Thyroid and Gonadal Dysfunction in the Adult after HSCT

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Thyroid Dysfunction after HSCT

- Compensated Hypothyroidism
- Primary/Secondary/Tertiary Hypothyroidism
- Autoimmune Thyroid Disease (Autologous or Allogeneic HSCT) (Hypo- or Hyperthyroidism)
- Thyroid Carcinoma as Secondary Neoplasm
Occurrence of Thyroid Dysfunction

Prolonged chronic graft-versus-host disease is a risk factor for thyroid failure in long-term survivors after matched sibling donor stem cell transplantation for hematologic malignancies.

Savani BN, Koklanaris EK, Le Q, Shenoy A, Goodman S, Barrett AJ

Risk Factors for Thyroid Dysfunction

Thyroid function following hematopoietic cell transplantation in children: 30 years' experience.


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Conditioning with Chemotherapy

Thyroid Dysfunction in Adult Long-term Survivors After Hematopoietic Stem-cell Transplantation (HSCT)

<table>
<thead>
<tr>
<th>Males</th>
<th>Normal*</th>
<th>Elevated**</th>
<th>Normal Response*</th>
<th>Elevated response*</th>
<th>TSH 0 min</th>
<th>TSH 30 min</th>
<th>TSH 60 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>25 (81%)</td>
<td>6 (19%)</td>
<td>13 (41%)</td>
<td>13 (41%)</td>
<td>13 (41%)</td>
<td>13 (41%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Females</td>
<td>37 (91%)</td>
<td>4 (10%)</td>
<td>15 (36%)</td>
<td>15 (36%)</td>
<td>20 (47%)</td>
<td>26 (64%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Cochran analysis:
* Normal levels: TSH 0.4–4.0 μIU/mL.
** Elevated levels: TSH >4.0 μIU/mL.
* Normal response: TSH levels up to five times greater than the basal values.
* Elevated response: TSH >5× TSH basal.

Chronic GvHD

Prolonged chronic graft-versus-host disease is a risk factor for thyroid failure in long-term survivors after matched sibling donor stem cell transplantation for hematologic malignancies


Associations between prolonged IST and Overt (C) and Subclinical (D) Hypothyroidism

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### Autoimmune Thyroid Disease (AITD)

<table>
<thead>
<tr>
<th>Author/year</th>
<th>HSCT</th>
<th>GvHD</th>
<th>Latency</th>
<th>Donor AITD/yr</th>
<th>Type of AITD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldouri/1990</td>
<td>allog.</td>
<td>----</td>
<td>9m</td>
<td>Hashimoto T./-14</td>
<td>Hashimoto T.</td>
</tr>
<tr>
<td>Wyatt/1990</td>
<td>allog.</td>
<td>no</td>
<td>36m</td>
<td>Hashimoto T./--</td>
<td>Hashimoto T.</td>
</tr>
<tr>
<td>Carlson/1992</td>
<td>autol.</td>
<td>no</td>
<td>----</td>
<td>--</td>
<td>Hashimoto T.</td>
</tr>
<tr>
<td>Vialleter/1993</td>
<td>allog.</td>
<td>yes</td>
<td>36</td>
<td>Hashimoto T./-4</td>
<td>Hashimoto T.</td>
</tr>
<tr>
<td>Thomsen/1995</td>
<td>allog.</td>
<td>----</td>
<td>8m</td>
<td>Hashimoto T./0.2</td>
<td>Hashimoto T.</td>
</tr>
<tr>
<td>Kishimoto/1996</td>
<td>allog.</td>
<td>yes</td>
<td>5m</td>
<td>Hashimoto T./0</td>
<td>Hashimoto T.</td>
</tr>
<tr>
<td>Karthaus/1997</td>
<td>allog.</td>
<td>yes</td>
<td>13m</td>
<td>Hashimoto T./-10</td>
<td>Hashimoto T.</td>
</tr>
<tr>
<td>Lamberti/1997</td>
<td>autol.</td>
<td>no</td>
<td>26m</td>
<td>----</td>
<td>Hashimoto T.</td>
</tr>
<tr>
<td>Marazuela/2000</td>
<td>allog.</td>
<td>yes</td>
<td>13</td>
<td>TAK/TPOAK/TSH-R</td>
<td>Hashimoto T.</td>
</tr>
<tr>
<td>Lee/2001</td>
<td>allog.</td>
<td>yes</td>
<td>13</td>
<td>Hashimoto T./--</td>
<td>Hashimoto T.</td>
</tr>
<tr>
<td>Kami/2001</td>
<td>allog.</td>
<td>5 yes/3</td>
<td>2-10m</td>
<td>----</td>
<td>Hashimoto T.</td>
</tr>
</tbody>
</table>

### Autologous HSCT

**Endocrine disorders during the first year after autologous stem-cell transplant**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median (range) or number (%)</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>1.56 (0.25-7)</td>
<td>0.3-3.5 mU/ml</td>
</tr>
<tr>
<td>Triiodothyronine</td>
<td>3.2 (1.9-4.4)</td>
<td>2.8-5.5 pg/ml</td>
</tr>
<tr>
<td>Thyroxine</td>
<td>10.5 (7-15.4)</td>
<td>6.6-18.0 pg/ml</td>
</tr>
<tr>
<td>Subclinical hypothyroidism</td>
<td>15 (10%)</td>
<td>--</td>
</tr>
<tr>
<td>Subclinical hyperthyroidism</td>
<td>9 (9%)</td>
<td>--</td>
</tr>
<tr>
<td>&quot;Lus T.&quot; syndrome</td>
<td>29 (30.6%)</td>
<td>--</td>
</tr>
<tr>
<td>Patients with antibodies to thyroid</td>
<td>11 (12%)</td>
<td>--</td>
</tr>
<tr>
<td>Number of subjects with antibodies</td>
<td>11 (12%)</td>
<td>--</td>
</tr>
</tbody>
</table>

**Table 2** Endocrine evaluation in the 95 patients at 3 and 12 months after autologous stem-cell transplant

**The European Group for Blood and Marrow Transplantation**
Acute Thyrotoxicosis

THYROID FUNCTION AFTER BONE MARROW TRANSPLANTATION: POSSIBLE ASSOCIATION BETWEEN IMMUNE-MEDIATED THYROTOXICOSIS AND HYPOTHYROIDISM

MAGHERIKA-EMLI D1,2, YOSHIKAI CHIKA2, SHIGEO KITAMURA2, TAKAKI HAYAKAWA, YOSHIHIRO SUZUKI, YOSHIKAZU KOJIMA, and HIROYA HIRAO

Table 4: Characteristics of patients developing hyperthyroidism

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Primary Disease</th>
<th>Conditioning</th>
<th>Pre-transplant TSH (mIU/l)</th>
<th>Post-transplant TSH (mIU/l)</th>
<th>T3 (nmol/l)</th>
<th>T4 (nmol/l)</th>
<th>Thyroid-stimulating hormone (mIU/l)</th>
<th>T3</th>
<th>T4</th>
<th>Hypothyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>56/46 M, CML, G-GITVH</td>
<td>M</td>
<td>II</td>
<td>Limited</td>
<td>Not detected</td>
<td>8.8</td>
<td>15.6</td>
<td>47</td>
<td>Not tested</td>
<td>1.6</td>
</tr>
<tr>
<td>2</td>
<td>56/46 M, CML, G-GITVH</td>
<td>M</td>
<td>II</td>
<td>104</td>
<td>0.4</td>
<td>7.8</td>
<td>10.6</td>
<td>25</td>
<td>Not tested</td>
<td>Negative</td>
</tr>
<tr>
<td>3</td>
<td>56/46 M, CML, G-GITVH</td>
<td>M</td>
<td>II</td>
<td>101</td>
<td>Not detected</td>
<td>7.8</td>
<td>21.4</td>
<td>220</td>
<td>Not tested</td>
<td>Negative</td>
</tr>
<tr>
<td>4</td>
<td>56/46 M, CML, G-GITVH</td>
<td>M</td>
<td>I</td>
<td>101</td>
<td>Not detected</td>
<td>8.8</td>
<td>0.4</td>
<td>20</td>
<td>Not tested</td>
<td>Negative</td>
</tr>
<tr>
<td>5</td>
<td>56/46 M, CML, G-GITVH</td>
<td>M</td>
<td>III</td>
<td>101</td>
<td>Not detected</td>
<td>7.8</td>
<td>21.4</td>
<td>220</td>
<td>Not tested</td>
<td>Negative</td>
</tr>
<tr>
<td>6</td>
<td>56/46 M, CML, G-GITVH</td>
<td>M</td>
<td>II</td>
<td>101</td>
<td>Not detected</td>
<td>7.8</td>
<td>21.4</td>
<td>220</td>
<td>Not tested</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Secondary Thyroid Carcinoma

EBMT Severe Aplastic Anaemia and Complications QoL WP | Budapest, Hungary | 1-3 Nov 2012
Summary – Thyroid Function

- Thyroid Dysfunction is frequent after HSCT
- Compensated Hypothyroidism
  L-T4 Treatment if TSH remains elevated or increases
- Autoimmune Thyroid Disease
- Secondary Neoplasm: Thyroid Carcinoma
- TSH/fT4 at 0/6/12m/yearly, Ultrasound 0/12m/yearly
Risk Factors for Gonadal Dysfunction

- **Chemotherapy**
  - Cyclophosphamide
  - Melphalan
  - Busulfan
  - Cisplatin
  - ............

- **Radiotherapy**

Dose and Fractionation

**Sex and Age**

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Radiotherapy and Fractionation

**Patterns of gonadal dysfunction following bone marrow transplantation**

AC Mertens¹, NKC Ramsey², S Kontzis³ and JP Neglin⁴

Days to first elevated gonadotrophin level or hormone replacement

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Influence of Sex

Patterns of gonadal dysfunction following bone marrow transplantation

AC Martens\textsuperscript{1}, NKC Romsey\textsuperscript{2}, S Kouris\textsuperscript{3} and JP Neglis\textsuperscript{4}

Table 2 Proportion of individuals, 20 years of age or older at last follow-up visit, with elevated gonadotrophin levels

<table>
<thead>
<tr>
<th>Age at BMT</th>
<th>Males</th>
<th>FSH level</th>
<th>LH level</th>
<th>Female</th>
<th>FSH level</th>
<th>LH level</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;15 years</td>
<td>8</td>
<td>42.9</td>
<td>50.0</td>
<td>6</td>
<td>66.7</td>
<td>66.7</td>
</tr>
<tr>
<td>16–25 years</td>
<td>32</td>
<td>66.7</td>
<td>56.3</td>
<td>23</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>≤26 years</td>
<td>76</td>
<td>85.3</td>
<td>72.4</td>
<td>41</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

\(P\) value for trend (both sexes combined): 0.04 (FSH), 0.004 (LH).

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Influence of Age

Patterns of gonadal dysfunction following bone marrow transplantation

AC Martens\textsuperscript{1}, NKC Romsey\textsuperscript{2}, S Kouris\textsuperscript{3} and JP Neglis\textsuperscript{4}

Days to first elevated gonadotrophin level or hormone replacement

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Gonadal Dysfunction in the Female

- Hypergonadotropic Hypogonadism (primary)
- Hypogonadotropic Hypogonadism (secondary/tertiary)
  - follicle:
    granulosa and thecal cells and germ cells

FSH and LH Levels after HSCT

Patterns of gonadal dysfunction following bone marrow transplantation

AC Martens¹, NRC Ramsay², S Kouris³ and JP Neglia⁴

Days to first elevated gonadotrophin level or hormone replacement

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Ovarian Failure after Radiation

Predicting age of ovarian failure after radiation to a field that includes the ovaries


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EBMT Severe Aplastic Anaemia and Complications QoL WP | Budapest, Hungary | 1-3 Nov 2012
Marker of Ovarian Failure

Anti-müllerian hormone as a marker of ovarian function in women after chemotherapy and radiotherapy for haematological malignancies

S. Lin Fong, P.I. Lugtenburg, U. Schipper, A.P.N. Themmen, E.H. de Jong, P. Sonneveld and J.S.E. Laverm

Figure 1: Decrease in serum AMH levels in relation to age in patients treated with multi-drug chemotherapy or stem cell transplant and controls:

- Serum AMH levels in patients treated with multi-drug chemotherapy
- Serum AMH levels in patients treated with stem cell transplant
- Serum AMH levels in healthy controls, with upper line = 95th percentile, middle line = 50th percentile and lower line = 5th percentile

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Treatment of Ovarian Failure

- Transdermal Patch
- Combination Oral Contraceptive

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Gonadal Dysfunction in the Male

- Hypergonadotropic Hypogonadism (primary)
- Hypogonadotropic Hypogonadism (secondary/tertiary)
  
  - Sertoli Cell Function
  - Leydig Cell Function

Sertoli Cell vs. Leydig Cell Function

- SC more sensitive to the effects of chemotherapy
- SC more sensitive to the effects of radiotherapy
  - spermatogonia 0.1 Gy
  - spermatocytes 2-3 Gy
  - spermatozoa 4-6 Gy
FSH and LH Levels after HSCT

Patterns of gonadal dysfunction following bone marrow transplantation

AC. Mortens1, NKC. Ramirez2, S. Kosiris3 and JP. Neglia4

Days to first elevated gonadotrophin level or hormone replacement

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Testes Volumes

Table: Testes Volumes

<table>
<thead>
<tr>
<th>Testes Volume</th>
<th>Testicular volume</th>
<th>Seminiferous tubules</th>
<th>Sperm count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>FSH normal</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LH normal</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>FSH low</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LH low</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

The European Group for Blood and Marrow Transplantation
Treatment of Testicular Failure

- Transdermal Patch/Gel
- Intramuscular Injections

Summary – Gonadal Function

- Gonadal Dysfunction is frequent after HSCT
- Hypergonadotropic Hypogonadism
- Transdermal Patch or Combination Oral Contraceptive
- Transdermal Patch/Gel or Intramuscular Injection
- Female: Evaluation of Recovery (1-2 years)
- LH/FSH, Estradiol/Testosterone, AMH (Female)