than normal, exhibiting symptoms of reduced libido and erection.[15] Wingard et al. using "Big Bu-Cy" regimen observed low testosterone in only one patient out of 42,[14] while Chatterjee reporting decreased function of leydig cells following BMT indicating that testosterone was more likely to be low in males aged over 45 years.[16] A recent study reported a remarkable, though transient, decrease in serum testosterone in the first 6 months after BMT, which may be an important factor contributing to reduced bone density.[17] We observed no reduction in leydig cell function, though azospermia was present in 4 patients in the year following BMT. FSH did not increase in azospermic patients before or after BMT with the exception of one case. It implies that FSH could not be relied on to evaluate spermatogenesis, a finding which is in contrast to those of Kreuser[18] and Clark,[19] indicating semen analysis is mandatory. A more prolonged study is needed to see whether spermatogenesis is reversible after BMT, as the probability increases with the passage of time. In this study, serum testosterone did not decrease 3 and 6 months after BMT.

Despite the high prevalence of improvement in male gonadal function in the Grigg[15] and Seattle[13] studies, ovarian function was not regained in any of the females, indicating both that low and high doses of cyclophosphamide exert irreversible damages on the ovaries in chemotherapy regimens used in Hodgkin's lymphoma such as MOPP, in which reversible gonadal function is more prominent in females than males.[19]

Several reports exist regarding pregnancy after concurrent use of cyclophosphamide and total body irradiation.[13] Pregnancy had been known to occur after BEAM, CBU (cyclophosphamide, BCNU, Etoposide) as well as high dose melfalan chemotherapy

regimens.[15] In our study, 3 months following BMT, primary hypogonadism (increase in both LH and TSH) developed in 5 females (4 adult and a girl who had not reached puberty before BMT). Amenorrhea was observed for 2 years following BMT in patients followed up and in two patients oral contraceptive pills were begun. In a 14-year-old female with aplastic anemia who had regular menstruation before BMT, both FSH and LH levels as well as menses remained normal two years following BMT.

Irreversibility of normal ovarian function following BMT in most patients highlights the necessity of timely hormone replacement therapy (estrogen and progesterone) to prevent osteoporosis and other complications resulting from the lack of the hormones.

Hyperprolactinemia, due to hypothalamus damage, has been observed following BMT in patients using total body or skull irradiation regimens.[20, 21] There have been no reports of hyperprolactenemia following the use of chemotherapy regimens for BMT, nor was this seen in our study.

Calcium metabolism and parathyroid function were not altered after BMT and no signs of hypocalcemia or secondary hyper-parathyroidism were observed. Although in thalassemic patients, pancreatic β-cells function improves after BMT due to reduced deposition of iron in the pancreas, in the present study the function of pancreatic β-cells, was normal before and after BMT. For further investigation, serum insulin and c-peptide along with serum plasma need to be measured during OGTT. These may, before BMT, show insulin resistance in the patients, which decreases following the transplant. A larger study of thalassemic patients is strongly recommended to assess whether or not insulin resistance prior to BMT shows any improvement after the transplant.

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