

# Insulin Resistance in Patients of End Stage Renal Disease on Hemodialysis - Effect of Short Term Erythropoietin Therapy

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## Abstract

**Aim:** Insulin resistance is a potentially modifiable cardiovascular risk factor and it can be considered as a therapeutic target in patients of chronic kidney disease (CKD), especially those undergoing Hemodialysis. The present study was conducted to assess insulin resistance (IR) in patients of End Stage Renal Disease (ESRD) on Hemodialysis and to evaluate effect of short term treatment with recombinant human erythropoietin therapy.

**Materials and Methods:** It was a prospective case control study which was carried out at a tertiary care hospital in North India, from May 2010 to September 2011. Adult patients of CKD (both diabetic and non diabetic) were enrolled in the study and were randomly assigned into two groups. Study group consisted of 20 patients (10 diabetics and 10 non diabetics) with ESRD who were on regular twice weekly hemodialysis and were given subcutaneous erythropoietin (80 to 120U/kg/wk) after each session of dialysis. Control group included 10 patients with ESRD on regular hemodialysis but did not receive erythropoietin.

**Results:** Mean baseline fasting insulin levels and insulin resistance as reflected by Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) were similar in the two groups. HOMA-IR was  $5.48 \pm 10.43$  in the study group and  $3.11 \pm 2.16$  in the control group. The levels decreased significantly to  $0.51 \pm 0.36$  ( $P < 0.041$ ) in the study group and increased insignificantly to  $3.84 \pm 4.08$  ( $P = 0.187$ ) in the control group after 6 months.

**Conclusion:** Fasting insulin level and insulin resistance is increased in CKD patients. Recombinant human erythropoietin therapy has a favorable effect on insulin sensitivity in addition to its role in the treatment of anemia in cases of CKD on dialysis.

**Keywords:** Insulin resistance; Chronic kidney disease; Fasting insulin levels; Homeostasis Model Assessment of Insulin Resistance

## Introduction

Insulin resistance is a characteristic feature of uremia. As long as hyperinsulinemia is adequate to overcome insulin resistance, glucose tolerance remains normal [1]. In addition to abnormalities in carbohydrate metabolism, the IR syndrome is accompanied by an elevation in non esterified fatty acid, abnormalities in visceral fat metabolism, elevated uric acid, endothelial dysfunction, and abnormalities in glucocorticoids leading to the development of atherosclerosis [2]. The influence of insulin resistance on cardiovascular risk is independent of age, body mass index, concomitant hypertension and dyslipidemia or C-reactive protein levels. Numerous factors implicated in the etiology of insulin resistance include uremic toxins, chronic metabolic acidosis, intracellular ion homeostasis disequilibrium, as well as qualitative as well as quantitative disturbances of insulin receptor on adipocytes, skeletal muscles and hepatocytes, cytokines produced by adipocytes (adipokines), chronic inflammation as well as low physical activity [3]. Although definitive evidence for the efficacy of some of these interventions on clinical outcomes such as cardiovascular end points or mortality is still lacking. However, management of insulin resistance in patients on hemodialysis is multifaceted. Treatment of insulin resistance in CKD patients can be achieved by hemodialysis, angiotensin-converting enzyme inhibitors, thiozolidinedione, treatment of calcium and phosphate disturbances and recombinant human erythropoietin [4]. Few studies have shown favorable effect of erythropoietin in decreasing insulin resistance [1,5-8]. However no Indian study is available on this issue. The present study was therefore conducted to assess insulin resistance in patients of CKD irrespective of diabetic status, to evaluate the effect of shortterm human erythropoietin therapy on insulin resistance.

## Materials and Methods

This was a prospective case control study carried over a period from May 2010 to September 2011. It included 30 patients of end stage renal disease (both diabetic and non diabetic) on regular twice weekly hemodialysis. Inclusion criteria were patients with end stage renal disease who were receiving regular Hemodialysis. They included diabetic and non diabetic patients. The exclusion criteria were factors or diseases affecting fasting insulin levels like congestive heart failure, patients on corticosteroids, patients on drugs like beta blockers, biguanides, ACE inhibitors, patients with end stage pulmonary disease & cancer. A total of 45 patients were enrolled for study, out of which 30 patients completed the study. 15 patients could not complete the study due to reasons like death before the completion of study, non compliance with the treatment or refusal to give informed consent etc. The remaining 30 patients were divided into two groups; Group I – Study group (n=20) consisted of patients (10 diabetics and 10 non diabetics) with ESRD who were on regular Hemodialysis & were given subcutaneous erythropoietin in a dose of 80 to 120kg/

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wk. Before starting erythropoietin, all patients received intravenous iron supplementation in a dose of 1000 mg to replenish deficient iron stores and were continued on the intravenous iron therapy 100mg/wk thereafter. Group II – Control group (n=10) included patients with ESRD on regular Hemodialysis but these cases were not receiving erythropoietin either because of the fact that their Hemoglobin was >8gm% or patients refused to take erythropoietin injections due to financial constraints or patients did not tolerate erythropoietin or had accelerated hypertension secondary to erythropoietin where erythropoietin had to be discontinued.

Study Group-1 included ten patients of diabetic nephropathy & ten were non diabetic patients of which four were chronic glomerulonephritis, two were hypertensive glomerulosclerosis, two of autosomal dominant and rest were obstructive uropathy. The control group-II had five cases of diabetic nephropathy and five of non diabetic nephropathy. Out of non diabetics (Group-II), two were autosomal dominant adult polycystic kidney disease, one was of hypertensive nephropathy, one of chronic glomerulonephritis and one was obstructive uropathy. All these cases were receiving regular 4 hours of twice weekly maintenance Hemodialysis.

All the patients were examined in detail and all basic laboratory investigations were done with a special emphasis on renal and various metabolic parameters. Blood samples were collected after an overnight fast of 8 hrs for basic biochemical / renal work up including serum fasting insulin levels, HBA1C, fasting and postprandial blood sugar levels at 8 AM in the morning. Serum fasting insulin was measured at baseline and at 6 months along with other renal parameters. Adequacy of dialysis was adjudged by KT/V, which was kept above 1. (K –dialyser clearance of urea, t- dialysis time, V – patient’s total body water). In study group, out of 10 diabetic patients 5 were on insulin and two were on oral antidiabetics (glimiperide) and 3 were not on any medication. While, in control group out of 5 diabetic patients, 2 were on insulin, 2 were on oral anti diabetic (Glimipride) and one was not on any medication.

Patients were evaluated every month for adherence to treatment, adverse effects and clinical outcome. Serum fasting insulin levels were measured by ADVIA CENTAUR CP model using Siemen’s kit [9]. Insulin resistance was calculated by HOMA-IR because of its simplicity. Data was analysed by using student t –test (paired and unpaired) and Pearson’s correlation coefficient (r).

$$\text{HOMA-IR [10]} = \text{Glucose X Insulin} / 22.5. \text{ Glucose in mmol/L}$$

$$\text{Or HOMA-IR} = \text{Glucose X Insulin} / 405. \text{ Glucose in mass unit's mg/dL}$$

The main limitations of the clamp approach are that it is time-consuming, labor intensive, expensive, and requires an experienced operator to manage technical difficulties. Thus, for epidemiological studies, large clinical investigations, or routine clinical applications (e.g., following changes in insulin resistance after therapeutic intervention in individual patients) application of the glucose clamp is not feasible.

## Results

Baseline biochemical parameters of the two groups were a like/ comparable and are shown in Table 1. The mean baseline hemoglobin level in study group was 8.57 ± 1.85g% and in control group was 8.4 ± 1.71g%.The hemoglobin level at end of study was 10.6 ± 1.25g% in study group and was 10.2 ± 1.50g% in control group. In the study group fasting insulin level of 5 patients on insulin were 74, 11.7, 30.5,

21.11 and 20.18 respectively where as in control group (2 cases) fasting insulin level of patients on insulin was 11.82 and 28.36 mU/mL.

The baseline mean fasting insulin levels in study participants showed a mean value of 11.40 ± 16.58 mU/L and at six months it decreased to 2.30 ± 0.40 mU/L and the fall was significant (p<0.019) showing that twice weekly erythropoietin had a significant effect on lowering fasting insulin levels in CKD patients. While, the control participants showed a significant increase in serum fasting insulin levels (Table 2) from baseline value of 9.72 ± 8.36 mU/L to mean value at six months of 12.79 ± 11.31 mU/L. (p=0.53). Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) levels in study group treated with erythropoietin significantly decreased from baseline value of 5.48 ± 10.43 to 0.5 ± 0.36 at end of study (p<0.041).But, there was no significant change in levels of HOMA-IR in control group participants from baseline levels of 3.11 ± 2.16 to 3.84 ± 4.08 at end of study (p=0.184).This study found that erythropoietin therapy significantly improved insulin resistance. Erythropoietin had a favorable effect on serum lipid profile (Table 3) in study group. Mean triglyceride decreased significantly at end of six months vs baseline value (p=0.02) in study group. Similarly, mean VLDL decreased significantly at sixth months as compared to baseline value (p=0.05). Mean HDL increased significantly at sixth months as compared to baseline value (p=0.009).

The control group had no significant decrease in mean triglyceride (p=0.12), cholesterol (p=0.6), LDL (p=0.76) during the course of study. There was a significant decrease in mean HDL values at sixth months as compared to baseline value (p=0.01). Mean fasting blood sugar and postprandial blood sugar values decreased significantly in study group after sixth months (p<0.001). There was no significant improvement in fasting blood sugar and postprandial blood sugar levels at sixth months vs baseline value in control group (p=0.77).

INVESTIGATION	Study group (Mean ± S.D.)	Control group (Mean ± S.D.)	p Value (Unpaired)
Blood Urea (mg%)	173.4 ± 67.48	215 ± 53.80	0.08
Serum Creatinine (mg%)	7.83 ± 3.46	9.65 ± 3.55	0.20
Serum Sodium (mE/L)	139.65 ± 12.31	147.3 ± 6.93*	0.04
Serum Potassium (mE/L)	4.55 ± 0.75	4.74 ± 0.74	0.52
Serum Uric Acid (mg%)	7.30 ± 3.23	7.89 ± 3.20	0.64
Serum Calcium (mg%)	8.16 ± 1.36	8.36 ± 1.20	0.68
Serum Phosphate (mg%)	6.29 ± 2.44	7.42 ± 1.86	0.17
SGOT (IU)	34.45 ± 22.48	68.8 ± 141.35	0.46
SGPT (IU)	33.55 ± 21.04	85.8 ± 167.60	0.35
Alkaline phosphatase (IU)	184.2 ± 112.81	175.1 ± 94.86	0.82
Serum Protein (g/dL)	5.86 ± 1.03	6.1 ± 0.68	0.44
Albumin: Globulin ratio	1.05 ± .20	1.08 ± 0.09	0.58

\*P<0.05 is significant

Table 1: Biochemical parameters at baseline in two groups.

	STUDYGROUP (Mean ± S.D.)	CONTROLGROUP (Mean ± S.D.)	Unpaired 'p' value
Fasting Insulin Levels (mU/L)			
0 month	11.40 ± 16.58	9.73 ± 8.36	0.71
6 month	2.30 ± 1.40	12.79 ± 11.31	0.033
Homeostasis Model Assessment of Insulin Resistance (HOMA-IR)			
0 month	5.48 ± 10.43	3.11 ± 2.16	0.338
6 month	0.51 ± 0.36	3.84 ± 4.08	0.101

\*P<0.05 is significant

Table 2: Comparison of fasting insulin levels and homa-ir of both groups before and after the study.

INVESTIGATION	Study group (Mean ± S.D)	Control group (Mean ± S.D)	p Value (Unpaired)
Blood sugar Fasting (mg%)	154.9 ± 62.97	153 ± 84.09	0.95
Blood sugar Post Prandial (mg%)	213.1 ± 91.62	234.6 ± 106.33	1
Serum Triglycerides (mg%)	145.45 ± 53.69	125.9 ± 35.02	0.242
Serum Cholesterol (mg%)	145.8 ± 50.39	149 ± 47.32	0.87
Serum HDL (mg%)	33.40 ± 12.44	35.3 ± 12.82	0.70
Serum LDL (mg%)	89.25 ± 45.19	88.6 ± 38.40	0.97
Serum VLDL (mg%)	26.8 ± 9.42	28.6 ± 9.24	0.62
Serum Ferritin (ng/l)	587.1 ± 582.49	828.41 ± 706.27	0.365
HBA <sub>1c</sub> (%)	6.43 ± 1.39	6.27 ± 1.48	0.78

\*P<0.05 is significant

**Table 3:** Comparison of the metabolic profile at baseline.

## Discussion

Insulin resistance and the metabolic syndrome are common in patients with Diabetes mellitus and CKD and they predict subsequent cardiovascular events and mortality. Insulin resistance results from a combination of genetic and environmental factors and contributes to type 2 diabetes mellitus, dyslipidemia, hypertension, central obesity, and cardiovascular disease [10]. Although traditional risk factors such as hypertension are more prevalent in this population, there has been increasing emphasis on the role of nontraditional risk factors such as anemia, hyperparathyroidism, dyslipidemia, divalent ion abnormalities, increased oxidant stress, inflammation, hyperhomocystenemia, neurohormonal overactivity, and malnutrition and insulin resistance [11]. Insulin resistance, as potentially modifiable cardiovascular risk factor, is currently considered as a therapeutic target in patients of CKD undergoing Hemodialysis. It is because of the nearly universal presence of insulin resistance and concomitant hyperinsulinemia in patients with diabetic and non diabetic chronic kidney disease in early stage of renal disease [12]. The epidemiologic correlation between insulin resistance and cardiovascular risk in the chronic kidney disease population has been documented. It has been found that erythropoietin also decreases insulin resistance in few studies conducted for short term [1,5-8].

In this study, insulin resistance was calculated by HOMA-IR (Homeostasis model assessment), a computer generated model, because of its simplicity and it requires only measurement of the fasting plasma insulin and plasma glucose. Other investigators have also calculated insulin resistance by HOMA-IR [1,5]. This study showed a significant improvement in fasting insulin levels as well as insulin resistance in study group. While in the control group, serum fasting insulin level increased significantly where as insulin resistance increased insignificantly. This study would suggest that Hemodialysis patients, receiving erythropoietin therapy, are insulin sensitive as compared to those not receiving erythropoietin therapies. A couple of other studies have also reported similar observations [1,5-8]. Improved insulin resistance by erythropoietin therapy has been postulated to be due to decreasing Plasma Cell Differentiation Antigen 1(PC-1) activity which has been found to be elevated in insulin resistant state. PC-1 inhibits insulin signaling either at the level of receptor or downstream at postreceptor site [13]. Improvements in oxygen supplementation and overcoming tissue hypoxia may explain improvement in insulin action [14]. Erythropoietin corrects anemia and improves appetite and nutritional status of patients with ESRD, thereby improving insulin resistance [15]. Improvement of insulin resistance with erythropoietin has also been explained through repair of chronic inflammation, as

reduced level of inflammatory cytokines, particularly TNF- $\alpha$ , and iron overload or ferritin level have been found in patients with ESRD on Hemodialysis [16].

In this study there was a significant reduction in mean fasting and postprandial blood sugar in study group indirectly suggesting reduction in insulin resistance. There was a significant fall in lipids in study group and rise in HDL levels. While in control group, lipids increased. HDL levels decreased significantly. This observation may be related to an improved response to insulin resistance in study group, because it is known that patients with increased insulin resistance have diminished lipoprotein activity, while triglyceride production remains the same. An excess PTH and hypoalbuminemia has also been implicated in the pathogenesis of insulin abnormalities in uremia [17]. However, in this study serum calcium, phosphorus and albumin were not significantly different in two groups. Apart from treatment with erythropoietin insulin resistance, hyperinsulinemia and glucose intolerance in uremic patients has been shown to improve with the use of Angiotensin converting enzyme inhibitor [18] ACE inhibitors, thiozolidenedione. However, their role can be easily excluded as part of improvement in insulin resistance as in this study all patients treated with ACE inhibitors or thiozolidenedione were excluded.

The observations made in this study show that serum fasting level and insulin resistance measured by HOMA-IR decreased significantly in study participants on twice weekly erythropoietin therapy as compared with control group. Also, erythropoietin therapy had a favorable effect on triglyceride and HDL levels in Hemodialysed patients.

Therefore, although long term further study should be performed to confirm the relationship between erythropoietin therapy and the possible causes of insulin resistance in Hemodialysis patients. However, regular erythropoietin therapy is advised in all Hemodialysis patients because of its favorable effect on insulin sensitivity and lipid profile, in addition to its role in the treatment of anemia in these populations.

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