


**Research Article**

## Correlation between Serum Testosterone Level and Erythrocytosis in Adolescent Males- A Cross-Sectional Study

Ariel Ben, Abu Arisha Rana\*, Bechor Ariel Tal, Yana Moshe, Leibzon Maor, Ben-Acon Michael and Sharon Nechama

### Abstract

**Background:** Androgens and testosterone can induce erythrocytosis in several mechanisms. Adolescent males often present to primary clinics with an elevated Red Blood Cell values without Hemoglobin abnormalities. We investigated the correlation between serum testosterone levels and red blood cell values.

**Methods:** 91 adolescents who were referred to the Emergency department were included in the trial, for which a complete blood count and serum testosterone were obtained, along with assessing Tanner score. Patients were divided into two groups with high and low red blood cell count. Mann-Whitney U test was performed to compare Serum testosterone level and Tanner score between the groups. Pearson's correlation coefficient was calculated to determine the correlation between red blood cell count and Testosterone levels.

**Results:** Testosterone levels was higher in the erythrocytosis group 14.05 (SD 5.53) vs non erythrocytosis group 11.94 (SD 7.38) although it did not meet statistical significance (p-value = 0.168). There is a weak positive correlation (Pearson's R = 0.146) between testosterone and erythrocyte levels.

**Conclusion:** In healthy adolescent males, whose serum testosterone levels are within normal range we observed erythrocytosis in 22% of patients. Testosterone levels was positively correlated with the Red blood cell count.

**Trial Registration:** Trial was registered in the Israeli ministry of health database – date 27/10/2020 – MOH\_2020-10-27-009444

### Introduction

Polycythemia exists when red blood cell (RBC) count, hemoglobin level and total RBC volume all exceed the upper limits of normal. In post pubertal individuals, RBC mass greater than 25% above mean normal value or a hemoglobin level greater than 18.5 g/dl in males indicates absolute erythrocytosis [1,2].

Erythrocytosis is usually classified either as primary or secondary, which can be of either congenital or acquired. Primary erythrocytosis is a condition in which the erythropoietic compartment is expanded independently of extrinsic influences or responding inadequately to them due to a primary abnormality of the erythroid precursor cells within the bone marrow. So far, the only molecularly characterized congenital primary erythrocytosis is caused by erythropoietin receptor (EPOR) gene mutations (familial erythrocytosis type 1, ECT1). The only known acquired form of a primary erythrocytosis occurs in polycythemia vera (PV), a clonal stem cell which primarily affect

#### Affiliation:

Department of Pediatrics, Laniado Hospital, Netanya, Israel

#### \*Corresponding author:

Sharon Nechama, Department of Pediatrics, Laniado Hospital, Netanya, Israel

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elderly patients [3]. Secondary polycythemia most often develops as a response to chronic hypoxemia, which triggers increased production of erythropoietin by the kidneys. The most common causes of secondary polycythemia include obstructive sleep apnea, obesity hypoventilation syndrome, obstructive pulmonary disease, asthma, heavy cigarette smoking and testosterone therapy [4].

Reference values for RBCs variables are lower in children in comparison with adults. Several studies which investigated hematologic parameters have been done in different populations, racial, ethnic and gender subgroups, even in different seasons [5-9]. Adolescents are a specific population whose normal levels are closer to adults than other pediatric population.

Clinical data suggests androgen replacement therapy, mainly testosterone can cause erythrocytosis among young man [10], and lack of testosterone causes anemia in older adults [11].

Androgens could stimulate erythropoiesis by several mechanisms. [12] Androgens can result in an increase in erythropoietin from renal tissue, by binding to cytoplasmic receptors, increasing RNA polymerase activity within a few hours. [13,14] Another mechanism is directly on bone marrow tissue – after entering the bone marrow, androgens are reduced to 17-keto-steroids, which then bind to the nucleus and increase the synthesis of mRNA. This generation of mRNA in uncommitted bone marrow cells results in their conversion from Epo-non-responsive to Epo-responsive cells [15].

Testosterone is known to stimulate iron (Fe) incorporation into erythrocytes [16] and increasing the red blood cell glycolysis [17].

Teenage boys often get referred to the hematology clinic for a solitary finding of elevated Red Blood Cells levels, with or without an absolute increase in hemoglobin levels.

That notion made us suspect there is a correlation between high levels of serum testosterone and high levels of RBC's, which was tested in this study.

## Methods

We conducted a Single center cross-sectional study on the population of pediatric patients aged 15y to 18y that referred to the Laniado Hospital Pediatric emergency department for various reasons. For each patient, after receiving informed consent from both parents, we obtained a Complete Blood Count, Serum Testosterone levels, and a urine sample for Toxicology. Each patient was asked about smoking habits, personal history of asthma, corticosteroid or drug use and ethnicity. Tanner score was assessed by the emergency department physician.

Patients with a positive toxic urine screen, sample disqualified by the lab or steroid use, and personal history of asthma were excluded from the trial.

## Patients grouping

Patients were assigned to two groups by Red Blood Cell count below 5.3 and equal or greater than 5.3. The latter defined as the Erythrocytosis group. RBC level cutoff was defined as 5.3 based on adolescent population studies [5,6].

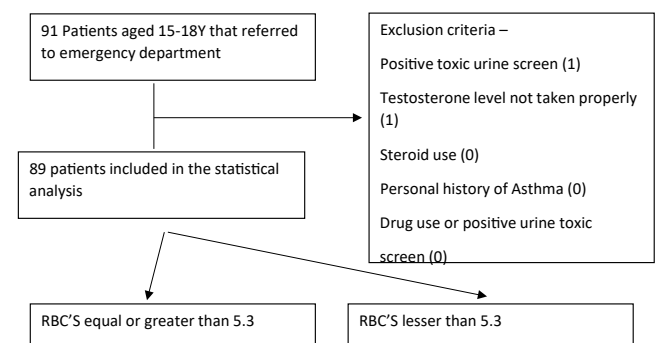
## Statistical Analysis

We performed a Two Way Mann-Whitney U test to compare the levels of testosterone between the Erythrocytosis and non-Erythrocytosis groups

We calculated the Pearson's correlation coefficient to determine the correlation between RBC levels and testosterone levels.

## Results

Parameters of Testosterone levels, MCV, Hemoglobin and Tanner score were compared among the two groups.



**Figure 1:** Flowchart presenting exclusion criteria and patient grouping.

Flowchart presenting exclusion criteria and patient grouping. For the exclusion criteria the number of patients excluded is presented within ().

**Table 1:** Characteristics of Patients.

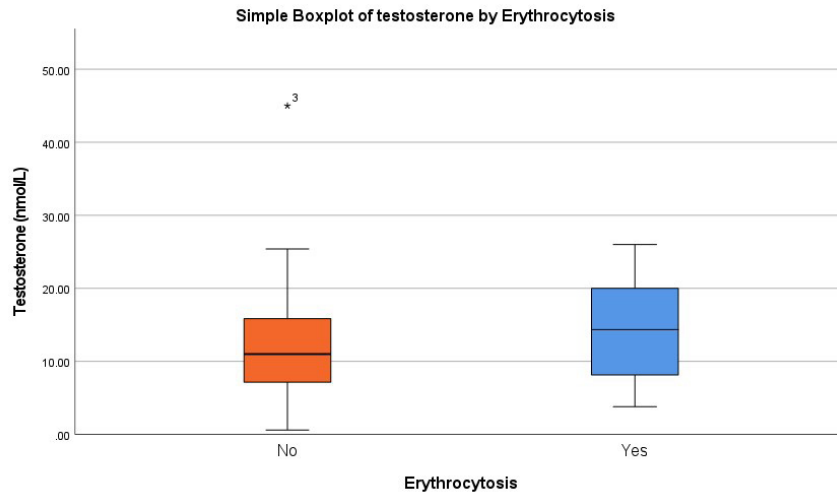
	Erythrocytosis (N=20)	non- Erythrocytosis (N=69)	P- value
Mean Age (SD)	16.62 (1.13)	16.3 (0.94)	0.261
Ethnicity			
Sephardic jew	5	39	0.011
Ashkenazi jew	10	22	0.152
Ethiopian jew	3	3	0.101
Other	2	5	0.345
Smoker	2	11	0.469

Table showing the demographic characteristics of patients in both groups. For age mean and SD are shown. For each ethnicity and also for smoking the number of patients is presented. P-value was calculated using the Mann-Whitney U test

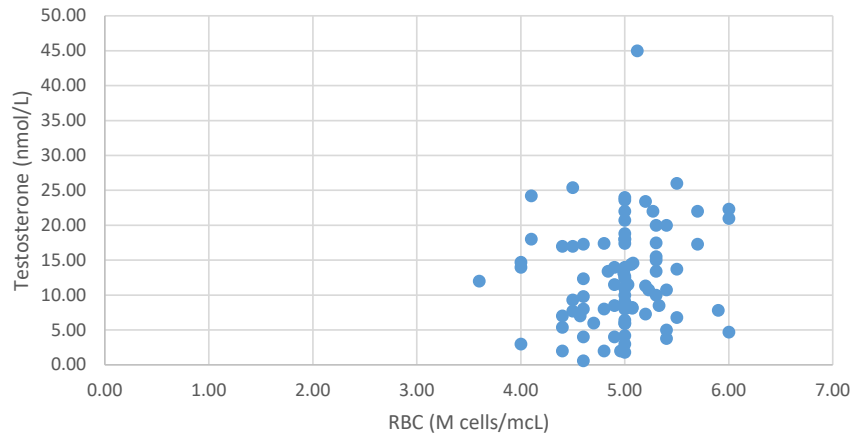
**Table 2:** Results.

	Erythrocytosis (N=20)	non- Erythrocytosis (N=69)	P- Value
Testosterone (nmol/L)	14.05 (5.53)	11.94 (7.38)	0.168
MCV ( $\mu\text{m}^3$ )	81.04 (4.8)	84.13 (4.0)	0.01
Hemoglobin (g/dl)	15.19 (1.19)	13.89 (1.12)	0.001
Tanner	4.85 (0.34)	4.57 (0.53)	0.31

Table showing results in erythrocytosis versus non erythrocytosis groups. For each parameter mean (SD) is presented. P- Value was calculated by using the Mann-Whitney U test



**Figure 2:** Box plot showing median and IQR for Erythrocytosis and non-Erythrocytosis groups.  
\* Single Individual with levels of testosterone exceeding normal levels in the non-erythrocytosis group.



**Figure 3:** Scatterplot in which X axis shows Red blood cell count and Y axis showing testosterone level.

There were higher levels of testosterone levels in the erythrocytosis group 14.05 (SD 5.53) vs non erythrocytosis group 11.94 (SD 7.38) although it did not meet statistical significance (p-value = 0.168). Hemoglobin levels were higher among erythrocytosis group as predicted with statistical significance (p-value = 0.001). MCV levels were slightly lower in erythrocytosis group (81.04 vs 84.13) with statistical significance (P-value =0.01). Tanner score was

quite similar between the two groups with no statistical significance (P-value= 0.34).

There is a weak positive correlation (Pearson’s R = 0.146) between testosterone and erythrocyte levels, scatterplot of RBC and Testosterone cases presented in Figure 2.

levels of testosterone by erythrocytosis and non-erythrocytosis subgroup presented in Boxplot in figure 3.

Of all cases one individual in the non-erythrocytosis group exceeded normal age-adjusted levels of testosterone (45 nmol/L, normal level 10-35 nmol/L).

## Conclusion

In this study we tried to figure out the correlation between high RBC's and serum testosterone level at a given time. This study included a small cohort of adolescents who all except one had normal levels of serum testosterone. Hemoglobin and Hematocrit levels were also normal; hence no individual met the definition of polycythemia.

As demonstrated by several publishers there are several proposed mechanisms in which testosterone can induce erythrocytosis, including through increased erythropoietin secretion, inducing responsiveness of stem cells to erythropoietin and increase iron intake and glycolysis in the mature red blood cell.

Although testosterone levels were slightly higher among Erythrocytosis group no statistical significance was achieved. Pearson's correlation coefficient showed a weak correlation between RBC's and testosterone levels. Even though, this could show there is a basis to our theory that higher testosterone levels can induce erythrocytosis in healthy individuals with testosterone not exceeding normal levels.

Regarding the Tanner score there was no significant difference between the two groups, and all patients were ranked Tanner 4 or 5 which was age appropriate. This is predicted regarding the fact all except one individual had normal levels of testosterone and have all gone through normal puberty.

Further research including patients with high testosterone levels or who take external testosterone supplementation can be done to further investigate this theory.

## Abbreviations

- RBC's – Red Blood Cells
- MCV- Mean Corpuscular Volume
- EPOR – Erythropoietin Receptor
- PV -Polycythemia Vera
- ECYT1 -familial erythrocytosis type 1

## Declarations

### Ethics Approval and consent to participate

Data collection and analysis was approved by the Institution's Helsinki committee (request number -0133-19-LND).

### Consent for Publication

Written informed consent for the publication was obtained from both parents of each individual participating in the trial.

## Availability of Data and Materials

N/A

## Competing Interests

I declare that the authors have no competing interests as defined by BMC, or other interests that might be perceived to influence the results and/or discussion reported in this paper.

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## Authors contributions

B.A and R.A.A - main authors, writers and editors, prepared and created the manuscript.

T.B.A, M.B.A, M. L, M.Y - data curation and creators of database

N.S and B.A- conceptualization and formatting the main research idea, aims and goals.

B.A - statistical analysis, creation of figures and tables

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This paper is part of resident's duties.

## Author's information

For any questions about this research please address Ben Ariel by Email: [benariel@gmail.com](mailto:benariel@gmail.com) or Nechama Sharon by email: [Nsharon@laniado.org.il](mailto:Nsharon@laniado.org.il)

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