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Higher Prevalence of Unrecognized Kidney Disease at High Altitude

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Informative title: risk for kidney disease at two different altitudes

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Abstract

Background High altitude renal syndrome has been described in populations with excessive erythrocytosis. We evaluated whether high altitude (HA) dwellers might be at increased risk for kidney disease.

Methods: We performed a cross-sectional study to investigate differences in prevalence of kidney function and metabolic syndrome in healthy subjects living at HA and sea level (SL) without any known history of hypertension, diabetes or chronic kidney disease.

Results. We examined 293 subjects, age 40 to 60 years, 125 from SL (154 m) and 168 HA (3640 m). HA subjects had higher serum creatinine, lower estimated glomerular function rate (eGFR) (69.5 ± 15.2 vs 102.1 ± 17.8 ml/min/1.73 m^2, p <0.0001), with more proteinuria and higher hemoglobin concentrations compared to SL subjects. HA subjects had a lower prevalence of metabolic. Hemoglobin concentrations correlated inversely with eGFR in women and men (p = 0.001 and p= 0.03, respectively) among subjects living at HA. Using logistic regression analysis to compare subjects with eGFR < 90 versus > 90 ml/min/1.73m^2, a lower eGFR was associated with gender (women) (OR adjusted: 5.65; 95% CI : 2.43-13.13, p = 0.001), high altitude (OR adjusted: 14.78, 95% CI : 6.46-33.79; p = 0.001), hemoglobin (OR adjusted: 1.68; 95% CI : 1.16-2.43; p = 0.001) and uric acid (OR adjusted: 1.93; 95% CI : 1.36-2.72; p = 0.001).

Conclusions: Subjects living at high altitude who are considered healthy have worse kidney function, a higher prevalence of proteinuria and a lower prevalence of metabolic syndrome compared to people living at SL.

Keywords: cardiovascular risk, high altitude, kidney function, proteinuria

Introduction

Chronic kidney disease (CKD) has many known causes, including diabetes, hypertension, glomerulonephritis and polycystic kidney disease. However, CKD may be caused by other mechanisms. We have hypothesized that living chronically at high altitude (HA) may be a risk factor for CKD related to the chronic exposure to hypoxia due to low ambient oxygen tension [1,2].

Recently we have reported that subjects living at HA are at risk for high altitude renal syndrome "HARS", a condition characterized by erythrocytosis, microalbuminuria, hypertension and hyperuricemia [3,4]. This is especially observed in subjects suffering from chronic mountain sickness (CMS), a form of altitude maladaptation characterized by excessive erythrocytosis (hematocrit > 65 %) and greater arterial hypoxemia ($SaO_2\%$ < 85) [5]. While the pathogenesis of HARS is not fully understood, it may relate to glomerular hyperfiltration associated with polycythemia [6], or the effects of hyperuricemia on glomerular hemodynamics and tubular function [7,8].

Given these issues, we compared two similar ethnic populations: one living at sea level (Lima, Peru, altitude 154 m) versus one at high altitude (La Paz, Bolivia, altitude 3,640-4,500 m). We specifically wanted to compare 'healthy' populations who had no known hypertension, diabetes or CKD. Our hypothesis was that, even within an apparently healthy population and those without CMS, subjects chronically living at high altitude would show more evidence for kidney dysfunction.

Material and Methods

Study Design.

This was a cross–sectional study that evaluated subjects from La Paz, a city in Bolivia located at an altitude between 3,640 – 4,500 meters and Lima, a city in Peru, which is located at 154 meters above sea level. Both cities are capitals of developing countries with similar economic conditions and mixed European - Andean heritage.

We performed screening campaigns in the community of both cities, and the subjects were selected by convenience sampling if they fulfilled criteria of selection in the first interview. After the results of laboratory testing were obtained, additional subjects could be excluded based on fasting blood glucose levels of >125 mg/dl (n=19) and/or significantly elevated serum creatinine (> 1.4 mg/dl, n=8). The remaining 293 participants were aged 40 to 60 years, with no prior known history of hypertension, diabetes, chronic kidney disease, CMS or other chronic medical conditions. Informed consent was obtained from all individual participants included in the study. The exclusion criteria included a history of any systemic disease, long-term use of medications and incomplete information of the subject's condition or laboratory data. The protocol followed the principles of the Declaration of Helsinki. The study was approved by the ethics committee of the Hospital Nacional Arzobispo Loayza in Lima, Peru.

Evaluation

A detailed history was obtained from all including past medical history, family history of diabetes and kidney disease, as well as life style habits (alcohol and tobacco use and physical activity). We used the International Society of Nephrology form: "Program for Detection and Management of CKD, Hypertension, Diabetes and Cardiovascular Disease in Developing Countries", which was adapted to the needs of the study [9]. Physical examination included weight, height (after removal of shoes and heavy clothing), waist circumference (measured at the midpoint between the bottom edge of the last rib and the iliac crest taking as a reference the mid-axillary line and taken at the end of expiration) and hip circumference (measured using the maximum circumference at the level of the buttocks). Body mass index (BMI) and waist-hip ratio (WHR) were calculated. Blood pressure was measured following recommended procedures after sitting for 15 minutes [10], after which three readings were recorded at intervals of three minutes using a calibrated automatic blood pressure monitor OMROM, model HEM-705CP. Venous blood was obtained after 12 hours of fasting for total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides, glucose, uric acid, hemoglobin, hematocrit, and creatinine with enzymatic methods. The data were processed in a computer model: STAT FAX 1935 PLUS, Roche Cobas C501. All coefficients of variation for original measurements were < 10%. Morning spot urine samples were evaluated for proteinuria and hematuria with a Dipstik test (Roche Diagnostics, Mannheim, Germany).

Definitions:

Overweight was defined as BMI between 25-30 kg/m^2 and obesity as BMI > 30 kg/m^2. Abdominal obesity was defined as WHR > 0.9 in men and > 0.85 in women. Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) four variables equation. Kidney Disease (KD) stages were classified according to Kidney Disease Outcomes Quality Initiative (KDOQI) [11]. Hematuria and proteinuria were defined as 1+ or greater on a dipstick test. The diagnosis of metabolic syndrome was based on the presence of 3 of the 5 following criteria: waist circumference > 94 cm in men and > 88 cm in women, triglyceride ≥ 150 mg/dl, high density lipoprotein HDL < 40 mg/dl in men and < 50 mg/dl in women, systolic blood pressure ≥ 130 mmHg and/or DBP ≥ 85 mmHg, fasting blood glucose ≥ 100 mg/dl [12]. The cardiovascular risk was calculated using the Framingham risk score [13]. This score addresses the following variables: age, sex, systolic blood pressure treated (medication and lifestyle changes) and untreated, BMI, smoking and diabetes. The consumption of alcohol and tobacco, and physical activity was recorded as present or absent.

Sample Size. We calculated a necessary sample size of 318 subjects to have 80 % power and a confidence interval of 95 % based on chronic KD prevalence of 10 % SL [14] and 19% for HA [15]. The sample calculation was obtained from the statistical package Stata v12 using the formula for comparison of two separate proportions.

Statistical analysis. An exploratory data analysis was done by obtaining measurements of central tendency such as: mean, standard deviation, median, minimum and maximum values for quantitative variables, and frequencies and percentages for qualitative variables. Before comparing means or medians, the distribution of the quantitative variables was evaluated using the Shapiro-Wilk test and the homogeneity of variance with Bartlett's test. To assess association between two qualitative variables in the bivariate analysis, Chi Square test or Fisher exact test were used respectively depending on the expected frequency number of more than 5 or not. Student's t-test was used for comparing two arithmetic means (when the distribution of the variable had a normal distribution), two-sample Wilcoxon rank-sum (Mann-Whitney) test was used for independent samples when the distribution of the variable was not normal. Multiple logistic regression was used to assess factors associated with renal disease (defined as CKD stage II, or an eGFR < 90 ml/min/1.73 m^2). The level of statistical significance considered was 0.05, for a two-tailed test. Statistical analysis was performed using the statistical package Stata v12.

Results

Baseline characteristics of study subjects. Of the 320 subjects selected, we excluded subjects with fasting glucose concentrations greater than 126 mg/dl who did not know whether they were diabetic (n = 19), and those with creatinine greater than 1.4 mg/dl (n = 8). Thus, 293 subjects were included in the final analysis (representing 92 % of the sample). Of these 125 were living at SL and 168 at HA. There were 145 men (65 SL, 80 HA) and 148 women (60 SL, 88 HA).

Baseline characteristics of subjects living at SL and HA. There were no significant differences in age or sex between the two groups. Compared to SL subjects, kidney function in the HA subjects was characterized by higher serum creatinine (1.05 ± 0.14 vs 0.77 ± 0.16 mg/dl, p < 0.0001), lower eGFR (69.5 ± 15.2 vs 102.2 ± 17.8 ml/min/1.73m^2, p < 0.0001), higher percentage of patients with eGFR < 60 ml/min/1.73 m^2 (28.0 % vs 0 %, p < 0.001) and proteinuria (10.7 % vs 3.2%, p = 0.03).

HA subjects had higher hemoglobin concentrations (15.4 ± 1.4 vs 13.9 ± 1.2 g/dl, p < 0.0001), HDL level (48.9 ± 12.0 vs 44.9 ± 10.9 mg/dl, p < 0.002) and fasting triglycerides level (159.9 ± 99.6 vs 123.4 ± 55.7 mg/dl, p < 0.001). In contrast, high altitude dwellers had less alcohol intake (40.5 % vs. 56.8 %, p < 0.05), lower systolic blood pressure (114.3 ± 15.9 vs 129.7 ± 17.2 mmHg, p < 0.0001) and diastolic blood pressure (71.5 ± 8.5 vs 76.3 ± 10.0 mm Hg, p < 0.0001), as well as lower weight (69.2 ± 10.9 vs 73.2 ± 14.2, p = 0.03), BMI (26.2 ± 3.6 vs 28.9 ± 4.3 kg/m^2, p < 0.0001), waist-hip ratio (0.96 ± 0.04 vs 0.92 ± 0.07, p < 0.0001), fasting serum glucose level (74.2 ± 8.4 vs 93.1 ± 10.9 mg/dl, p < 0.0001), LDL level (126.2 ± 41.3 vs 144.9 ± 33.4, p < 0.0001), prevalence of metabolic syndrome (27.4 % vs 49.6 %, p < 0.0001) and Framingham risk score (0.91 ± 1.15 vs 2.13 ± 2.65, p < 0.001 (**Table 1).**

Values of hemoglobin, kidney function, metabolic syndrome and Framingham risk score in men and women living at SL and HA are shown in **Table 2.**

Multivariable logistic regression was used to compare subjects with evidence for stage 2 CKD or worse (eGFR 90 ml/min/1.73m^2) versus those with normal renal function (defined as eGFR > 90 ml/min/1.73m^2). After adjusting for age, sex, place of residence, hemoglobin, triglycerides, metabolic syndrome, uric acid, a lower eGFR was associated with being a woman (OR adjusted: 5.65; 95% CI: 2.43-13.13, p = 0.001), living at high altitude (OR adjusted: 14.78;

95% CI : 6.46-33.79; p = 0.001), having a higher hemoglobin (OR adjusted: 1.68; 95% CI: 1.16-2.43; p = 0.001) and

for each unit of increase in uric acid (OR adjusted: 1.93; 95% CI: 1.36-2.72; p = 0.001), Table 3

Relationship between eGFR and hemoglobin in women and men.

In HA women and men, hemoglobin correlated inversely with eGFR (p = 0.001 and p = 0.03, respectively; r = - 0.2,

p = 0.01), but no significant correlation was observed in women or men living at SL (**Figures 1 and 2**).

Discussion

In this cross-sectional study of 293 healthy ethnically similar participants from two cities of different altitude in

South America, we found that individuals living at high altitude had significantly worse renal function than those

living near sea level, amounting to a mean difference of eGFR of 30 percent. The worse kidney function and greater

proteinuria observed at higher altitude occurred despite similar age and lower prevalence of metabolic syndrome

compared to people living near sea level.

The prevalence of eGFR < 60 ml/min/1.73 m^2 and proteinuria was 28.0 % and 10.7 % respectively, among subjects

living at HA and this was observed after excluding subjects with hypertension, diabetes, or known CKD. This

prevalence is higher than values reported in Tibet, which are 2.1% for CKD and 2.4% for proteinuria [15]. One

possible explanation is that Tibetans have been living at high altitude for many more generations than any groups in

the Andes [16] and are therefore better adapted to the high altitude hypoxic environment, as evidenced by their

higher arterial oxygen saturation and lesser hemoglobin concentration.

Potential mechanisms for the worse renal function at HA could be chronic hypoxia, leading to erythrocytosis.

Increased red cell volume leads to reduced renal plasma flow (RPF) which eventually results in higher filtration

fraction (FF) as glomerular filtration rate is preserved [6,17]. These characteristics resemble a model of chronic

hyperfiltration, with its known consequences of glomerular damage and proteinuria [18]. The population at HA in

our study did not have excessive erythrocytosis typical of CMS (hematocrit > 65%), nonetheless increased

hemoglobin concentration was associated with worse kidney function.

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The renal medulla is hypoxic with a range of PO_2 between 10-20 mmHg [2,19] and is highly susceptible to injury by hypoxia [20]. Medullary hypoxia is likely more severe among high altitude dwellers given their lower arterial oxygen saturation and no off-setting higher renal blood flow (2), thus further increasing the risk of renal injury. Indeed, hypoxia is a well-known risk factor for progressive CKD in various experimental animal models [19]. Similarly, subjects with kidney disease also have higher serum uric acid concentrations, which are known to be elevated in hypoxic conditions. While uric acid can function as an antioxidant [21], it can also stimulate oxidative stress in a variety of cell types, and can also cause endothelial dysfunction, and systemic and glomerular hypertension [22] thereby predisposing to the risk of CKD. We also found that HA subjects tended to have higher serum uric acid concentrations, although this was not statistically significantly different compared to the SL group. This may be due to the higher frequency of the metabolic syndrome in the SL group, which is also associated with hyperuricemia.

We also found a lower frequency of metabolic syndrome at HA. While it may be argued that the higher frequency of metabolic syndrome among SL dwellers might reflect different dietary or economic factors, the HA subjects were also urban residents in a large city (La Paz) with a comparable socioeconomic environment. Other factors may also be important for example, physical activity was more common among men but not women at HA, and might explain differences in weight. The metabolic responses to chronic hypoxia may also have protective effects on the development of the metabolic syndrome. HA residents are known to have lower serum glucose concentrations than inhabitants at SL [23]. Consistent with this observation, a lower incidence of diabetes has been observed at HA [24]. A lower fasting serum glucose concentration was observed in our study and contributes to a lower incidence of the metabolic syndrome in the population at HA. Furthermore, living at HA is also associated with higher HDL concentrations [25]. Not all studies, however, have found that the metabolic syndrome is lower at HA. A prior study from Peru found no difference in the metabolic syndrome between high altitude and sea level dwellers (22.2 % vs. 16.9 % respectively; p = 0.28) [26]. In another study, the metabolic syndrome was extremely high (60 %) among individuals living at high altitude with excessive erythrocytosis (mean age 61 yr) compared to a prevalence of 35 % among high altitude residents without erythrocytosis (mean age 55 yr) [27]. Another study of the Peruvian population also reported that subjects living at higher altitude had a metabolically healthier profile than those living at sea level [28].

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The Framingham risk score is a quantitative method that estimates the likelihood of coronary heart disease over a period of time, and has been validated in various ethnic groups [29]. The population at HA (both men and women) had a lower Framingham score compared to the population living at sea level. The lower score in HA residents was primarily due to the higher HDL concentrations, lower prevalence of smoking, and lower blood pressure. Among women, the variables of age, cholesterol, HDL and smoking were similar, so that the lower Framingham score at HA was primarily due to a lower blood pressure. A study in Tibet reported a lower Framingham risk score than what we found in our Andean population: 16. 3% for men and 0.6 % for women [30].

Our study has several limitations. First, it was a study of healthy individuals, and we did exclude subjects with known hypertension, diabetes or CKD. Therefore, it is not a study of overall prevalence of CKD. However, the striking finding that eGFR was 30 percent lower in the presumably healthy population at HA remains remarkable. Second, we did not assess for microalbuminuria. We also excluded subjects with hypertension, which may be part of the high altitude renal phenotype. However, by excluding subjects with hypertension we could also remove the possibility that the kidney disease was secondary to hypertension alone. A final limitation is that we failed to gather information on dietary history and measured the laboratory values only once. Nevertheless, the strength of the study is the robust differences identified in prevalence of kidney disease and metabolic syndrome.

In conclusion, apparently healthy subjects living at high altitude had a remarkably higher frequency of kidney disease and proteinuria independent of a history of hypertension or diabetes. This provides some of the strongest evidence to date that long-term living at high altitude carries an increased risk for kidney disease. The characteristics of kidney disease observed at high altitude may be a new form of CKD that might be mediated by chronic hypoxia and its effects. Given that there are more than 140 million people worldwide living at high altitude, further studies to better investigate the etiology and treatment of high altitude CKD are critical.

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Ethical approval:

"All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards."

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Table 1 Clinical and laboratory characteristics of people living at Sea level and High altitude

Variables	Sea level (n=125)		High altitude (n=168)		p*
	Mean ± SD	95 %CI	Mean ± SD	95%CI	
Age (years) [1]	50.79 ± 6.86	49.57 - 52.00	50.58 ± 5.79	49.70 - 51.46	0.679
Sex (men / women)[4,a]	65/60	0.39 – 0.56	80/88	0.44 – 0.60	0.458
Alcohol [5,a]	71 (56.8%)	0.47 – 0.65	68 (40.5%)	0.32 – 0.47	0.0001*
Smoking [5,a]	21 (16.8%)	0.10 – 0.23	17 (10.1%)	0.55 – 0.14	0.114
Physical Activity [5,a]	51 (40.8%)	0.32 – 0.49	73 (43.4%)	0.35 – 0.51	0.649
Systolic blood pressure (mmHg) [3]	129.71 ±17.22	126.66 – 132.76	114.34 ± 15.90	111.92 – 116.76	0.0001*
Diastolic blood pressure (mmHg) [3]	76.37 ± 10.04	74.59 – 78.15	71.51 ± 8.50	70.22 – 72.81	0.0001*
Pulse (beats per min) [1]	69.60 ±10.20	67.79 – 71.40	73.51 ± 3.85	72.93 – 74.10	0.0001*
Weight (kg) [3]	73.16 ± 14.16	70.65 – 75.67	69.24 ± 10.95	67.57 – 70.91	0.030
Height (cm) [3]	158.7 ± 9.57	157.00 – 160.39	162.48 ± 6.70	167.46 – 163.50	0.0001*
Body mass index(kg/m^2) [3]	28.90 ± 4.29	28.14 – 28.66	26.18 ± 3.61	25.63 – 26.74	0.0001*
Waist circumference (cm) [2]	102.84 ± 9.28	101-20 – 104.49	101.04 ± 10.47	99.44 – 102.63	0.283
Hip circumference (cm)[2]	99.58 ± 8.94	98.00 – 101.16	93.90 ± 13.82	91.79 – 96.01	0.0001*
Waist-hip ratio [2]	0.96 ± 0.04	0.96 – 0.97	0.92 ± 0.07	0.91 – 0.93	0.0001*
Hemoglobin (g/dl) [1]	13.91 ± 1.22	13.69 – 14.12	15.43 ± 1.36	15.23 – 15.64	0.0001*
Glucose (mg/dl) [1]	93.07 ± 10.94	91.13 – 95.01	74.23 ± 8.36	75.95 – 75.50	0.0001*
Creatinine (mg/dl) [3]	0.77 ± 0.16	0.74 – 0.80	1.05 ± 0.14	1.03 – 1.08	0.0001*
eGRF (ml/min/1.73m^2) [1]	102.15 ± 17.82	98.99 – 105.31	69.52 ± 15.18	67.21 – 71.84	0.0001*
eGRF level (ml/min/1.73m^2) [4,a]					
> 90	96 (69.23%)		25 (14.88%)		
60 - 89	29 (30.77%)		96 (57.14%)		0.001*
< 60	0 (0.0%)		47 (27.98%)		
Urine					
Hemoglobin (positive)	12 (9.6%)		16 (9.5%)		0.88
Proteinuria (positive)	4 (3.2%)		18 (10.7%)		0.03
Total cholesterol (mg/dl) [1]	216.90 ± 41.63	209.53 – 224.27	209.32 ± 54.13	201.08 – 217.57	0.08
Low density lipoprotein (mg/dl) [1]	144.86 ± 33.40	138.94 – 150.77	126.22 ± 41.28	119.93 – 132.50	0.0001*

High density lipoprotein (mg/dl) [1]	44.92 ± 10.90	42.99 – 46.85	48.92 ± 11.97	47.10 – 50.75	0.002*
Triglycerides (mg/dl) [1]	123.42 ± 55.68	113.56 – 133.28	159.89 ± 99.58	144.72 – 175.06	0.001*
Uric acid (mg/dl) [1]	4.92 ± 1.18	4.71 – 5.13	5.11 ± 1.43	4.89 – 5.33	0.379
Metabolic syndrome [4,a]	62 (49.6%)	0.40 – 0.58	46 (27.38%)	0.20 – 0.34	0.0001*
Framingham risk score [1]	2.13 ± 2.65	1.66 – 2.60	0.91 ± 1.15	0.73 – 1.08	0.001*

(Mean ± Standard Deviation)

(N° and % ± Standard Error) [a]

1 Mann–Whitney test

2 Student's t-test with unequal variances

3 Student's t-test with equal variances

4 Chi-square test

5 Fisher's exact test

P* Contrast Bonferroni

Table 2 Characteristics of hemoglobin, kidney function, metabolic syndrome and Framingham score in men and women living at SL and HA

Variables	men			women		
	Sea level n = 65	High altitude n = 80	p	Sea level n = 60	High altitude n = 88	p
Hemoglobin (g/dl) [1]	14.6 ± 0.8	15.5 ± 0.9	0.001	13.1 ± 1.1	15.3 ±1.6	0.001
Creatinine (mg/dl) [3]	0.88 ± 0.14	1.05 ± 0.14	0.001	0.64 ± 0.08	1.05 ± 0.14	0.001
eGRF (ml/min/1.73m^2) [1]	99.2 ± 18.8	80.4 ± 12.6	0.001	105.3 ±16.2	59.7 ± 9.6	0.001
eGRF level (ml/min/1.73m^2) [4]						
> 90	45 (69.2%)	24 (30.0%)		51 (85%)	1 (1.1%)	
60 - 89	20 (30.8%)	54 (67.5%)	0.001	9 (15%)	42 (47.7%)	0.001
< 60	0 (0.0%)	2 (2.5%)		0 (0.0%)	45 (51.1%)	
Metabolic syndrome [4]	32 (49.2%)	25 (31.3%)	0.04	30 (50%)	21 (23.9%)	0.001
Framingham risk score [1]	3.22 ± 3.06	1.49 ± 1.37	0.001	0.95 ±1.36	0.38 ± 0.50	0.001

(Mean ± standard deviation; n° and %)

1 Mann–Whitney test

2 Student's t-test with unequal variances

3 Student's t-test with equal variances

4 Chi-square test

Table 3: Unadjusted and Multivariable-adjusted Odds of eGFR < 90 ml/min/1.73m2

Variables	OR	95%CI OR	p	OR adjusted	95%CI adjusted	p
Age (years)	1.00	0.97-1.04	0.64	1.02	0.97-1.08	0.34
Sex: Female	1.58	0.99-2.53	0.05	5.65	2.43-13.13	0.001
High altitude	20.86	11.39-38.21	0.001	14.78	6.46-33.79	0.001
Hemoglobin (g/dl)	2.22	1.76-2.80	0.001	1.68	1.16-2.43	0.001
Triglycerides (mg/dl)	1.00	1.00-1.00	0.001	1.00	0.99-1.00	0.51
Metabolic syndrome	0.54	0.33-0.87	0.01	0.48	0.21-1.11	0.08
Uric acid (mg/dl)	1.46	1.20-1.79	0.01	1.93	1.36-2.72	0.001

Adjusted for age, sex, high altitude, hemoglobin, triglycerides, metabolic syndrome, uric acid.
P-values calculated using logistic regression.
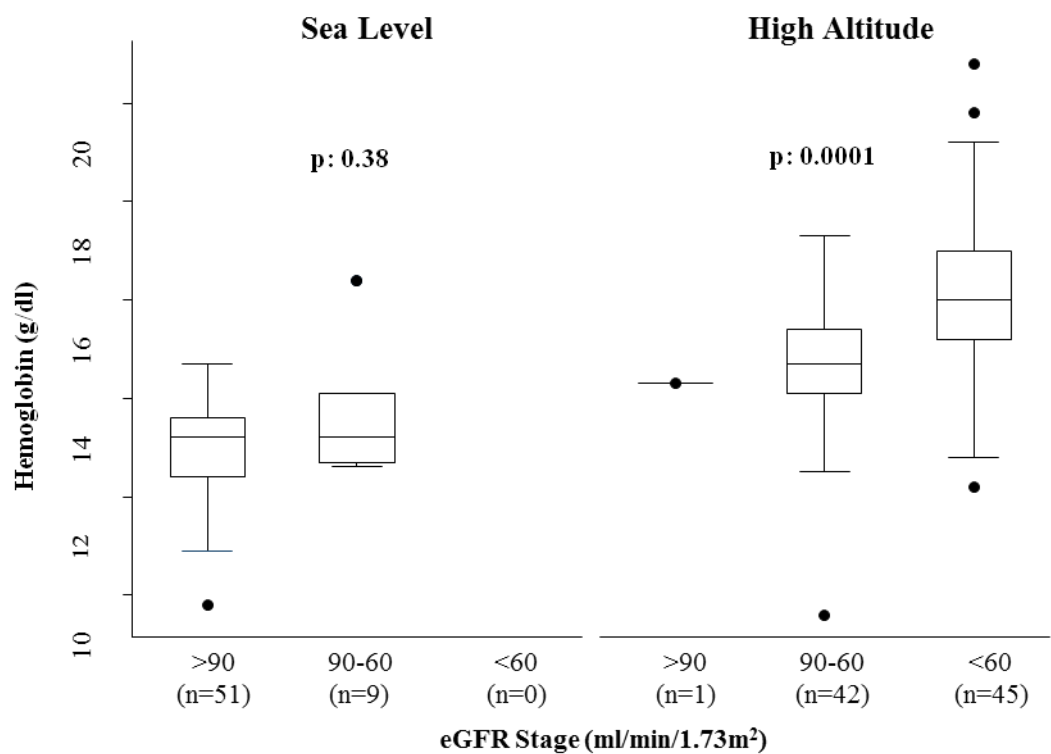OR, odds ratio; CI, confidence interval

Figure 1: Estimated glomerular filtration rate versus hemoglobin level at different altitude in women.

Box-plot diagram of the relationship between estimated glomerular filtration rate (eGFR) and hemoglobin level in women, at high altitude hemoglobin increased significantly with decreasing eGFR levels ($p = 0.001$; $r = - 0.2$, $p = 0.01$), but no in women living at sea level. Statistical: Kruskal-Wallis, Spearman.
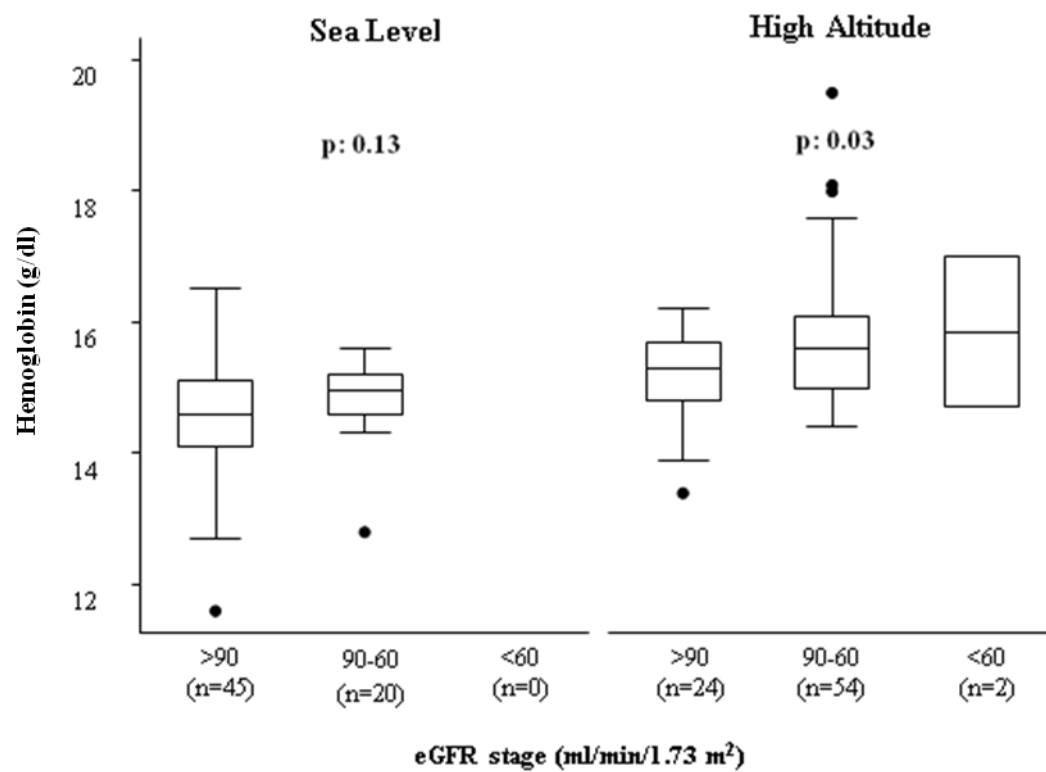
Figure 2: Estimated glomerular filtration rate versus hemoglobin level at different altitude in men

Box-plot diagram of the relationship between estimated glomerular filtration rate (eGFR) and hemoglobin level in men. at high altitude hemoglobin increased significantly with decreasing eGFR levels (p = 0.03: r = - 0.2, p = 0.01), but no in men living at sea level. Statistical: Kruskal-Wallis, Spearman.