

THE INFLUENCE OF ERYTHROPOIETIN THERAPY ON SERUM LEVEL OF TUMOR NECROSIS FACTOR ALPHA IN ANEMIC PATIENTS WITH EARLY STAGES OF DIABETIC NEPHROPATHY

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Background

Anemia is a common and often unrecognized complication of diabetes and diabetic nephropathy.

Diabetic patients with anemia are at increased risk of adverse outcomes from diabetic nephropathy and cardiovascular disease.

Anemia in patients with early stages of diabetic nephropathy is multifactorial.

It may result from various factors including:

- erythropoietin deficiency,
- iron deficiency,
- vitamin B12 and/or folate deficiencies,
- inflammation,
- autoimmune disorders,
- hemolysis,
- adverse effects of some drugs and others.

Inflammation, diabetes and chronic kidney disease are linked via a number of fundamental mechanisms.

Hyperproduction of proinflammatory cytokines in patients with diabetic nephropathy is related to:

- obesity,
- insulin resistance,
- hyperglycemia,
- dyslipidemia,
- endothelial dysfunction,
- oxidative stress and
- local activation of inflammatory pathways in renal tissue.

We have previously shown that patients with early stages of diabetic nephropathy are characterized by a negative correlation between hemoglobin level and serum level of tumor necrosis factor alpha, TNF alpha (Figure 1).

Management of patients with diabetic nephropathy includes anemia correction as an essential part of treatment.

In recent years many non-hematopoietic effects of erythropoiesis-stimulating agents have been discovered (Figure 2). It could be hypothesized that treatment of anemia has anti-inflammatory effects.

The aim of this study was to assess the influence of treatment with erythropoietin alpha on serum level of tumor necrosis factor alpha in patients with early diabetic nephropathy.

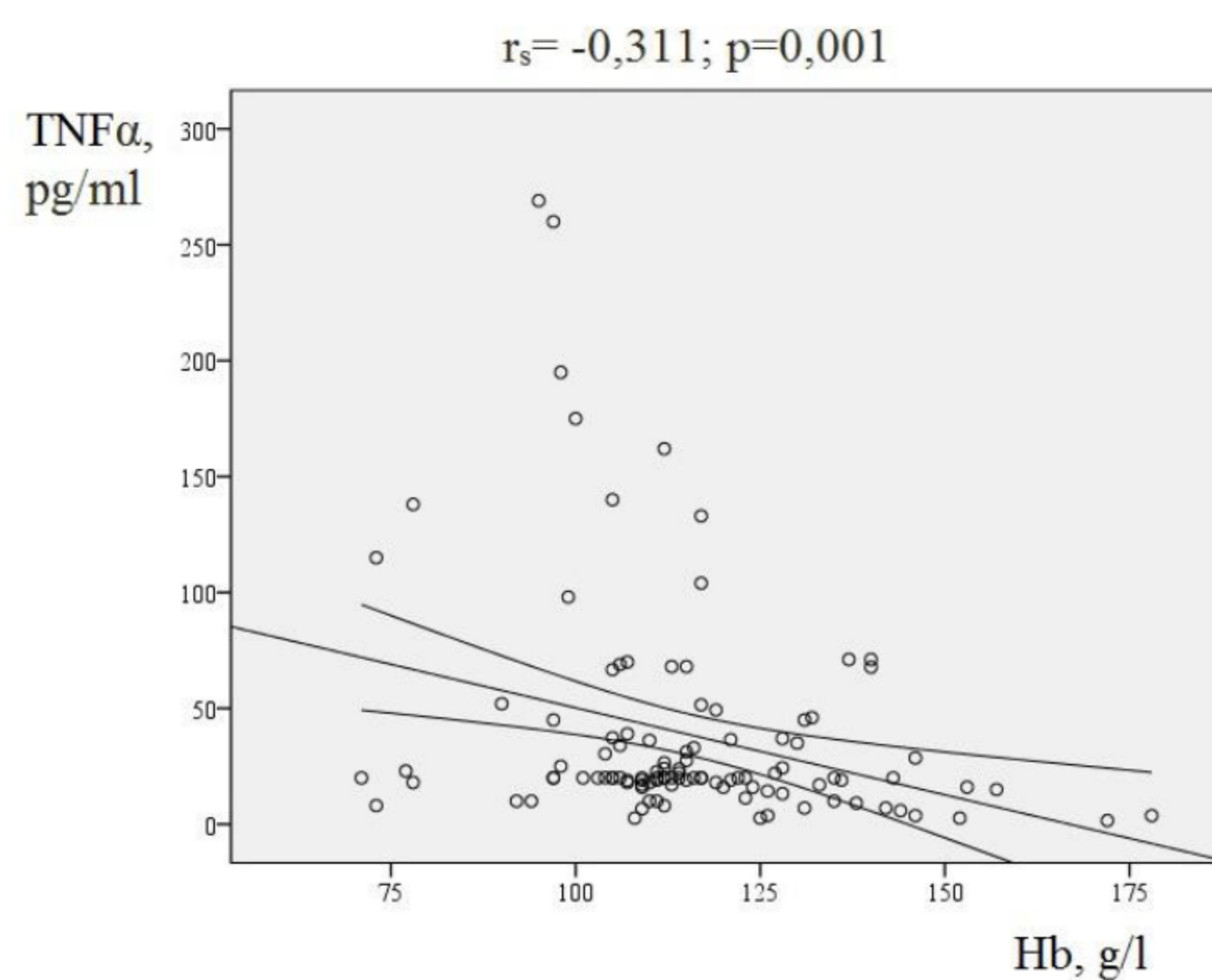


Figure 1. The relationship between hemoglobin level and serum TNF alpha concentration in patients with early stages of diabetic nephropathy. $r_s = -0,311$; $p = 0,001$ (I.Y. Pchelin, A.N. Shishkin, 2012)

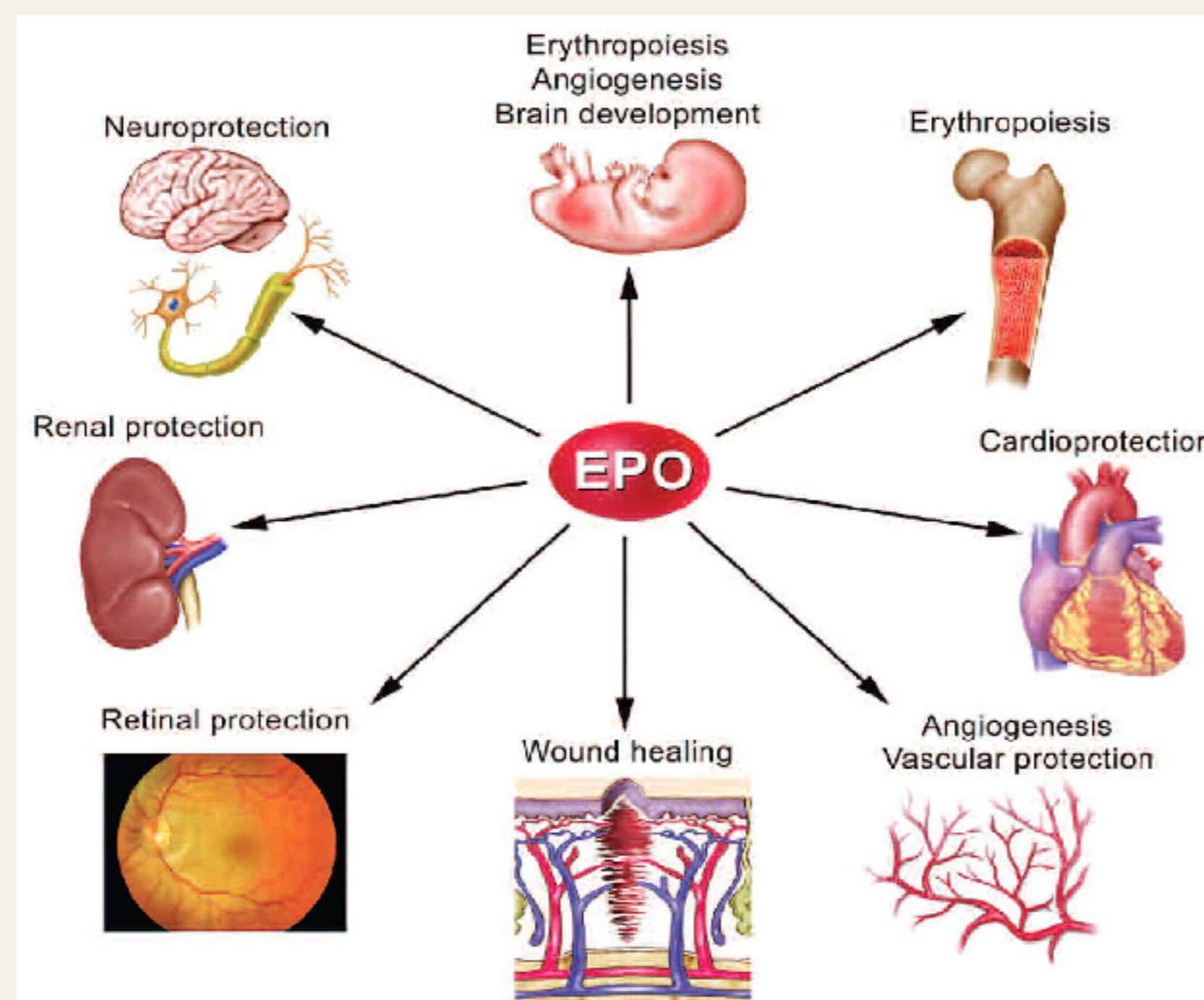


Figure 2. Non-erythroid effects of erythropoietin

Patients & Methods

We included 36 patients with type 2 diabetes mellitus and early diabetic nephropathy (CKD stages 1-3) complicated with renal anemia ($Hb < 110$ g/l), not receiving renal replacement therapy.

Glomerular filtration rate was calculated by the Cockcroft-Gault formula.

The **main group (17 patients)** received standard doses of erythropoietin alpha subcutaneously (starting from 30 IU/kg with further correction of dose according to NKF-K/DOQI Guidelines, 2006) and iron medication orally (ferrous sulfate, 200 mg per day) for 16 weeks.

The **control group (19 patients)** received only oral iron medications (ferrous sulfate, 200 mg per day) for the same period of time.

Besides performing routine clinical tests we measured serum concentrations of proinflammatory cytokines **before** and after **16 weeks** of treatment.

Serum levels of TNF alpha were measured by enzyme-linked immunosorbent assay (test systems by Protein Contour Ltd., St. Petersburg, Russia).

Reference value was < 50 pg/ml.

Mann-Whitney test was used to compare mean levels of TNF alpha in study groups.

The Wilcoxon non-parametric test was used to compare the level of TNF alpha in the studied groups.

Results

Before treatment serum levels of TNF alpha varied from 1,56 to 269 pg/ml.

The prevalence of elevated levels of TNF alpha levels in anemic patients with diabetic nephropathy was 21.1%.

We found the following mean serum levels of TNF alpha in the main group and in the control group, respectively ($p = 0,05$):

$30,8 \pm 9,6$ and $27,5 \pm 8,2$ pg/ml.

After 16 weeks of treatment both groups had no significant changes in concentrations of TNF alpha as compared to initial values.

Mean serum levels of TNF alpha were as follows:

main group – $25,0 \pm 3,6$ pg/ml,

control group – $31,1 \pm 4,2$ pg/ml

($p > 0,05$ for the difference between studied groups).

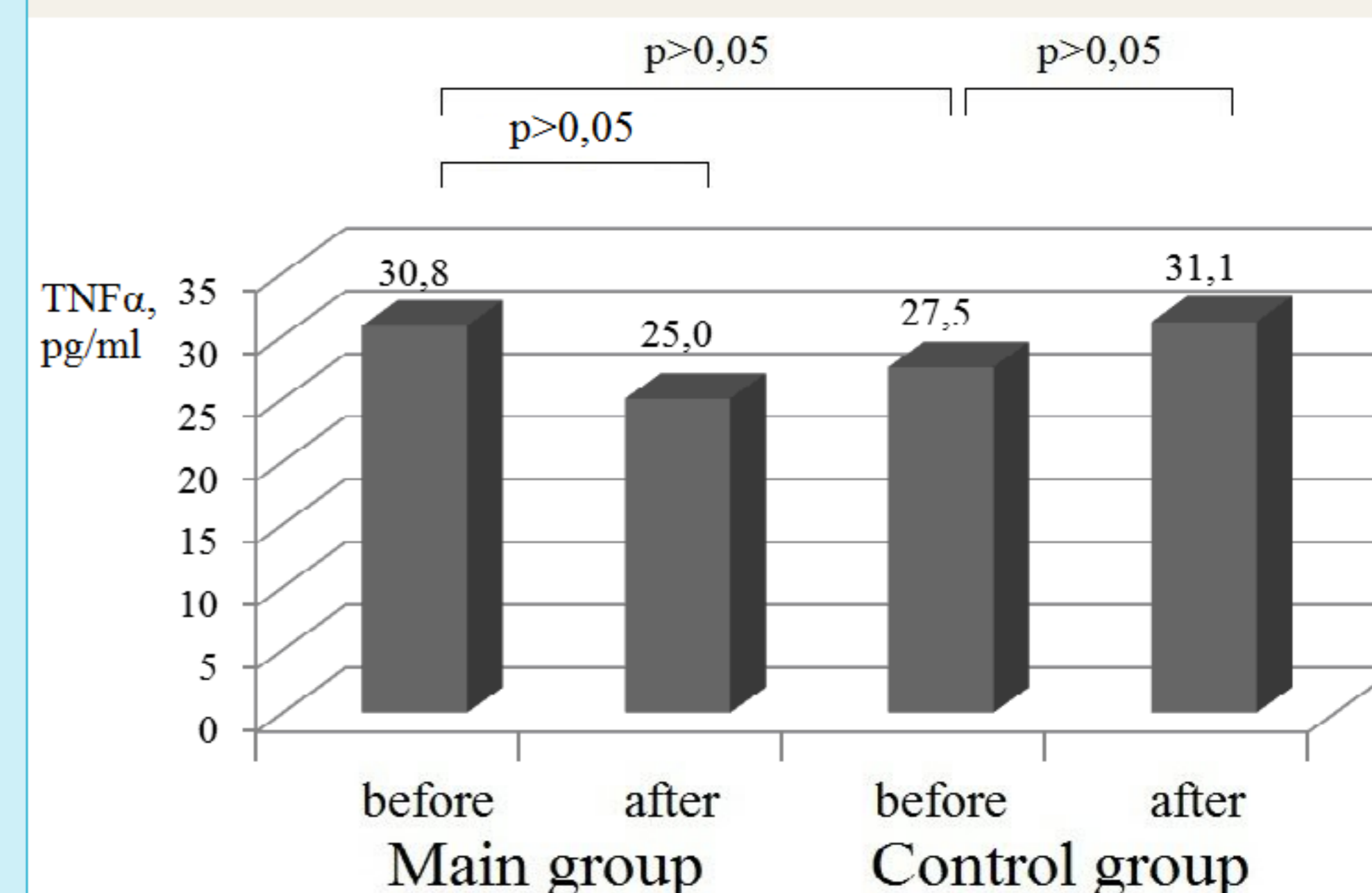


Figure 3. Serum levels of TNF alpha before and after the treatment

Conclusion

The results of the study suggest that neither treatment with iron sulfate nor comprehensive antianemic therapy with erythropoietin alpha and iron medication don't lead to a reduction in serum concentration of TNF alpha in anemic patients with early stages of diabetic nephropathy.

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