

## The association between secondary hyperparathyroidism and endogenous EPO resistance in CKD

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**Background/Aims:** Resistance to endogenous erythropoietin (EPO) is an important pathophysiological feature in anemia of chronic kidney disease (CKD). Secondary hyperparathyroidism (SHPT) is known to contribute to the anemia of CKD. We aimed to investigate the associations between SHPT and endogenous EPO resistance in patients with CKD.

**Methods:** This study included 502 patients with CKD [glomerular filtration rate (GFR) < 60 ml/min/1.73m<sup>2</sup>] who were not on dialysis therapy. Patients on exogenous EPO therapy and patients with iron deficiencies were excluded. Baseline valuables [age, gender, diabetes, hypertension, eGFR, albumin, calcium, phosphate, total cholesterol, body mass index, C-reactive protein (CRP), hemoglobin (Hb), endogenous EPO, ferritin, transferrin saturation, intact parathyroid hormone (PTH)] were investigated in the study population. Endogenous EPO resistance was assessed by calculating the ratio of endogenous EPO to Hb (endogenous EPO/Hb ratio). The associations of the endogenous EPO/Hb ratio with clinical and laboratory variables were investigated by univariate (Pearson's correlation, *r*) and multivariate analysis (multiple linear regression analysis,  $\beta$ ).

**Results:** Table 1 shows the baseline characteristics. There were significant differences in age, hypertension, eGFR, albumin, calcium, phosphate, CRP, Endogenous EPO, hemoglobin, endogenous EPO/Hb ratio, and intact PTH among the 3 CKD stages. Table 2 shows the univariate and multivariate analysis for variables associated with endogenous EPO/Hb ratio in the study population. In univariate analysis, the endogenous EPO/Hb ratio was correlated with CRP ( $r = 0.142$ ,  $P = 0.009$ ) and intact PTH ( $r = 0.138$ ,  $P = 0.005$ ). Multiple regression analysis revealed that the endogenous EPO/Hb ratio level remained significantly associated with the intact PTH ( $\beta = 0.102$ ,  $P = 0.009$ ) and CRP ( $\beta = 0.125$ ,  $P = 0.035$ ).

**Conclusions:** This study showed that intact PTH was independently associated with the endogenous EPO/Hb ratio in CKD patients, suggesting that the SHPT is an independent predictor of the endogenous EPO resistance.

Table 1. Baseline characteristics of the study population (n = 502)

	CKD stage 3 (n = 272)	CKD stage 4 (n = 135)	CKD stage 5 (n = 95)	P
Age (years)	56.3 ± 8.2	58.3 ± 5.1	60.2 ± 8.1	0.025
Sex, male	52.9%	53.1%	54.8%	0.723
Diabetes	55.4%	54.2%	56.3%	0.841
Hypertension	56.2%	62.8%	79.5%	0.015
GFR (ml/min/1.73m <sup>2</sup> )	40.2 ± 7.9	23.2 ± 5.4	9.0 ± 2.1	<0.001
Albumin (g/dl)	4.2 ± 0.2	4.0 ± 0.2	3.7 ± 0.3	<0.001
Calcium (mg/dl)	9.1 ± 0.3	8.9 ± 0.4	8.6 ± 0.4	<0.001
Phosphate (mg/dl)	3.5 ± 0.9	4.1 ± 0.7	4.9 ± 1.3	<0.001
Total cholesterol (mg/dl)	221.2 ± 37.3	213.0 ± 35.2	211.5 ± 38.2	0.415
Body mass index (kg/m <sup>2</sup> )	23.9 ± 2.3	23.8 ± 1.9	24.2 ± 1.9	0.285
CRP (mg/dl)	0.5 ± 0.3	0.8 ± 0.9	1.5 ± 1.1	<0.001
Endogenous EPO (mIU/ml)	18.1 ± 5.3	16.1 ± 5.4	8.9 ± 2.4	<0.001
Hb (g/dl)	11.5 ± 2.5	9.5 ± 2.1	7.2 ± 1.3	<0.001
Endogenous EPO/Hb ratio (dIU/g)	1.7 ± 0.4	1.6 ± 0.3	1.1 ± 0.3	<0.001
Ferritin (ng/ml)	194.1 ± 73.2	195.4 ± 50.2	192.0 ± 58.4	0.425
Transferrin saturation (%)	26.8 ± 6.3	25.3 ± 5.8	26.9 ± 5.4	0.282
Intact PTH (pg/ml)	74.5 ± 39.6	150.2 ± 70.7	235.4 ± 90.1	<0.001

Data are presented as means ± SDs or as proportions (%). CRP, C-reactive protein; EPO, erythropoietin; GFR,

glomerular filtration rate; Hb, hemoglobin; PTH, parathyroid hormone

Table 2. Associations of the endogenous EPO/Hb ratio with demographic and clinical variables by univariate and multivariate analyses (n = 502)

	Univariate		Multivariate	
	<i>r</i> <sup>a</sup>	P	$\beta$ <sup>b</sup>	P
Age (years)	0.028	0.523	-	-
Sex, male	0.089	0.151	-	-
Diabetes	-0.035	0.465	-	-
Hypertension	0.102	0.184	-	-
GFR (ml/min/1.73m <sup>2</sup> )	0.085	0.352	-	-
Albumin (g/dl)	-0.048	0.231	-	-
Calcium (mg/dl)	-0.021	0.452	-	-
Phosphate (mg/dl)	0.152	0.568	-	-
Total cholesterol (mg/dl)	-0.015	0.654	-	-
Body mass index (kg/m <sup>2</sup> )	0.026	0.412	-	-
CRP (mg/dl)	0.142	0.009	0.125	0.035
Ferritin (ng/ml)	0.052	0.285	-	-
Transferrin saturation (%)	0.003	0.874	-	-
Intact PTH (pg/ml)	0.038	0.005	0.102	0.009

<sup>a</sup>*r* means Pearson's correlation coefficients. <sup>b</sup> $\beta$  means standardized regression coefficients. CRP, C-reactive protein;

EPO, erythropoietin; GFR, glomerular filtration rate; Hb, hemoglobin; PTH, parathyroid hormone