Erythropoietin and soluble transferrin receptor concentrations in high altitude residents with excessive erythrocytosis

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Outlook and objectives in 2005-2007

The general data base of patients with CMS and EE is scanty. Therefore it was planned:

1) To take for the ALFA Continuation Phase (LA) additional samples from patients with CMS and EE.
2) Do a careful anamnesis of these subjects which was not always possible in the previous study.
3) To associate erythropoietic markers with the iron metabolism.
4) To quantify [EPO] in healthy high altitude natives/long time residents and in subjects with EE or CMS.
In order to complete the data of the previous study, we looked into the clinical histories of 25 Patients.

**Signs and symptoms:**

- Cyanosis (6)
- Headache (5)
- Overweight \( \text{BMI} > 25 \text{ kg/m}^2 \) (22)
- Pulmonary Hypertension (10)
- Smokers (2)
- Frequent blood-letting (16) (1 per month ~ 400 ml)
## EPO and sTfR in altitude residents

### N=25

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>St. Des</th>
<th>MIN</th>
<th>MAX</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Females</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hct [%]</td>
<td>61,57</td>
<td>2,63674</td>
<td>60</td>
<td>67</td>
</tr>
<tr>
<td>Hb [g·dl⁻¹]</td>
<td>20,30</td>
<td>0,86023</td>
<td>19,80</td>
<td>22,10</td>
</tr>
<tr>
<td>[EPO] [U·l⁻¹]</td>
<td>38,54</td>
<td>24,90430</td>
<td>14,06</td>
<td>82,32</td>
</tr>
<tr>
<td>[sTfR] [nmol·l⁻¹]</td>
<td>56,62</td>
<td>22,37458</td>
<td>39,63</td>
<td>98,30</td>
</tr>
<tr>
<td>[Age] [years]</td>
<td>68,57</td>
<td>8,734</td>
<td>53</td>
<td>80</td>
</tr>
<tr>
<td>[BMI] [m/kg²]</td>
<td>31,7571</td>
<td>1,41522</td>
<td>30,40</td>
<td>34,10</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hct [%]</td>
<td>65,05</td>
<td>4,34501</td>
<td>60</td>
<td>71</td>
</tr>
<tr>
<td>Hb [g·dl⁻¹]</td>
<td>21,43</td>
<td>1,42669</td>
<td>19,80</td>
<td>23,40</td>
</tr>
<tr>
<td>[EPO] [U·l⁻¹]</td>
<td>50,37</td>
<td>48,45769</td>
<td>8,85</td>
<td>212,96</td>
</tr>
<tr>
<td>[sTfR] [nmol·l⁻¹]</td>
<td>65,64</td>
<td>30,57779</td>
<td>32,71</td>
<td>140,65</td>
</tr>
<tr>
<td>[Age] [years]</td>
<td>66,28</td>
<td>11,396</td>
<td>45</td>
<td>85</td>
</tr>
<tr>
<td>[BMI] [m/kg²]</td>
<td>30,0444</td>
<td>4,33158</td>
<td>24,30</td>
<td>40,40</td>
</tr>
</tbody>
</table>

### N=7

**Note:** The values for Males and Females are based on different sample sizes (N=25 and N=7, respectively) with implications for statistical significance and interpretation.
Correlation blood-letting vs EPO

- Two patients deserve special attention:

**B-14:**
Blood-letting 4/7/2005
Sample Collection: 6/7/2005
[EPO]: 109.4 U/l
[sTfR]: 93.51 nmol/l

**B-21:**
Blood-letting 14/9/2005
Sample Collection: 15/9/2005
[EPO]: 212.96 U/l
[sTfR]: 140.65 nmol/l

[EPO] cut-off 36 U·l⁻¹  [sTfR] cut-off 28 nmol·l⁻¹.

This fact suggests that blood letting, although used frequently in EE patients, is not recommendable.
Methods (I).

We included 75 patients from “La Rinconada” in Puno-Peru.

- The place, a gold mine, is located at 5,435 m.
- The Rinconada is the highest permanent human settlement in the world.

Inclusion criteria:

- Whole life at high altitude: (3,800 - 5,435 m).
  The Rinconada residents came from nearby high-altitude places and became permanent residents.
- Excessive erythrocytosis: [Hct > 60 %]
- CMS Score
Excessive Erythrocytosis. (EE)

- Asmus (Leadville CO. USA, 1993)
  EE → CMS: \( \text{Hct} \geq 56\% \text{ males} \)
  \( \text{Hct} \geq 51\% \text{ females} \)

- Vasquez (Potosi-Bolivia, 2001)
  EE → \( \text{Hct} \geq 61\% \text{ \ Hb} \geq 21\ g/dL \text{ males} \)
  \( \text{Hct} \geq 56\% \text{ \ Hb} \geq 19\ g/dL \text{ females} \)

- Consensus Statement high altitude diseases
  (Xining, China 2004).
  CMS → EE: \( \text{Hb} \geq 21\ g/dL \text{ males} \)
  SS,SH,PH \( \text{Hb} \geq 19\ g/dL \text{ females} \)
The Qinghai CMS score

- Breathlessness 0. Absent
- Sleep disturbance 1. Mild
- Cyanosis 2. Moderate
- Dilatation of veins 3. Severe
- Paresthesia Absent Score = 0-5
- Headache Mild Score = 6-10
- Tinnitus Moderate Score = 11-14
- Hb Severe Score > 15
EPO and sTfR in altitude residents

La Rinconada 5,435 m
Puno – Perú
EPO and sTfR in altitude residents

La Rinconada 5,435 m
Puno – Perú

The Rinconada Mine
Methods (II).

- Blood samples were taken by **venipuncture**.

- **Hemoglobin** (Hb) and **Hematocrit** (Hct) were measured directly.

- Aliquots of serum were stored at **-20°C** and sent to Charité Universitätsmedizin Berlin for analysis.

- By **ELISA** we assessed concentrations of
  - **Erythropoietin** ([EPO], cut-off 36 U·l⁻¹).
  - **soluble Transferrin Receptor** ([sTfR], cut-off 28 nmol·l⁻¹).
RESULTS (I) (Age)

\( N = 75 \) Males
- Mean = 35.9
- Min = 16
- Max = 58
RESULTS (II)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>Standard Deviation</th>
<th>MIN</th>
<th>MAX</th>
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</thead>
<tbody>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hct [%]</td>
<td>67,8</td>
<td>3,90</td>
<td>61</td>
<td>80</td>
</tr>
<tr>
<td>Hb [g·dl⁻¹]</td>
<td>22,3</td>
<td>1,28</td>
<td>20,1</td>
<td>26,4</td>
</tr>
<tr>
<td>[EPO] [U·l⁻¹]</td>
<td>30,6</td>
<td>27,7</td>
<td>2,1</td>
<td>105,2</td>
</tr>
<tr>
<td>[sTfR] [nmol·l⁻¹]</td>
<td>25,12</td>
<td>7,17</td>
<td>15,0</td>
<td>56,4</td>
</tr>
<tr>
<td>[Age] [years]</td>
<td>35,9</td>
<td>10,3</td>
<td>16</td>
<td>58</td>
</tr>
</tbody>
</table>
EPO and sTfR in altitude residents

Distribution: Patients by CMS Score

CMS
- Absent: 0 - 5
- Mild: 6 - 10
- Moderate: 11 - 14
- Severe: >15

Distribution:
- Severe: 2.7%
- Moderate: 5.3%
- Mild: 50.7%
- Absent: 41.3%
RESULTS (III).

No correlation between Hct and Hb with [Age]
RESULTS (IV).
No correlation between Hct and Hb with [EPO]
RESULTS (V).

No correlation between age with [EPO] and [sTfR]
RESULTS (VI).

No correlation between Hct and Hb with \([sTfR]\)
RESULTS (VII)

$R^2 = 0.001$

$\text{[EPO]}$ (U/l)

$\text{[sTfR]}$ (nmol/l)
Group A) with “normal” [EPO] (≤ 38 U·l⁻¹)
Group B) with very high [EPO] (≥ 78 U·l⁻¹)
Differences between two high-altitude populations in LA. (male subjects)

- **El Alto – Bolivia (4100 m)**
  (n=71)

- **La Rinconada – Peru (5500 m)**
  (n=75)
RESULTS (A).
No Significant differences between Males from El Alto and La Rinconada for Hct (p=0.122) and Hb (p=0.055).
RESULTS (B).
Significant differences between Males from El Alto and La Rinconada for Age (p=0.000); EPO (p=0.002); sTfR (p=0.000)
DISCUSSION (I).

Possible explanation of the differences between the two populations.

HYPOTHESIS:
The expression of high [sTfR] in subjects from El Alto could be related to low levels of IRON (iron deficiency) in plasma caused by frequent blood letting.

On the other hand, normal [sTfR] in subjects from La Rinconada could explain a normal iron metabolism related with age in spite of the altitude level.
DISCUSSION (II).

- Since the males from El Alto were significantly older than the males from La Rinconada, we must presume a relatively high prevalence of **Chronic Obstructive Pulmonary Disease (COPD)** among these people.

- Unfortunately, no data on the prevalence of COPD in LA PAZ/El Alto exist.

- The only study on prevalence of COPD available, was carried out by Dr. Ingrid Melgarejo in 5 hospitals in La Paz with the result of 12,09 %.
  
  (Ingrid Melgarejo, IIBA-2005, personal communication)
DISCUSION (III)

• Serum **soluble transferrin receptor** increases in **iron deficiency** as reported in literature.

• In general, to increase sensitivity and specificity, the measurement of serum **sTfR** should be performed in combination with other tests:
  • iron status
  • ferritin
  • TIBC
  • serum iron
CONCLUSIONS

• The subjects of La Rinconada had never been submitted to **blood-letting**, which could be the reason for the normal [EPO] values found in this population.

• We found normal [sTfR] in the majority of the subjects without correlation to [EPO].

• Measurements of [EPO]+[sTfR] in high-altitude residents with normal Hb and Hct values are necessary in order to establish a cut-off parameter for high-altitude.
Thank you for your attention.