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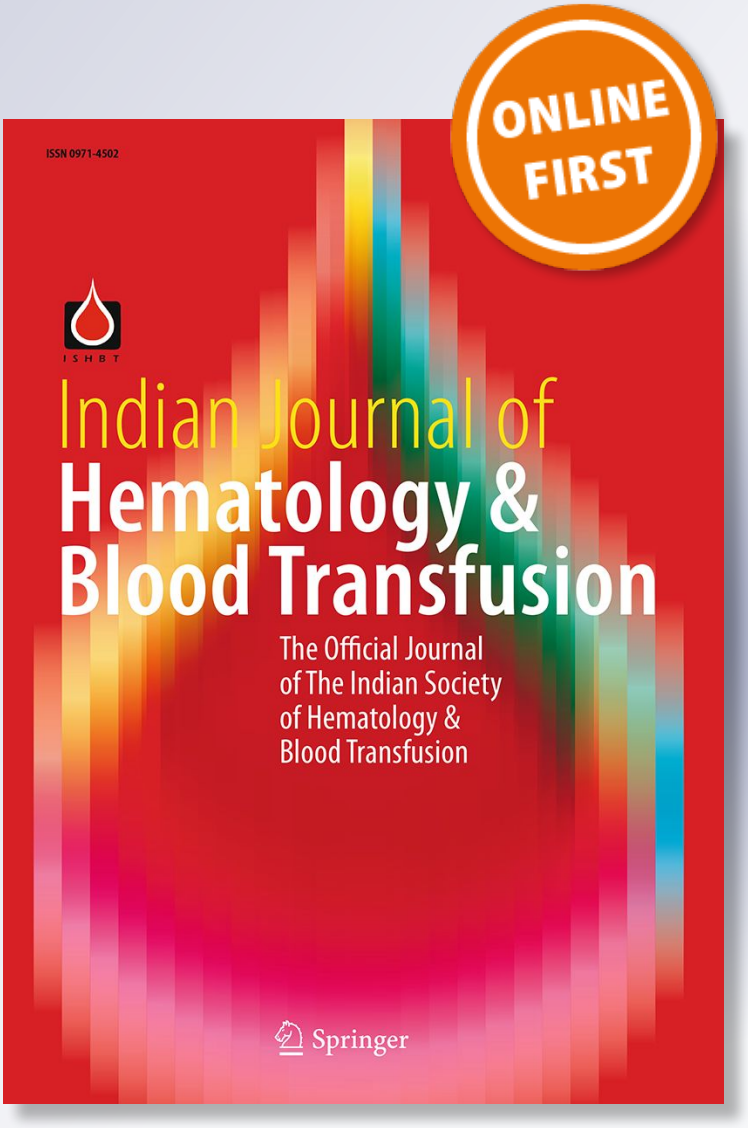

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ORIGINAL ARTICLE

Endocrine Challenges and Metabolic Profile in Recipients of Allogeneic Haematopoietic Stem Cell Transplant: A Cross-Sectional Study from Southern India

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Abstract Although haematopoietic stem cell transplant has been successfully employed in the cure of several malignant and non-malignant conditions, survivors often suffer from delayed effects involving the endocrine system and cardio-metabolic risk factors. In this cross-sectional study, we aimed to assess the prevalence of endocrine dysfunction and alterations in metabolic profile in 63 recipients of allogeneic stem cell transplantation as compared to 65 age, sex and body mass index matched controls. Hypogonadism emerged as the most prevalent endocrinopathy, present in 23/60 (38.3%) of subjects, followed by overt and subclinical hypothyroidism in 10/63 (15.9%) of cases. The metabolic parameters, that included plasma glucose and lipid profile were not significantly different between cases and controls. However, insulin resistance, as assessed by surrogate markers employing HOMA IR (3.82 vs. 1.97) and QUICKI (0.338 vs. 0.373) was significantly higher among cases than in controls ($P < 0.05$). Abnormal glucose tolerance was observed in about one-third of the study cohort. The prevalence of overt diabetes (7%) was similar to that in the general population across India (8%); the prevalence of pre-diabetes (21%) was however considerably higher than the national average of 10%. Thus, although the process of haematopoietic stem cell transplant is often curative for the primary haematological disease, it may be associated with various delayed effects on the endocrine system and metabolic profile. Therefore, it is imperative that recipients be screened for the potential development of these late effects subsequent to the transplantation procedure.

Keywords Allogeneic haematopoietic stem cell transplant · Endocrine dysfunction · Metabolic profile

Introduction

Over the last six decades, the procedure of haematopoietic stem cell transplant (HSCT) has made remarkable strides in the treatment of various disorders involving the haematopoietic system. The unique potential of these stem cells to reconstitute the entire haematopoietic system, has led to the cure of various conditions for which it is indicated namely leukaemia, lymphoma, thalassaemia and other non-haematological conditions [1].

Nevertheless, although several recipients of HSCT survive the transplant and disease related morbidity, they may not be endowed with the same longevity as the general population. HSCT survivors suffer from "late effects" that increase morbidity and mortality and adversely affect their working capacity and health related quality of life [2].

There has been an increase in the incidence of non-communicable diseases such as metabolic syndrome and cardiovascular disease in these subjects [3]. This is likely mediated by an increase in the occurrence of atherosclerosis, hyperlipidemia, impaired glucose tolerance and increase in visceral adiposity. Endocrine glands, especially the gonads are particularly susceptible to the cytotoxic effects of chemotherapy and total body irradiation employed in conditioning regimens [4].

Although a few studies have assessed the prevalence of endocrinopathies following HSCT, the study population was

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heterogenous, with inclusion of recipients of both autologous and allogeneic HSCT. The presence of endocrinopathy and abnormal metabolic parameters may adversely affect the quality of life of long-term survivors. Early identification of these abnormalities would serve to assist in timely initiation of remedial measures as appropriate.

Therefore, this study was undertaken to analyse the prevalence of endocrine dysfunction in recipients of allogeneic HSCT, and also to study their metabolic profile, in comparison to a healthy control group.

Methodology

This was a cross-sectional study conducted between February 2016 to November 2017 wherein study subjects included recipients of allogeneic transplant, aged 18–45 years who were recruited from the Haematology-Transplant OPD at least 9 months after and not later than 6 years following the transplant. At recruitment, they were off all immunosuppressants for a period of at least 6 months. The age, gender and BMI matched control group was recruited from the local community. Those who were outside the defined age limits, recipients of autologous transplant, thalassaemia major, those with disease recurrence and pregnant individuals were excluded from the study.

Ethical clearance was obtained from the Institutional Review Board.

Sample Size Calculation

From a previous study [5] that assessed germ cell damage after allogeneic HSCT, where the prevalence of germ cell damage was $\sim$ 90%, using the formula $4PQ/D^2$ (P—Prevalence of germ cell failure from previous study, Q—100—P, D—Allowable error, i.e., 5–20% of P), the sample size was estimated to be $\sim$ 44.

Assessment

History and Clinical Examination

Symptoms pertaining to endocrine dysfunction and details of the transplant procedure were documented. Clinical examination included anthropometry, assessment of blood pressure, signs of insulin resistance (acanthosis nigricans), sexual maturity rating [6, 7], general physical and systemic examination.

Biochemical Assessment Including Analytical Methods

Plasma glucose was analyzed by the hexokinase method and HbA_1C by high performance liquid chromatography (HPLC). Serum cortisol, FSH, LH, TSH, total and free T4, insulin and testosterone were measured by chemiluminescent immunoassay (CLIA) using commercial kits. Serum oestradiol was analysed using electro-chemiluminescent assay (ECLIA). Colorimetric methods were used for total cholesterol and triglycerides; HDL and LDL were analyzed enzymatically.

Definitions Used

Overt primary, subclinical and central hypothyroidism were defined biochemically as per standard definitions [8, 9].

Hypogonadism

In males, biochemical hypogonadism was defined a morning serum total testosterone $\leq$ 300 ng/dL [10]. A low level of serum testosterone ($\leq$ 300 ng/dL) with a serum FSH or LH $>$ 10 mIU/mL was classified as primary hypogonadism [11]. A low serum testosterone with inappropriate FSH or LH ($<$ 10 mIU/mL) was classified as secondary hypogonadism. In females, ovarian dysfunction was defined as the presence of amenorrhea for at least three months and/or serum oestradiol $<$ 20 pg/mL [12]. The presence of ovarian dysfunction with FSH $>$ 20 mIU/mL was defined as primary ovarian failure [13]. Female patients with ovarian dysfunction and an inappropriate FSH response ($\leq$ 20 mIU/mL) were classified as having secondary hypogonadism.

Adrenal Insufficiency

A low serum 8 AM cortisol $<$ 5.0 mcg/dL was defined as hypocortisolemia [14]. Plasma ACTH levels were not assessed.

Metabolic Profile

Metabolic syndrome was defined by the criteria laid down by the IDF [15]. Standard definitions were used for type 2 diabetes mellitus, pre diabetes, impaired fasting glucose, impaired glucose tolerance, hypercholesterolemia and hypertriglyceridemia [16]. Homeostasis Model Assessment Insulin resistance [HOMA IR, calculated as fasting insulin (mIU/mL) * fasting plasma glucose (mg/dL)/405] $>$ 2.5 or Quantitative Insulin sensitivity Check Index [QUICKI, calculated as 1/log fasting insulin + log fasting plasma glucose] less than 0.331 indicates insulin resistance [17].

Statistical Methods

Data were entered into an electronic database and analyzed using SPSS (v 21, Chicago, IL, USA). Continuous

variables were expressed as mean (SD) and categorical variables as frequencies and percentages. Comparison of means of continuous and categorical variables was done using students *t* test or ANOVA and Chi square test respectively. Correlation was expressed using Pearson's or Spearman's coefficient as appropriate. Statistical significance was defined by a *P* value that was < 0.05.

Results

A total of 63 subjects, who had undergone allogeneic HSCT for various haematological indications, were recruited on fulfilling the eligibility criteria after having signed the written informed consent. The mean (SD) age of the study cohort was 31.3 (7.9) years and consisted of 43 (68.3%) males and 20 (31.7%) females. The duration since HSCT ranged from 9 to 64 months, with a mean (SD) of 27.7 (16.6) months.

The common indications for which allogeneic HSCT was performed included aplastic anaemia, acute myelogenous leukaemia, acute lymphoblastic leukaemia, Hodgkin's lymphoma, paroxysmal nocturnal haemoglobinuria, myelodysplastic syndrome and chronic myeloid leukaemia. The various conditioning regimens used included Fludarabine-Melphalan, Busulphan–Fludarabine, Fludarabine–Cyclophosphamide and Cyclophosphamide with total body irradiation (TBI). GvHD (Graft versus host disease) prophylaxis was given to all patients and utilized cyclosporine, methotrexate, tacrolimus or cyclophosphamide. The baseline demographic characteristics, with primary diagnoses, type of conditioning regimen, use of TBI (total body irradiation) and occurrence of GvHD is as shown in Table 1.

Table 1 Baseline characteristics of the transplant recipients

Variable	N	Percentage
Gender		
Male	43	68.3
Female	20	31.7
Primary diagnosis		
Malignant	39	61.9
AML	22	34.9
ALL	9	14.3
Hodgkin's lymphoma	1	1.6
MDS	4	6.3
CML	3	4.8
Non malignant	24	38.1
Severe aplastic anaemia	23	36.5
PNH	1	1.6
Conditioning regimen		
Myeloablative	21	33.3
Non myeloablative	30	47.6
Reduced intensity	12	19.1
TBI	26	41.3
GvHD	25	40.0
Acute	6	9.5
Grade 2	5	7.9
3	2	3.2
4	2	3.2
Chronic	16	25.4
Limited	13	20.6
Extensive	6	9.5
Acute and chronic	3	4.8

[A] Assessment of Endocrinopathy

Recipients of allogeneic HSCT recruited in this study were assessed for the presence of thyroid dysfunction, hypogonadism and hypocortisolemia. The proportion of subjects with these abnormalities is depicted in Table 2.

Thyroid Dysfunction

In the study group, 2/63 (3.2%) patients had overt primary hypothyroidism, and were initiated on levothyroxine supplementation. Sub-clinical hypothyroidism was seen in 8 (12.7%) of the study subjects. Among cases, there was no significant difference in the occurrence of thyroid dysfunction in the sub-groups classified based on the presence or absence of GvHD and type of conditioning regimen.

Table 2 Prevalence of endocrine and metabolic dysfunction in the study cohort

Category	Frequency	Percentage (%)
Subclinical hypothyroidism	8/63	12.7
Overt primary hypothyroidism	2/63	3.2
Primary hypogonadism (males)	9/40	22.5
Secondary hypogonadism (males)	3/40	7.5
Premature ovarian failure (females)	11/20	55
Hypocortisolemia	3/60	5
Diabetes mellitus	5/61	8.2
IFG	3/61	4.9
IGT	5/52	9.6
Prediabetes	13/61	21.3

Gonadal Dysfunction

Males Among male recipients of allogeneic HSCT, 9/40 (22.5%) had primary hypogonadism, 3/40 (7.5%) had secondary hypogonadism. Among the male subjects with hypogonadism, primary and secondary hypogonadism were seen in 75% and 25% respectively. Majority of the subjects (28/40; 70%) had normal serum testosterone levels.

However, among the subjects with normal serum testosterone, it was noted that 5/28 subjects had an isolated involvement of the germ cell component, as indicated by elevated FSH levels (18%) with intact Leydig cell function. The occurrence of hypogonadism was not significantly different in various sub-groups classified based on GvHD and type of conditioning.

Females Among female subjects, primary ovarian failure was seen in 11/20 (55%). There was no evidence of secondary hypogonadism. Nine of the subjects (45%) had normal gonadal function. In female recipients, the mean (SD) serum estradiol levels were lower in the group that had received myeloablative conditioning as compared to the group that had received non-myeloablative/reduced intensity regimens [12.1 (14.6) vs. 96.4 (77.8) pg/mL, $P = 0.001$]. The mean serum estradiol was not significantly affected by the presence or absence of GvHD [$P > 0.05$]. The proportion of females with primary ovarian failure was significantly higher in the group that had received myeloablative conditioning (6/6) than in the non-myeloablative/reduced intensity group (5/14) [100% vs. 35.7%, $P = 0.008$]. Also, the proportion of female subjects with primary ovarian failure was significantly higher in those more than 25 years of age (N = 10/13) as compared to those younger than 25 years (N = 1/7) (77% vs. 14%, $P = 0.017$).

Comparison of Male and Female Hypogonadism The proportion of primary hypogonadism was significantly higher in female subjects as compared to males (55% vs. 22.5%; 95% CI 1.3 to 13.3, $P = 0.019$).

Hypocortisolemia

In the study group, 3/60 (5%) were found to have hypocortisolemia. Majority of the subjects, 57/60 (95%) had normal serum cortisol levels. The mean serum cortisol was not significantly affected by the presence or absence of GvHD and type of conditioning regimen used prior to HSCT.

Time Since Transplant and Endocrine Dysfunction

On comparing the prevalence of endocrinopathy in two groups stratified by time since transplant, (6 months-2 years—group 1 and > 2 years—group 2), it was found that there was no significant difference in the prevalence of endocrine dysfunction between the two groups.

[B] Assessment of Metabolic Profile

The presence of cardio-metabolic risk factors was assessed by measurement of blood pressure, anthropometry, biochemical parameters [fasting blood glucose, HbA1C, fasting lipid profile] and assessment of insulin resistance using HOMA-IR and QUICKI. A comparison of anthropometric and metabolic parameters in cases and controls is shown in Table 3. The fasting plasma glucose and lipid profile were not significantly different in cases and controls. In cases versus controls, the proportion of subjects with hypercholesterolemia (35/55, 63% vs. 43/65, 66%) and hypertriglyceridemia (17/58, 29% vs. 15/65, 23%) were not significantly different ($P = 0.848$).

Insulin Resistance

As depicted in Table 3, although plasma glucose and fasting lipid profile were not significantly different in both groups, recipients of allo-HSCT had greater insulin resistance when compared to controls ($P = 0.017$ for HOMA and $P = < 0.001$ for QUICKI). The mean fasting (103 vs. 90 mg/dL) and post prandial glucose (121 vs. 101 mg/dL), HbA1C (5.6 vs. 5.1%) and HOMA IR (5.3 vs. 2.4) were significantly higher in subjects older than 30 years of age (N = 32) than in those younger than 30 (N = 31) years ($P < 0.05$).

Diabetes Mellitus, IFG, IGT and Prediabetes

Among cases, the proportion of subjects with diabetes mellitus, IFG, IGT and prediabetes are shown in Table 2.

Metabolic Syndrome

The prevalence of metabolic syndrome was not significantly different between cases and controls (15/57 vs. 13/65; $P = 0.518$). However, on analyzing cases stratified by the time since transplant (6 months-2 years as group 1 and > 2 years as group 2), the prevalence of metabolic syndrome was significantly higher in group 2 as compared to group 1 (4/31 vs. 11/26; $P = 0.017$).

Table 3 Comparison of anthropometric and metabolic parameters in cases and controls

Variable	Cases (N = 63) mean (SD)	Controls (N = 65) mean (SD)	*P* value
Height (SD) (cm)	166.5 (8.7)	163.3 (6.6)	0.025
Weight (SD) (kg)	67.0 (12.8)	67.6 (12.5)	0.765
BMI (SD) (kg/m^2)	24.2 (4.1)	24.8 (4.2)	0.352
Systolic BP (mm Hg)	120 (16)	126 (17)	0.049
Diastolic BP (mm Hg)	83 (14)	78 (14)	0.05
FPG (mg/dL)	96.5 (20.7)	90.9 (28.6)	0.212
Fasting insulin (mIU/L)	15.1 (15.5)	8.2 (6.7)	0.002
Total cholesterol (mg/dL)	172.8 (37.2)	166.1 (32.1)	0.295
Triglycerides (mg/dL)	131.2 (76.8)	125.5 (83.8)	0.695
HDL (mg/dL)	40.4 (9.1)	40.5 (11.2)	0.937
LDL (mg/dL)	113.4 (29.9)	114.6 (52.0)	0.868
HOMA IR	3.82 (5.2)	1.97 (2.2)	0.017
QUICKI	0.338 (0.04)	0.373 (0.05)	< 0.001

Discussion

This cross-sectional study presents data on the late effects of allogeneic haematopoietic stem cell transplant on the endocrine glands and cardio-metabolic risk factors in subjects aged 18–45 years at a median duration of 22 months post allo-HSCT.

In male subjects, the prevalence of primary and secondary hypogonadism was 75% and 25% respectively. In a study on 122 recipients of allogeneic HSCT for acute leukaemia, out of 58 males, 49 subjects (84%) were found to have low testosterone. Among them, the prevalence of primary and secondary hypogonadism was 59% and 41% respectively [18]. About one fifth of males in our study had isolated involvement of the germ cell compartment (as assessed by serum FSH levels), with normal levels of serum testosterone. This is consistent with previous reports from literature which states that the leydig cells are less vulnerable than germ cells to the damaging effects of chemo-radiotherapy. The pre-transplant conditioning chemotherapy as well as an acute GvHD involving the testes have been implicated in causing gonadal dysfunction [19].

Ovarian failure and associated infertility are serious delayed complications that occur in female recipients of HSCT [20]. Our study demonstrated the prevalence of ovarian failure to be 55% and proportion of primary ovarian failure was significantly lower in women aged less than 25 years as compared to individuals more than 25 years of age. In a study on 144 women who underwent stem cell transplant for acute leukaemia, all women developed hypergonadotrophic amenorrhoea [21]. On follow up, ovarian function recovered in 31% of women aged < 26 years and permanent ovarian failure was seen in all above this age. Age at transplant (< 21 years) may be an important predictor of ovarian function recovery due to presence of higher follicular reserve in younger individuals [22]. The seemingly lower proportion of primary hypogonadism in females in our study is probably due to small sample size. It may also be related to the greater use of non-myeloablative/reduced intensity regimen than myeloablative conditioning.

Overall, in our study, primary hypogonadism was significantly more in female subjects as compared to male subjects. This is in keeping with available literature which states that compared to the testes, the ovaries are more sensitive to the damaging effects of irradiation and gonadotoxic chemotherapy [2].

In our study, overt and subclinical hypothyroidism were seen in 3.2% and 12.7% of the recipients of allo-HSCT. Our findings were similar to a study by Medinger et al., in 229 patients with AML, who had undergone allo-HSCT in which the prevalence of overt primary and subclinical hypothyroidism was 3.8% and 19% respectively [23]. Another study from northern India that assessed the prevalence of endocrine dysfunction in 50 subjects post HSCT (39 allogeneic and 11 autologous, non TBI based regimen), thyroid dysfunction comprising overt and subclinical hypothyroidism was noted in 4% of subjects. Some of the risk factors for the development of thyroid dysfunction have been cited as the presence of GvHD, exposure to TBI [24, 25] and the development of autoantibodies.

In this study, adrenal insufficiency as defined by a morning serum cortisol less than 5 mcg/dL was seen in 5% of the subjects. Adrenal insufficiency has been reported to occur in about 13% after allogeneic HSCT [26]. A cross sectional study done in northern India by Gundhurthi et al., on the prevalence of various endocrinopathies after HSCT, the prevalence of adrenal insufficiency was reported to be 60% [27]. However, this study had included recipients of both allogeneic and autologous transplants as well as

individuals in the extremes of age. The adrenal insufficiency is likely to be secondary to HPA axis suppression caused by exogenous glucocorticoid administration, and is related to the cumulative dose and total duration of steroid therapy. The lower prevalence of adrenal insufficiency in our study is probably due to individual variation in the susceptibility of HPA axis suppression by exogenous glucocorticoids.

In our study the prevalence of diabetes in post HSCT recipients was 8%, IFG was seen to occur in 5% and 16% had IGT. Overall, abnormal glucose tolerance was seen in about one third of the subjects. In India, the overall prevalence of diabetes is about 7% (4.3–10.0%), and the prevalence of prediabetes is about 10.3% [28]. However, the prevalence of pre-diabetes in post HSCT subjects was about 21%, which is seemingly higher than what is encountered in the general population. The mechanism of diabetes in HSCT recipients is probably related to the toxic effects of chemotherapeutic drugs, pancreatic irradiation, the effect of cytokines, the presence of GvHD which is a chronic inflammatory state and the use of immunosuppressants and glucocorticoids [29].

It was observed that post allo-HSCT recipients had a significantly higher HOMA IR and significantly lower QUICKI when compared to controls. However, these findings have to be interpreted with caution as the number of subjects studied was small. In a study of 45 subjects by Bizarri et al., insulin resistance as measured by HOMA IR was significantly higher in cases as compared to controls [30]. The occurrence of dyslipidemia is an important delayed complication of HSCT. A retrospective analysis on 194 subjects who underwent allo-HSCT between 1994 and 2008 demonstrated the prevalence of hypercholesterolemia (> 240 mg/dL) and hypertriglyceridemia (> 200 mg/dL) to be 43% and 51% [31]. Our study showed the corresponding figures to be 66% and 29% respectively. The apparent difference in the prevalence of hypercholesterolemia is probably because of the lower cut off used in our study. On stratifying the study cohort based on time since transplant, it was found that the prevalence of metabolic syndrome was higher in group 2 (> 2 years) as compared to group 1 (6 months—2 years). This is in keeping with literature which mentions the occurrence of metabolic syndrome as one of the delayed effects of haematopoietic stem cell transplant [3].

The fact that this is the first study from India to evaluate the occurrence of endocrine and metabolic dysfunction in a homogenous cohort of allogeneic HSCT recipients testifies to the strength of this research work. Notwithstanding, this study is limited by its cross-sectional design, small sample size and lack of measurement of plasma ACTH and a synacthen stimulation test. The observed findings with regard to endocrine and metabolic dysfunction need to be prospectively studied in a large cohort.

Future Perspectives

Among recipients of allogeneic HSCT, 51% had at least one endocrinopathy. Hypogonadism emerged as a significant problem in both male and female recipients of HSCT. Therefore, a thorough pre-transplant assessment of gonadal function is necessary to detect these changes early and to initiate appropriate treatment. Women with primary ovarian failure should be considered for hormone replacement therapy (HRT), for cardiovascular protection and preservation of bone health. Clearly, infertility is an important concern in both young women and men undergoing HSCT. Patients planned for HSCT should be counselled about the potential for permanent gonadal damage and infertility. Fertility issues should be addressed in all subjects in the reproductive age group. In females, in vitro fertilization and embryo cryopreservation, oocyte cryopreservation and ovarian tissue banking are acceptable strategies for preservation of fertility. In men and post pubertal males, sperm banking may be a viable option [32]. It is important to raise awareness among patients and their caregivers about available options that may assist in fertility preservation. Moreover, the increased longevity of post HSCT subjects warrants that they be followed up closely for the development of diabetes and dyslipidemia as these factors can potentially increase cardiovascular risk and associated morbidity.

Conclusion

Recipients of allogeneic haematopoietic stem cell transplant ought to be pre-emptively screened for the development of endocrine dysfunction and metabolic changes. Early identification of potential abnormalities will enable timely initiation of appropriate treatment and lead to an improved health-related quality of life in these subjects.

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Compliance with Ethical Standards

Conflict of interest The authors declare that there are no conflicts of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964

Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Written informed consent was obtained from all study participants.

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