

## THE PREVALENCE OF ANAEMIA IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AND LOW TESTOSTERONE

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Several studies found the risk of testosterone deficiency on increased frequency of anaemia in men with type-2 diabetes mellitus. Testosterone stimulates erythropoiesis via production of haematopoietic growth factors and possible improvement of iron bioavailability. The aim of this study was to investigate the prevalence of anaemia in patients with type 2 diabetes and hypogonadism, and to assess the hemoglobin and hematocrit levels during treatment with testosterone undecanoate. We evaluated 38 patients, with type 2 diabetes and confirmed hypogonadism. The subjects were between 48 and 61 years. The diagnosis of hypogonadism was based on the presence of symptoms and signs suggestive of testosterone deficiency (low libido, erectile dysfunction, decreased muscle mass and strength) and hormonal determinations. Results were compared with values obtained for 34 control subjects with type 2 diabetes but without hypogonadism. The hemoglobin are used to diagnose anaemia; according World Health Organization the anaemia is defined in men (15 years of age and above) as mild 110-129, moderate 80-109 or severe lower than 80 (hemoglobin in grams per litre). 1000 mg testosterone undecanoate was injected intramuscular every 10 to 14 weeks. Total testosterone, hemoglobin and hematocrit was assayed at baseline and after 3, 12, 24 months of treatment. Mean age of the study group participants was  $55.03 \pm 2.40$  years and the control group mean age was  $55.27 \pm 2.55$  years. 10 patients (26.31%) of the study group and 2 patients (5.88%) of the control group were diagnosed with anaemia; 6 patients of study group had mild anaemia and 4 moderate anaemia. The 2 patients of control group had moderate anaemia. Treatment with testosterone undecanoate generates significant changes in hemoglobin and hematocrit ( $13.03 \pm 1.36$  g/dl vs.  $14.55 \pm 0.99$  g/dl  $p < 0.001$ ,  $35.93 \pm 3.11\%$  vs  $42.47 \pm 5.76\%$   $p < 0.001$ ). Total testosterone concentrations during treatment were correlated significantly with changes in hemoglobin ( $p < 0.009$ ) but not with hematocrit changes ( $p < 0.18$ ). These findings suggest that testosterone deficiency may contribute to the increased frequency of anaemia in men with type 2 diabetes. Treatment with testosterone undecanoate generates significant changes in hemoglobin and hematocrit levels.

*Key words:* hemoglobin, hematocrit, diabetes mellitus, testosterone replacement therapy.

### INTRODUCTION

Anaemia is a frequent condition in patients with type 2 diabetes<sup>1, 2</sup>. Several studies have found the risk of testosterone deficiency on increased frequency of anaemia in men with type 2 diabetes mellitus. Testosterone stimulates erythropoiesis via

production of haematopoietic growth factors and possible by iron bioavailability improvement<sup>3</sup>. Testosterone deficiency contributed to an increased frequency of anemia in men with type 2 diabetes mellitus and low testosterone and chronic inflammation contributed to mild anemia in type 2 diabetic men<sup>4, 5</sup>.

Several studies have found that men with diabetes have lower testosterone levels compared to men without a history of diabetes, and low testosterone are now being recognised as an independent risk factors for obesity, metabolic syndrome and type 2 diabetes<sup>6,7</sup>.

Hemoglobin and hematocrit increase significantly under the action of testosterone, and erythrocytosis is the most frequent adverse event associated with testosterone therapy<sup>8,9</sup>. The mechanisms by which testosterone stimulates erythropoiesis are poorly understood, both testosterone dose and mode of delivery affect the magnitude of hematocrit elevation<sup>8-10</sup>.

The Endocrine Society Guideline on Androgen Deficiency Syndromes in Men recommends hematocrit monitoring 3 months after initiation of testosterone therapy and annually thereafter<sup>8</sup>.

The aim of this study were to investigate the prevalence of anaemia in patients with type 2 diabetes and hypogonadism, and to assess the hemoglobin and hematocrit levels during treatment with testosterone undecanoate.

## MATERIALS AND METHODS

We evaluated 38 patients, with type 2 diabetes and confirmed hypogonadism. The subjects were between 48 and 61 years. The diagnosis of hypogonadism was based on the presence of symptoms and signs suggestive of testosterone deficiency (low libido, erectile dysfunction, decreased muscle mass and strength) and hormonal determinations. Low testosterone levels were confirmed by two separate blood testosterone measurements. The hemoglobin is used to diagnose anaemia; according World Health Organization the anaemia is defined in men (15 years of age and above) as mild 110–129, moderate 80-109 or severe lower than 80 (hemoglobin in grams per litre)<sup>11</sup>. Prior to testosterone initiation, all patients were screened with a detailing questionnaire about their family history of prostatic cancer, and a detailed examination in order to exclude a risk of pre-existing prostatic cancer, prostate-specific antigen more than 4 ng/ml, hematocrit greater than 50%, severe sleep apnea, congestive heart failure, benign and malignant liver tumors,

severe hepatic or renal insufficiency. Results were compared with values obtained for 34 control subjects with type 2 diabetes but without hypogonadism.

1000 mg testosterone undecanoate was injected intramuscular every 10 to 14 weeks in patients with type 2 diabetes and hypogonadism. Regular monitoring of the total testosterone, hemoglobin and hematocrit were performed. Total testosterone, hemoglobin, and hematocrit levels were assessed at baseline and after 3, 12, 24 months of treatment.

### Statistical analyses

Data are presented as mean  $\pm$  SD. Clinical characteristics were compared using the t Student Test. Pearson's moment-product correlation coefficients were calculated to evaluate relationships between variables. Significance was defined at the 0.05 level of confidence. All calculations were performed using the Statistical Package for Social Sciences Software (SPSS) version 15.

## RESULTS

The groups were similar in terms of age but there were statistically significant differences for the recorded parameters in patients with type 2 diabetes and hypogonadism and control subjects. 10 patients (26.31%) of the study group and 2 patients (5.88%) of control group are diagnosed with anaemia. 6 patients of study group present mild anaemia and 4 moderate anaemia; the 2 patients of control group present moderate anaemia.

Treatment with testosterone undecanoate generate significant changes in serum total testosterone (246.66 $\pm$ 51.50 ng/dl *verso*, 482.29 $\pm$ 50.78 ng/dl,  $p < 0.001$ ), hemoglobin and hematocrit levels (13.03 $\pm$ 1.36 g/dl *verso* 14.55 $\pm$ 0.99 g/dl  $p < 0.001$ , 35.93 $\pm$ 3.11% *verso* 42.47 $\pm$ 5.76%  $p < 0.001$ ). Characteristics of patients during treatment with testosterone undecanoate are presented in Table 1. Changes in hemoglobin and hematocrit levels during treatment with testosterone undecanoate are presented in Figures 1 and 2.

Table 1

Characteristics of patients during treatment with testosterone undecanoate

	Baseline characteristics	Characteristics of subjects after 24 months of treatment	P
Total testosterone (ng/dl)	<b>246.66<math>\pm</math>51.50</b>	<b>586.23<math>\pm</math>48.22</b>	$p < 0.001$
Haemoglobin levels (g/dl)	13.03 $\pm$ 1.36	<b>14.55<math>\pm</math>0.99</b>	$p < 0.001$
Hematocrit levels (%)	<b>35.93<math>\pm</math>3.11</b>	<b>42.47<math>\pm</math>5.76</b>	$p < 0.001$

Comparison is significant at the 0.05 level:  $p < 0.05$

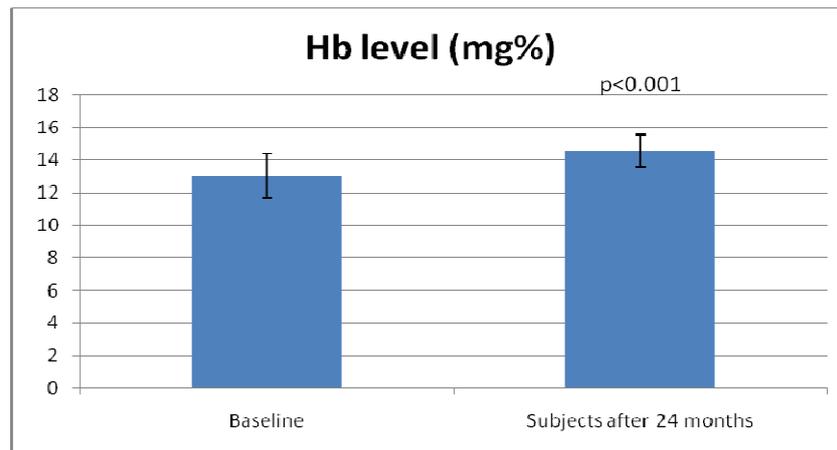


Fig. 1. Changes in haemoglobin levels during treatment with testosterone undecanoat.

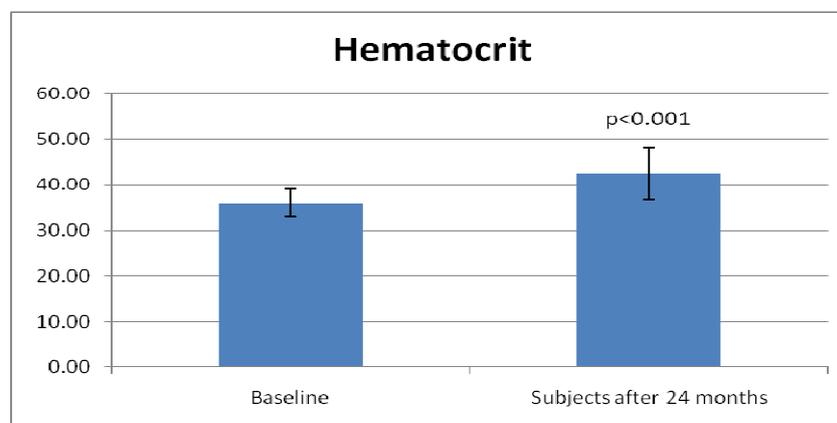


Fig. 2. Changes in hematocrit levels during treatment with testosterone undecanoat.

Total testosterone concentrations during treatment were correlated significantly with changes in hemoglobin (Pearson correlation coefficient  $p=0.009$ ) but not with hematocrit (Pearson correlation coefficient  $p=0.18$ ).

## DISCUSSION

Increase in hematocrit is a predictable effect of testosterone therapy<sup>8, 9, 12</sup>. The mechanisms by which testosterone stimulates erythropoiesis remain poorly understood. In 2008, Andrea D. Coviello, et al published in the *The Journal of Clinical Endocrinology & Metabolism* a study about Effects of Graded Doses of Testosterone on Erythropoiesis in Healthy Young and Older Men. Authors state that "It is possible that testosterone stimulates erythropoiesis through a direct effect on the bone marrow hematopoietic stem cells, these direct erythropoietic effects involve IGF-I induction through androgen receptor-mediated mechanisms. Androgens have been shown to

stimulate erythroid colony-forming units in the bone marrow and promote their differentiation into erythropoietin-responsive cells. Testosterone enhances intestinal iron absorption, iron incorporation in red blood cells, and hemoglobin synthesis. Androgen-treated men with end-stage renal disease have been reported to have longer erythrocyte survival and higher levels of 2,3-diphosphoglycerate than controls"<sup>14</sup>.

In a meta-analysis of randomized clinical trials to determine the risks of adverse events associated with testosterone replacement in men, Calof OM *et al.* reaffirm that testosterone replacement therapy was associated with a significantly higher risk of hematocrit  $>50\%$  than was placebo; hematocrit increase was the most frequent adverse event associated with testosterone replacement<sup>15</sup>.

Our data confirm clinical experience that treatment with testosterone undecanoate generates significant changes in hemoglobin and hematocrit levels.

However, for safety reasons a man receiving testosterone treatment require cessation of therapy,

or dose adjustment and/or periodic phlebotomy may be necessary to keep hematocrit below 52% to 55%<sup>15-17</sup>.

## CONCLUSIONS

These findings suggest that testosterone deficiency may contribute to the increased frequency of anaemia in men with type 2 diabetes.

Treatment with testosterone undecanoate generates significant changes in hemoglobin and hematocrit levels.

The Endocrine Society Guideline on Androgen Deficiency Syndromes in Men recommended hematocrit monitoring 3 months after initiation of testosterone therapy and annually thereafter.

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