

Abstract

144 haemodialysis chronic renal failure (CRF) patients on haemodialysis (HD) program of 4 hours/3 times a week investigated for thyroid gland function and try to answer the question if the thyroid function abnormality affect the response of the haemodialysis CRF patients response to recombinant human erythropoietin (rHuEPO). His compares the results of the thyroid gland markers T3, T4, TSH which tested by radioimmunoassay of the patients with the patient multivitamin (PCV) values of the patients and checked if the haemodialysis CRF with hyper or hypothyroidism affect the response of the patients to the rHuEPO and if there are differences in the values of the PCV between the groups of the patients after their the duration and the time of the HD session and the same dose and rate of the rHuEPO. The results analyzed statistically and discussed and from that we can concluded there are hyperresponsiveness of the rHuEPO in patients with CRF and hypothyroidism in haemodialysis and for this reason we advise to search any haemodialysis patients for thyroid function.

INTRODUCTION

The interaction between kidney and thyroid function and how for years (1, 2). Thyroid hormones (TH) are necessary for growth and development of the kidney and for the maintenance of water and electrolyte homeostasis. On the other hand, kidney is involved in the synthesis and elimination of TH. From a clinical practice viewpoint, it should be mentioned that both hypothyroidism and hyperthyroidism are accompanied by remarkable alterations in the metabolism of water and electrolyte, as well as in cardiovascular function (3). All these effects generate changes in water and electrolyte balance.

management (4 and 7). Moreover, the decline of kidney function is accompanied by changes in the synthesis, secretion, metabolism, of TH (5). Thyroid dysfunction appears special characteristics in these patients with advanced kidney disease (6). On the other hand, the different treatments used in the management of patients with kidney and thyroid diseases may be accompanied by changes or adverse events that affect thyroid and kidney function respectively (8).

Chronic kidney disease affects both hyperthyroidism (thyroiditis) and T4 peripheral metabolism (9 and 10). Glucocorticoids influence the function and size of thyroid (11, 12 and 13). Glucocorticoid patients have an increased thyroid volume compared with subjects with normal renal function and a higher prevalence of goiter, mainly in women (14, 15 and 16). Also, thyroid nodules and thyroid carcinoma are more common in chronic patients than in the general population (17).

Low TSH concentrations are usually normal or elevated in chronic kidney disease, but its response falls reducing hormone (TSH) is generally low (18, 19, 20, 21 and 22). These findings suggest the presence of hypothalamic and pituitary dysfunction associated with uremia (23). Also, both TSH stimulate thyroxine and T4 production are altered in chronic kidney disease (CKD). The latter may compress TSH bioactivity (24).

Free and total T3 and T4 concentrations are usually normal or low in patients with CKD (25, 26, 27 and 28). The reduction in T3 levels (low T3 syndrome) is the most frequently observed thyroid alteration in these patients (9, 11, 12, 24 and 29). This reduction in T3 concentration has been linked to a decrease in the peripheral synthesis of T3 from T4 (5). Chronic metabolic acidosis associated

with the CKD may contribute to this effect (30). Although free and total T4 concentrations may be normal or slightly reduced, sometimes free T4 may be high due to the effect of heparin used in anticoagulation during haemodialysis (31), which inhibits T4 binding by its binding proteins (32).

CKD is associated with a higher prevalence of primary hyperthyroidism, both overt and subclinical, but not with hypothyroidism (9, 11, 24 and 28). In fact, the prevalence of primary hyperthyroidism, mainly in the subclinical form, increases as GFR decreases (33). A recent study has shown a prevalence of subclinical hyperthyroidism of 7% in patients with estimated GFR (ml/min/1.73 m²) that increases to 17.6% in subjects with GFR < 30 ml/min per 1.73 m² (34). The prevalence of hyperthyroidism is higher in women and is associated with an increased frequency of high titers of anti-thyroid antibodies (34).

A greater prevalence of non-autoimmune primary hyperthyroidism has been reported in patients with advanced kidney dysfunction under conservative treatment in comparison with non-dialysis patients with nephropathy. It is possible that these patients had impaired renal handling of iodine resulting in an elevation of serum iodine levels with a prolongation of the Wolff-Chaikoff effect (35).

The prevalence of hypothyroidism in CKD is similar to that found in general population (36). In areas with iodine intake of iodine (36). On the other hand, chronic patients undergoing dialysis with hypothyroidism due to either Graves' disease or toxic multinodular goiter, can be adequately treated with therapeutic doses of ¹³¹I (34 and 38). Moreover, hypothyroidism has been considered as one of the many causes of uremia related to end-organ failure

erythropoietin (rHuEPO) in CKD patients on HD with adequate response to erythropoietin treatment (36).

The kidney contributes to the iodine clearance primarily through glomerular filtration (37). Serum iodine concentrations are high in CKD but are not correlated with the degree of kidney failure (38). The iodine source has been linked to increased prevalence of goiter and hypothyroidism reported in CKD (34 and 37). A high exposure to iodine facilitates the development of hypothyroidism in CKD patients (36). Some authors have reported that a restriction of dietary iodine in chronic patients on HD can correct the hypothyroidism existing the need for hormone replacement with levothyroxine (38).

Most HD patients are euthyroid. Hypothyroidism is not infrequent in these patients. However, a diagnosis of hypothyroidism in HD patients should not be made solely on the basis of elevated T₄ and T₃ levels but requires determination of subclinical TSH elevation (TSH > 5 mU/L but < 10 mU/L) may occur in 20% of chronic patients and are more indicative of non-thyroid illness than hypothyroidism (39). HD is associated with alterations in the concentration of circulating T₄, usually in a reduction in serum total and free T₄ concentration. This reduction is associated with systemic acidosis, urea or dialysis, and some markers of endothelial damage and inflammation (36). Low T₄ may be a protective adaptation for nitrogen excretion and therefore hypoproteinemic T₄ supplementation can result in excessive protein nitrogen wasting in these patients. HD influences the cellular transport of T₄. This effect could act as a compensatory mechanism to maintain the thyroid dysfunction in order to maintain euthyroid status (34).

Treatment with ablation of ¹³¹I has been successfully used in the treatment of differentiated thyroid carcinoma in patients on HD (24, 32, 33 and 34). HD removes more ¹³¹I from blood than from thyroid and helps to reduce radiation (34).

Many authors believed that patients on regular HD suffer from chronic illness not involve the thyroid. However, they may have low serum thyroxine (T₄) and triiodothyronine (T₃) concentrations (34 and 37). It was found that total serum T₄ and free T₄ (FT₄) concentrations were significantly higher immediately after HD than before HD session (35, 37). They explained that chronic renal failure affects thyroid function in multiple ways, including low levels of circulating thyroid hormone concentration, altered peripheral hormone metabolism, disturbed binding to carrier proteins, possible reduction in thyroid hormone content and increased iodine stores in thyroid gland. Both plasma T₄ and T₃ levels are reduced. The low serum T₄ is not due to increased T₄ degradation or to decreased thyroid T₄ secretion but is a result of impaired renal thyroid T₄ or T₃ excretion. The reduction in T₄ is attributed to the presence of circulating inhibitors, which impair binding of T₄ to thyroxine binding globulin (34).

Some authors, believed that the response of TSH to TSH in haemodialysis and end-stage patients was significantly less than in normal subjects (34, 40 and 41) and others confirmed that the response of TSH to TSH is not normal as in normal subject and they concluded that because free T₄ and a deficient neuronal surge of TSH were observed in haemodialysis suggesting a deficient neuronal surge of TSH to be important in impaired thyroid function (32).

Different drugs used in thyroid disease may have adverse effects on the kidney, and vice versa. Agents used in the treatment of renal disease may develop undesirable effects on the thyroid. Hypothyroidism induced by thiazolidines (glimepiride, glipizide, and gliclazide) (42) may cause kidney failure. Lithium salts adverse effects both on the thyroid gland. Hypothyroidism induced by thiazolidines (glimepiride, glipizide, and gliclazide) (42) may cause kidney failure. Lithium inhibits synthesis and release of T₄ (3). The studies on the interaction of the effect of the erythropoietin in CKD on haemodialysis with hypothyroidism is not much enough to give us a complete idea about the extent of the treatment of uremia in these type of the patients and how much the effect of the hypothyroidism on the response of patients to treatment the exogenous EPO on haemodialysis program and at the same time they affect free hypothyroidism or low T₃ and T₄ or high TSH. In this study we analyze explain part of many question regarding thyroid subject.

TITLE AND METHODS

144 patients of CRF on haemodialysis program of 4 hours/3 times a week in nephrology and artificial kidney unit of Merjan teaching hospital, Hilla, Babylon, Iraq. The study started on January 14, 2012 and finished on April 8, 2013. They are 76 female and 68 male and the mean age of patients in this study was 55.54 ± 12.53 years. All the patients investigated for the thyroid function test (T₃, T₄ and TSH) blood urea, serum creatinine, serum sodium, potassium, calcium, phosphate and PCV.

The TSH, T₃, T₄ measured by VIDAS (Ref: 80 400 BioMérieux SA, RC3 Lyon, France), the PO4 (serum phosphate) measured by spectrophotometer Cecil 1001 at 810 nm, also the serum calcium measured by the spectrophotometer (Cecil 1011) but at 370 nm by titan react kit. The sodium and potassium measured by electrolyte calcium Na, K, Ca and Ph analyzer.

Statistical analysis was carried out using SPSS version 18. Continuous variables were presented as means with their 95% confidence interval (CI). Independent sample t-test was used to compare means between two groups. One way analysis of variance (ANOVA) was used to compare means among more than two groups. A p-value of < 0.05 was considered as statistically significant, meanwhile a p-value of < 0.01 was considered as strongly statistically significant.

RESULTS

The overall mean age of patients who did for haemodialysis dialysis was 55.58 ± 12.53 years. There was no significant difference between the mean age for male (58.84 ± 14.20 years) and female (51.82 ± 11.88 years) (p=0.181, df=147, p=0.794).

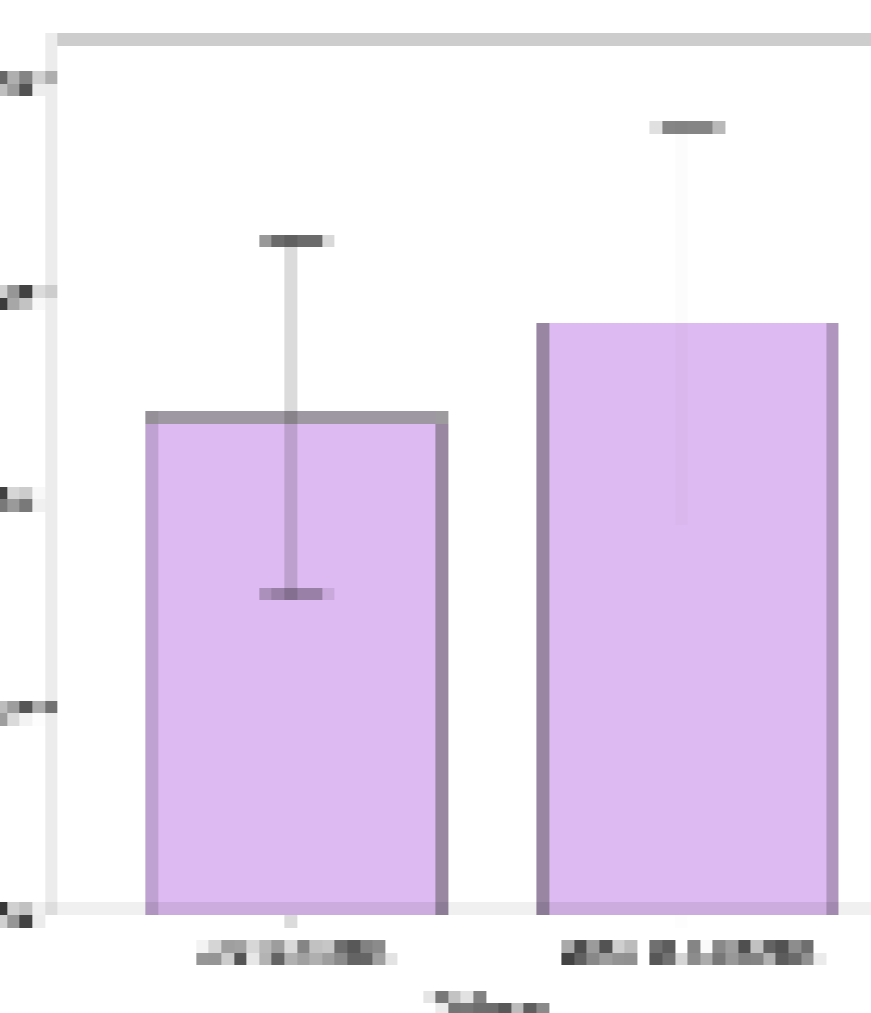


Figure 1 shows the mean differences of PCV by T3 levels. There was significant difference between PCV means for low and normal T3.

t-test=5.780, p<0.001**
Figure 1: Mean differences of PCV by T3 levels

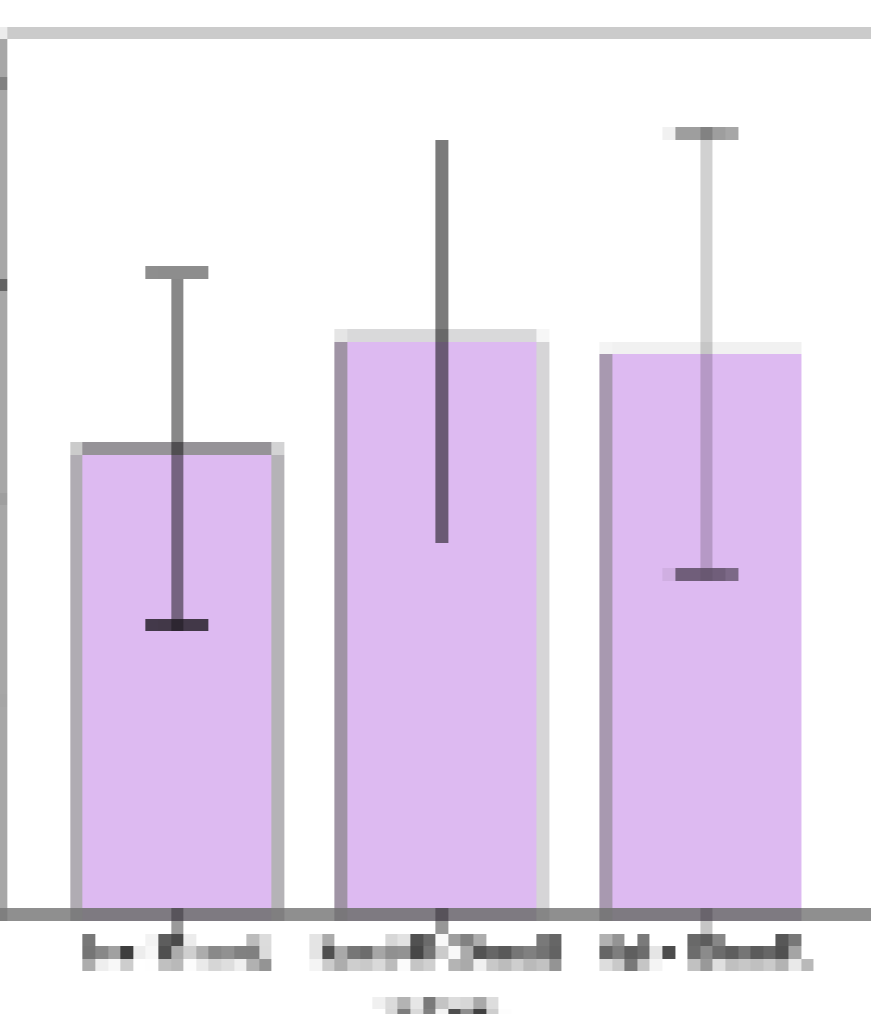


Figure 2 shows the mean differences of PCV by T4 levels. There was significant difference between PCV means for low, normal and high T4.

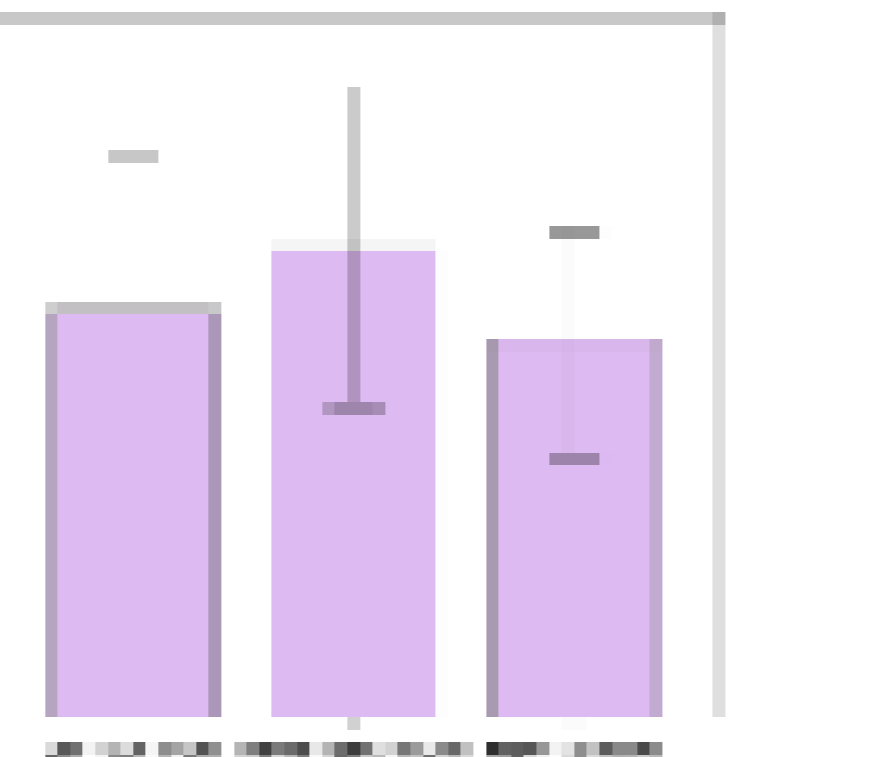


Figure 3 shows the mean differences of PCV by TSH levels. There was significant difference between PCV means for low, normal and high TSH.

F= 24.039, p< 0.001**
Figure 3: Mean

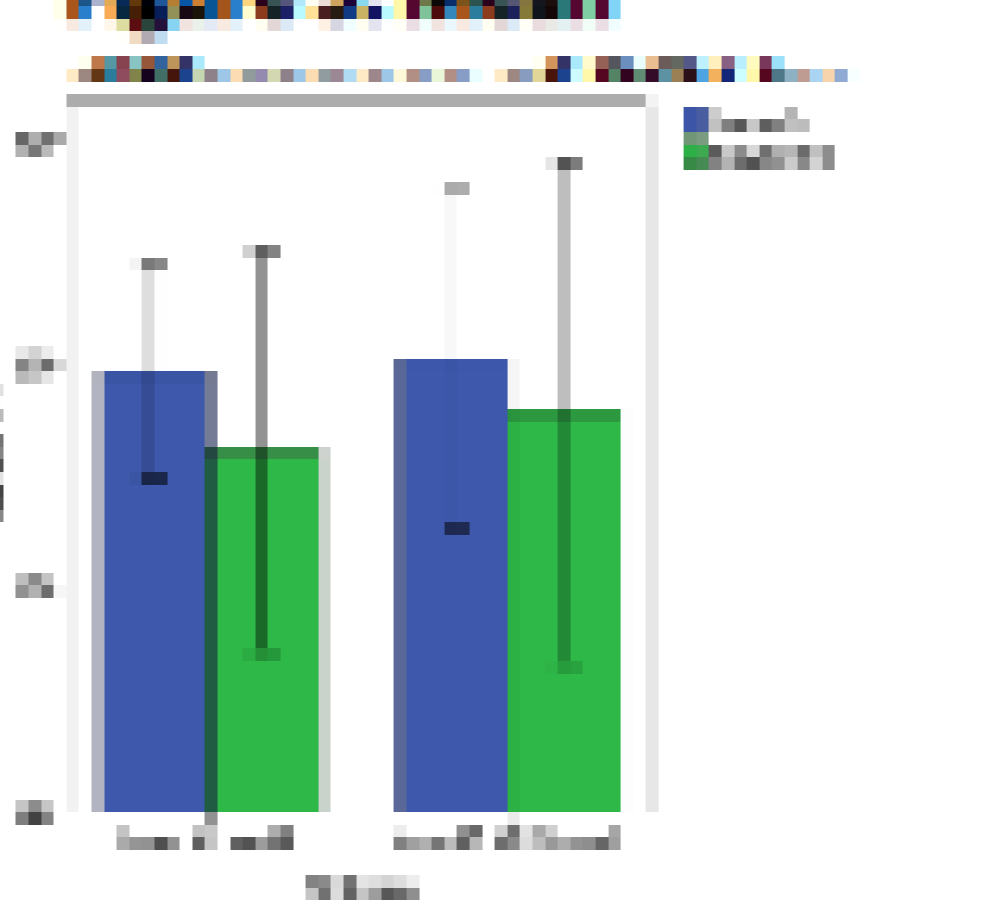


Figure 4 shows the mean differences of serum Ca and PO4 by T3 levels. There were no significant differences between serum Ca and PO4 means for low and F= 0.305, p=0.551 (S.Ca) F= 1.943, p=0.054 (S.PO4) Figure 4: Mean differences of serum Ca and PO4 by T3 levels

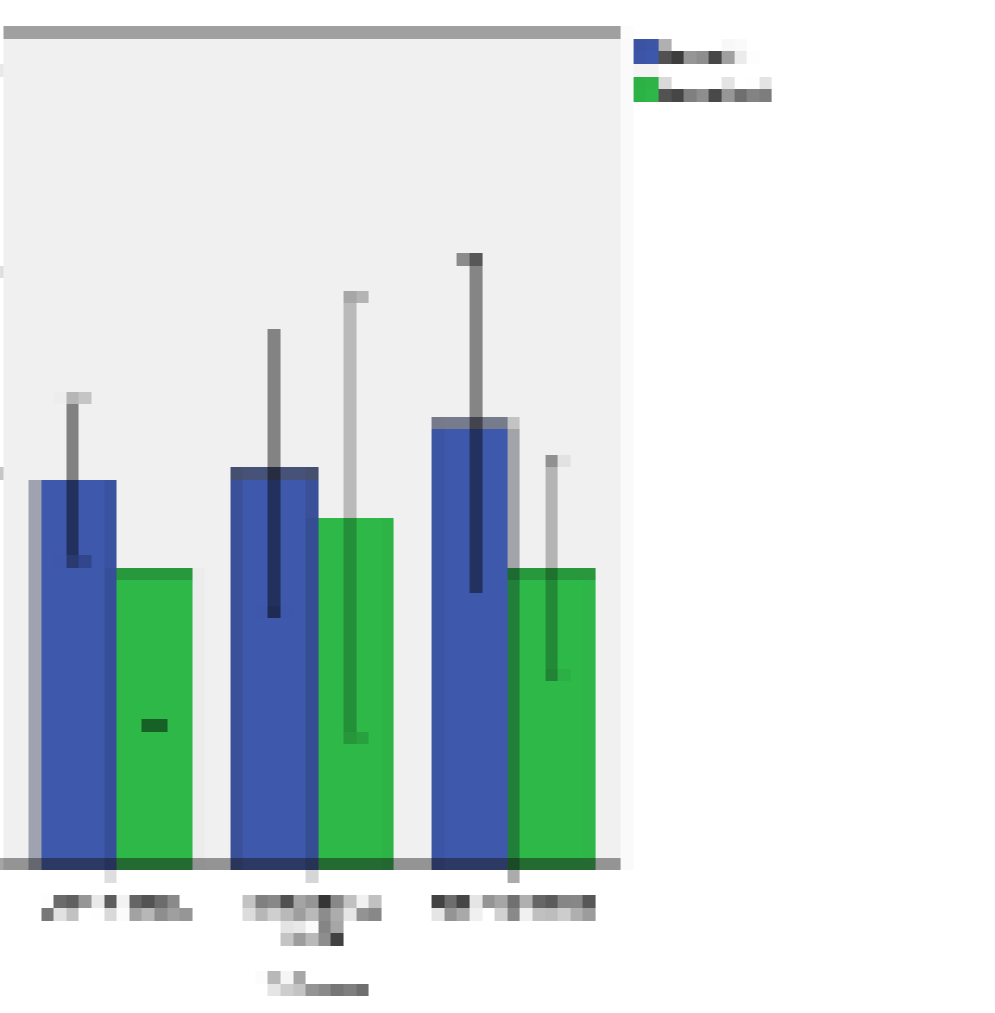


Figure 5 shows the mean differences of serum Ca and PO4 by T4 levels. There were no significant differences between serum Ca and PO4 means for low, normal and high T4. F= 0.275, p=0.610 (S.Ca) F= 2.884, p=0.084 (S.PO4) Figure 5: Mean differences of serum Ca and PO4 by T4 levels

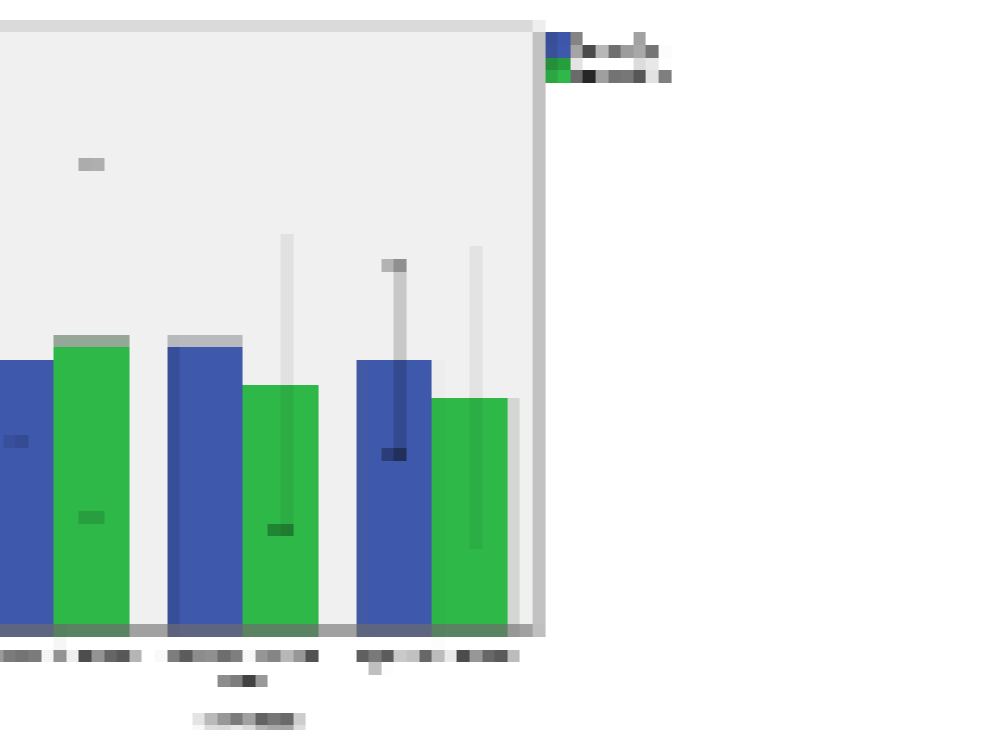


Figure 6 shows the mean differences of serum Ca and PO4 by TSH levels. There F= 0.275, p=0.610 (S.Ca) F= 1.875, p=0.183 (S.PO4) Figure 6: Mean differences of serum Ca and PO4 by TSH levels

Discussion

are highly significant relationship between the PCV values and thyroid function in haemodialysis chronic renal failure patients who are treated with rHuEPO in order to improve the anemia condition. This relationship belonging to the direct relation between the thyroid hormones T₃, T₄, TSH, and the response to erythropoietin. We are first in this study when there were hypothyroidism in haemodialysis CRF patients there are the lesser response in the rHuEPO and this relationship can be proved in the normal thyroid function state where we found when the patients in euthyroid or normal thyroid function the PCV values are within the acceptable values for the haemodialysis patients. This data agreed with the results of Chang (4), Ghali (4), Longo C et al (4) where they found that a state of euthyroidism is essential for the action of EPO on bone marrow (34, 40).

Valen-Graeme et al (4) found that levothyroxine therapy did not appear to aid iron therapy adequately in subclinical hypothyroid patients. The addition of levothyroxine, on the other hand, caused a significant improvement of hemoglobin and blood count variables. These findings support the clinical observation regarding the presence of a group of patients resistant to oral iron because of their existing subclinical hypothyroidism and they found that these patients might benefit from addition of levothyroxine to their treatment regimen, and this might be an indication for treating subclinical hypothyroidism in iron deficiency anemia patients. The authors suggest that stimulation of erythropoiesis by thyroid hormones is not the sole mechanism, but thyroid hormone affects on iron

metabolism are also involved (7). Our data not agreed with this idea we suggest that the hypothyroidism independently affect the EPO responsiveness in bone marrow precursors where the results indicate that there is no relationship with calcium ions which is important for the maturation and development of the blood cells.

Animal and human studies show that thyroid hormones stimulate red cell production (14 and 15). In hypothyroidism, the erythrocyte life span remains normal, and there is hypoproliferative erythropoiesis (14). There have been several suggestions to try to explain how thyroid hormones stimulate erythropoiesis. Increased metabolic rate and its related increase in oxygen demand and have been the major explanations (7). The proposed mediator was erythropoietin. Consistent with this suggestion, Christ-Crain et al (12) found elevated erythropoietin levels after levothyroxine therapy in subclinical hypothyroid women this agreed with our idea and results of Chen-Jiang et al (4) which indicated that hypothyroidism a cause of resistance to erythropoietin treatment and suggest that euthyroid state is essential for the action of erythropoietin on the bone marrow and they proved that increment in hemoglobin and hematocrit after initiation of levothyroxine without adding other factors like iron.

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