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REVIEW

Serum testosterone levels and excessive erythrocytosis during the process of adaptation to high altitudes

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Populations living at high altitudes (HAs), particularly in the Peruvian Andes, are characterized by a mixture of subjects with erythrocytosis (16 g dl^{-1}<haemoglobin (Hb)$\leqslant$21 g dl^{-1}) and others with excessive erythrocytosis (EE) (Hb>21 g dl^{-1}). Elevated haemoglobin values (EE) are associated with chronic mountain sickness, a condition reflecting the lack of adaptation to HA. According to current data, native men from regions of HA are not adequately adapted to live at such altitudes if they have elevated serum testosterone levels. This seems to be due to an increased conversion of dehydroepiandrosterone sulphate (DHEAS) to testosterone. Men with erythrocytosis at HAs show higher serum androstenedione levels and a lower testosterone/androstenedione ratio than men with EE, suggesting reduced 17beta-hydroxysteroid dehydrogenase (17beta-HSD) activity. Lower 17beta-HSD activity *via* Δ4-steroid production in men with erythrocytosis at HA may protect against elevated serum testosterone levels, thus preventing EE. The higher conversion of DHEAS to testosterone in subjects with EE indicates increased 17beta-HSD activity *via* the Δ5-pathway. Currently, there are various situations in which people live (human biodiversity) with low or high haemoglobin levels at HA. Antiquity could be an important adaptation component for life at HA, and testosterone seems to participate in this process.
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INTRODUCTION

Testosterone exerts widespread effects in organisms. It has metabolic and reproductive properties, and its effects are clearly observed when differences between genders are studied. For instance, haemoglobin (Hb) levels are higher in men than in women, and this difference is observed in puberty when serum testosterone levels begin to increase.[1] Gender differences in ventilation and in response to high-altitude exposure have also been observed, and in these cases, testosterone may be a participating factor.

These effects are reviewed here with special emphasis on the role of testosterone in erythropoiesis and in natives living at high altitudes (HAs). This is an important topic, as more than 200 million inhabitants worldwide live at altitudes over 2500 m; 80 million of these inhabitants are located in Asia,[2] and 55 million live in Latin America.

POPULATIONS AT HAS

Most of the populations permanently living at HA are in Asia, Eastern Africa, Latin America and North America. These populations differ according to the antiquity of life in the highlands and patterns of adaptation.[2–5] The oldest populations living at HA are the Tibetans and Ethiopians.[2,3] Tibetans have resided at HA for more than 25 000 years.[2]

The Andean population is likely to have originated from migration from Asia. In fact, by the end of the middle Palaeolithic period (approximately 40 000 years ago), human beings had spread throughout the world, except for Australia and the Americas. The migration to the Americas seems to have occurred during the last Ice Age, from Asia to North America through the Bering Strait.[6] In Peru, most findings suggest that the first presence of humans in the highlands occurred between 12 000 and 13 000 years BC.[7]

The Spanish conquest of Peru occurred in the sixteenth century. This conquest included an important admixture with the aboriginal population. This admixture could have stopped or reversed the adaptation process to HA, which had occurred over more than 10 000 years. Currently, there are three characteristic population groups living at HA in Peru: Aymara (the oldest population living at HA), Quechua and the admixture, primarily with Spaniards.[8–10]

In Tibet, there are two ethnic groups living in the highlands, the Tibetans and the Hans. The Hans have resided there for no more than 70 years, and they show higher Hb levels than the Tibetans.[2,5] Similarly, Peruvian populations located in the southern Andes show lower Hb levels and longer generational lives than populations in the central Andes[4] (**Table 1**).

The presence of these groups may explain the different Hb levels observed in populations residing at the same altitude in the same country.[5,11] Hence, multigenerational residence at HA may affect Hb concentrations.

In the various adaptation processes, the endocrine system has an important role.[12–14] Recently, the endocrine system has been proposed to be important for the high-altitude adaptation process, which involves the regulation of Hb levels.[15,16]

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Table 1 Patterns of adaptation to high altitudes observed in different populations and based in the presence of erythrocytosis and low pulse oxygen saturation

	Longer antiquity at highlands	*Erythrocytosis*	*Arterial hypoxemia*
Sea level	−	−	−
Ethiopian highland	+	−	−
Tibetans in Tibet	+	−	+
Hans in Tibet	−	+	+
Peruvian Central Andes	−	+	+
Peruvian Southern Andes	+	−	+

−, less antiquity and absence of erythrocyotis and absence of arterial hypoxemia; +, longer antiquity at high altitudes, erythrocytosis and higher arterial hypoxemia. Data were obtained from Refs. 3–5, 12 and 23.

Life at HA is characterized by exposure to permanent hypoxia. However, there can be various responses to the same hypoxic stimulus.[17–19] In the Peruvian Andes, a great range of values of pulse oxygen saturation has been described in people living at the same altitude.[20–23] Differences in hormone levels may explain some of these varying responses to hypoxic stimuli,[11,15,21] according to several studies.

CHRONIC HYPOXAEMIA AND CHRONIC MOUNTAIN SICKNESS (CMS)

Chronic hypoxaemia is a long-standing condition in which arterial oxygen pressure (PaO_2) is lower than that observed in normal subjects at sea level. Chronic hypoxaemia can be observed in people living at HA and in those living at sea level but with chronic obstructive pulmonary disease. In both cases, PaO_2 may reach values below 60 mmHg, whereas normal values at sea level are 100 mmHg.

Andean HA natives have a lower (blunted) hypoxic ventilatory response (HVR), lower effective alveolar ventilation and lower ventilation at rest and during exercise compared to newcomers acclimatized to HA.[24] One of the causes of hypoventilation at HA seems to be sleep apnoea.[25] At HA, normal people often develop periodic breathing during sleep and recurring periods of hyperpnoea and apnoea. This phenomenon is most likely explained by the instability of the negative feedback system in controlling ventilation.[26]

The first chronic syndrome described in HA dwellers in Peru was CMS, which has a large component of relative hypoventilation and secondary erythrocytosis.[2] This disease is also observed in the highlands in immigrants who lived at sea level and were subsequently exposed to HA for several years.[27]

This disease mainly occurs in populations with short-term residence at HA, as in some Andean[28] and most Han[29] and North American[30] inhabitants, whereas it is less common in Tibetans,[31] the group with the longest residence time in highland places. Hypoventilation, particularly during sleep, appears to be the dominant cause of hypoxaemia in patients with CMS.[32]

One characteristic of this disease is excessive erythrocytosis (EE).[28] The prevalence of EE increases with age in men[33] and women.[15] Menopausal status in Andean women at HA has also been related to an increase in the CMS score,[34] suggesting that a reduction in ovarian hormones may represent a contributing factor for the development of CMS. Experimental studies have demonstrated that treatment of rats with oestradiol may prevent CMS,[35] suggesting a role for ovarian hormones.

High serum testosterone in the morning hours has been related to a high degree of nocturnal oxygen desaturation during sleep.[36] Additionally, men at HA with high testosterone levels have more disturbances during sleep and higher Hb levels.[37]

León-Velarde *et al.*[38] demonstrated that men from Cerro de Pasco (altitude of 4340 m) have lower pulse oxygen saturations, higher Hb concentrations and higher end-tidal CO_2 pressures ($PETCO_2$) than pre-menopausal women of similar age. This is an important finding, as both men and women are exposed to similar environmental hypoxic conditions. Therefore, these gender differences seem to be due to variations in sex hormone levels, which is further supported by their disappearance after menopause.[34]

Additional recent studies refer to other factors responsible for CMS pathogenesis. These include increased angiogenic growth factors,[39] exaggerated oxidative stress[40] and elevated serum testosterone levels.[41] Cardiac function is also affected in patients with CMS.[42]

TESTOSTERONE AND VENTILATION

At sea level, several breathing disorders such as obstructive sleep apnoea and sudden infant death syndrome show clear sex differences in terms of prevalence.[43] Gender differences exist in the respiratory functions of the upper airway. In fact, sleep apnoea syndromes are less common in women than in men.[44]

The prevalence of sleep apnoea/hypopnoea syndrome is twice as high in men as in women.[45] In addition, testosterone administration increases sleep apnoeas in men.[46] Moreover, women with apnoea-hypopnoea indices greater than 10/h of sleep showed significantly lower serum levels of 17-OH-progesterone, progesterone and oestradiol than those with lower apnoea-hypopnoea indice.[47] Total testosterone was positively correlated to total apnoea-hypopnoea index in women with polycystic ovary syndrome.[48] These sleep apnoeas may result in hypoventilation and low arterial oxygen saturation, and both could be aggravated under living conditions at HA, in which low environmental oxygen pressure is predominant.

The effects of the menstrual cycle, pregnancy, testosterone and progesterone on resting ventilation have been well documented.[49] In relation to the effects of sex hormones on hypoxic (HVR) and hypercapnic ventilatory responses (HCVR), female rats have a greater HVR than male rats at old age, and at middle age, female rats have a greater HCVR than male rats.[49] Among other things, relative alveolar hypoventilation has been suggested to result from reduced circulating female sex steroid hormone concentrations.[50–53] All of these data suggest that high serum testosterone levels and/or low serum oestradiol levels may be participating in hypoventilation, which may result in erythrocytosis and CMS in high-altitude populations. Testosterone can contribute to hypoventilation during sleep. However, in the case of CMS, causation due to an increased number of apnoeic events has not been proven.[32] Moreover, no studies have been conducted in humans during the daytime to show an association between ventilation and testosterone levels at HA. The classic ventilatory blunting of healthy high-altitude natives[24] does not necessarily result in lower SpO_2. Therefore, it can be argued that high-altitude natives do not ventilate more because it is not necessary, possibly because of improved gas exchange (e.g., pulmonary diffusion). The proposed

effect of testosterone on ventilation assumes a consequent drop in SpO_2 and EE. This mechanism would involve erythropoietin (EPO). However, EPO is not always increased in CMS patients.[16] Thus, testosterone may be playing a minor role in ventilation at HA, and it likely has a major role in erythropoiesis *via* ventilation-independent mechanisms (**Figure 1**).

It is also possible that testosterone may act in the lungs. In fact, there is increasing clinical evidence for sex differences in the incidence, morbidity and mortality of lung diseases including allergic diseases (such as asthma), chronic obstructive pulmonary disease, pulmonary fibrosis and lung cancer, as well as pulmonary hypertension.[54,55] A recent study showed that the androgen receptor (AR) is expressed in type II pneumocytes and the bronchial epithelium of murine lung and that androgen treatment increases AR protein levels in lung cells,[56] suggesting an important role for androgens in lung function.

TESTOSTERONE AND ERYTHROPOIESIS

Testosterone is considered both a hypoventilatory and an erythropoietic hormone.[36,37,57,58] Oestradiol, in contrast, limits EPO and red blood cell production.[59]

The association between testosterone and EPO is still ambiguous. Total androgen blockage reduces Hb levels but moderately increases EPO,[60] suggesting that the reduction in Hb levels is due to the reduction in serum testosterone levels and that a reduction in Hb levels may increase EPO levels. In addition, serum testosterone levels are related to erythrocytosis rather than EPO levels in hypogonadal men treated for up to 21 years with subcutaneous testosterone pellets.[61] In another study, testosterone was shown to dose-dependently increase the Hb/haematocrit rate, but did not show a related increase in erythropoietin.[62]

A recent study observed increased human erythropoiesis as a result of the acceleration of the conversion of dehydroepiandrosterone sulphate (DHEAS) to testosterone by activation of 3-beta-hydroxysteroid dehydrogenase 2 (3beta-HSD2) and/or 17beta-HSD3, resulting in high serum testosterone levels and high Hb levels.[63]

The conversion of testosterone to dihydrotestosterone[64] or to oestradiol[65] is not essential for the mediation of its effects on erythropoiesis.

It has been suggested that testosterone stimulates erythropoiesis through the production of haematopoietic growth factors and/or the possible improvement of iron bioavailability. At the level of erythropoiesis, testosterone is suggested to act directly on bone marrow, and specifically, the polychromatophylic erythroblasts.[66] Furthermore, erythropoietin and testosterone have been postulated to act synergistically to create the biochemical machinery for the synthesis of Hb, the macromolecule that characterizes the erythropoietic process.[67] However, survival-enhancing or growth-stimulatory effects of androgens on haematopoietic progenitor cells are minimal and mostly restricted to mature erythroid progenitors in experiments using human purified ($CD34^+$) erythroid progenitors *in vitro*.[68] Moreover, no AR expression has been observed in erythroid cells.[69] Instead, androgens act through AR to modulate the mRNA expression of several haematopoietic growth factors in bone marrow stromal cells. The effect of testosterone on erythroid progenitors could occur *via* bone marrow stromal cells.[70]

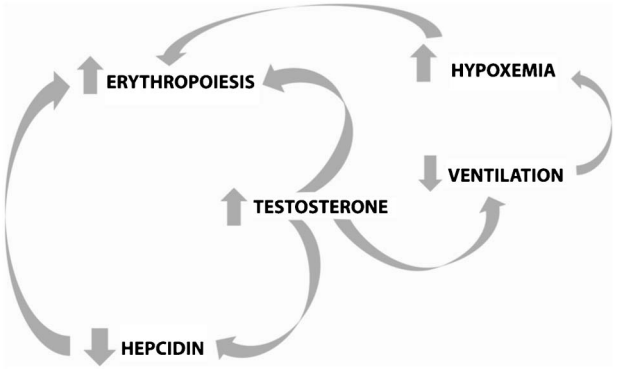

Figure 1 Elevated serum testosterone levels at high altitudes result in hypoventilation, lower serum hepcidin levels and increased erythropoiesis.

Although animal studies suggest that androgen administration increases the synthesis and secretion of erythropoietin,[58] results in men do not demonstrate this association.[60,61] Recent studies suggest that testosterone may be acting on iron bioavailability. In fact, testosterone administration has been associated with the suppression of serum hepcidin, and the reduction in serum hepcidin levels is associated with a greater increase in haematocrit in older men during testosterone therapy.[71] Women with polycystic ovary syndrome, who have decreased oestrogen and increased testosterone levels, also show reduced serum hepcidin levels.[72]

Hepcidin is a peptide hormone produced in the liver that binds and degrades the iron channel ferroportin,[73] resulting in an inhibition of bioavailable iron. Low hepcidin is associated with increased iron absorption, increased systemic iron transport, and erythropoiesis.[74] In mammals, iron bioavailability for erythropoiesis and other vital organic functions is regulated at three principal sites: placental or duodenal uptake, release from hepatic stores and recycling of scavenged iron from senescent red blood cells *via* reticuloendothelial macrophages.[75] Hepcidin regulates iron bioavailability, and it has been demonstrated that alterations in iron metabolism are only sufficient to produce erythrocytosis.[76] Thus, an increase in the level of serum testosterone may reduce serum hepcidin levels, consequently increasing the bioavailability of iron, which increases the Hb levels (**Figure 1**).

Approximately 70% of the iron in the body is associated with Hb in circulating red blood cells, and daily erythropoiesis requires approximately 25–30 mg of iron per day.[77] This iron is provided by macrophages through haem iron recycling following phagocytosis of senescent red blood cells and haem catabolism. Intestinal iron absorption (1–2 mg day^{-1}) only compensates for daily iron losses.[78] In the erythropoietic compartment, hypoxia stimulates erythropoiesis and promotes Hb synthesis, which largely depends on iron availability.[79,80]

It is well known that in the Peruvian Andes, Hb concentration increases as altitude increases.[81] Similarly, CMS or lack of adaptation to HA, which occurs in natives or long-term residents at altitudes above 3000 m, also increases in a similar fashion.[82,83] These high Hb levels in populations at HA seem to be due to reduced levels of serum hepcidin. During exposure to hypoxia at HA, the levels of hepcidin are reduced, and this reduction is not driven by a reduction in iron storage.[84]

EPO is the hormone responsible for erythropoiesis and has also been related to improved hypoxic ventilatory response.[85] An increase in EPO levels has been observed after acute exposure to HA.[86] However, after prolonged exposure to hypoxia, EPO does not increase further; on the contrary, its level tends to decrease.[87] In addition, serum EPO levels do not increase further in men with EE at HA.[41] These data suggest that EPO is not responsible for EE at HA and that other hormones/factors account for EE at HA. Testosterone also stimulates erythropoiesis.[58] Therefore, an increase in serum testosterone

levels at HA may accentuate hypoxaemia and may produce excessive erythropoiesis.[16,41] Moreover, a recent study showed that high-altitude erythrocytosis may be induced by an EPO-independent haematopoietic stem cell mechanism in the bone marrow.[88]

It is also possible that EE at HA could be due to increased iron availability. This effect could also occur without affecting the serum EPO levels, based on recent findings suggesting that administration of statins may increase erythropoiesis by targeting the hepcidin and iron regulatory pathways independent of erythropoietin.[89]

TESTOSTERONE AND ENVIRONMENTAL HYPOXIA: THE CASE OF NATIVES AT HAS

During acute exposure to HA, hyperventilation associated with increased heart rate is the first response of the organism. Similarly, serum testosterone levels increase in men and male rats exposed to acute hypoxia.[15,90–92] Because testosterone is a hypoventilatory hormone, we have suggested that an increase in serum testosterone is related to a negative feedback mechanism of hyperventilation to avoid an exaggerated response of the organism that could result in respiratory alkalosis and symptoms.[15] An increase in serum testosterone may also enhance erythropoiesis, supporting acclimatisation. Thus, increased serum testosterone levels during acute exposure to HA may improve acclimatisation.[15]

The situation in natives or subjects chronically exposed to HA is different. If serum testosterone is high, as observed in several studies,[16,21,41,93] this may be a contributing factor in reducing ventilation, increasing sleep apnoeas and consequently reducing arterial oxygen saturation,[16,21,41] generating hypoxaemia. At the same time, increased testosterone levels may activate erythropoiesis, reduce hepcidin and increase Hb levels up to the level of EE, resulting in CMS.[16,41]

Therefore, testosterone may be important in regulating ventilation and erythropoiesis at HA but when its value increases over a threshold, an accentuation of hypoventilation and erythropoiesis may occur, thus increasing the risk of CMS.

Testosterone in men and adaptation to altitude

The possibility that variations in the normal physiological range of testosterone concentrations modulate the adaptation of men to hypobaric high-altitude hypoxia through the stimulation of Hb production and/or respiratory disturbances and the exacerbation of hypoxaemia during sleep has been previously suggested.[37] In the referenced study, urban adult men living at HA showed higher salivary testosterone concentrations than rural men as well as significantly higher average Hb concentrations. In addition, older urban men living at HA had more frequent respiratory disturbances during sleep, which were associated with significantly greater hypoxaemia.[37]

It is likely that the higher bioavailability of testosterone over many years at HA[93] may be responsible for sleep apnoeas, resulting in hypoventilation, greater hypoxaemia and EE. All of these may contribute to the cause of CMS.[82] It is known that subjects with EE at HA show an increased incidence of CMS compared to subjects with lower Hb levels.[94] Similarly, spontaneous baroreflex sensitivity is significantly lower in subjects with EE.[95] Periodic breathing with apnoea has also been observed in high-altitude newcomers.[96] Furthermore, serum testosterone levels are increased after acute exposure to HA.[15] Therefore, testosterone may play a role in high-altitude tolerance, most likely increasing the HVR and HCVR; however, if the effect of testosterone on sleep apnoeas prevails over other functions, testosterone may have a negative impact on the adaptation process. When equilibrium is disturbed, testosterone-induced sleep hypoventilation and EE may produce CMS.[16,41,97]

It is possible that the improvement of HVR and HCVR by testosterone[98] could be due to an aromatase-dependent mechanism. In fact, the long-term facilitation of respiratory motor output in gonadectomized male rats induced by testosterone is dependent on the conversion of testosterone to oestradiol by aromatase.[99] However, testosterone *per se* increases sleep apnoeas, inducing hypoventilation. In addition, sleep fragmentation eliminates ventilatory long-term facilitation and attenuates HCVR.[100]

The HVR in many mammals is biphasic, with an initial stimulation followed by a decline or roll-off. A number of factors influence the ventilatory decline, including sex, arousal state, anaesthesia, $PaCO_2$ and O_2 ventilatory plasticity. Adenosine plays a role in this decline in ventilatory response. The roll-off respiratory response to hypoxia in adults is attenuated by non-selective adenosine receptor blockade with methylxanthines.[101]

Serum testosterone response to the hypothalamic hormone, gonadotropin releasing hormone, has been studied in native men at altitudes of 2600 m,[102] 3400 m[103] and 4340 m (Coyotupa, Llerena and Guerra-Garcia, 1977, presented as an abstract). Serum testosterone levels at HA remain high at 180 min after injection, whereas at sea level, their values returned to basal levels. This high testosterone response occurred despite the fact that serum luteinizing hormone levels increase in similar magnitudes at sea level and at HA.[103]

These authors suggest a higher sensitivity of Leydig cells to luteinizing hormone at HA. However, it is also possible that higher levels of serum testosterone could be due to a reduction in the catabolic rate rather than a higher testosterone production rate. Recent studies have also shown that prolonged exposure to high-altitude hypoxia (3–4 days at 4350 m) does not affect the hypophyseal response to hypothalamic hormones.[104]

Human chorionic gonadotropin hormone (hCG) acts on Leydig cells in the luteinizing hormone receptors. At HA (4340 m), low urinary excretion of testosterone after intramuscular injection of 2500 IU hCG has been observed.[105] However, a similar increase in serum testosterone with respect to basal values after injection of 1000 IU of hCG has been observed at 3400 m, whereas at 4340 m, a higher response was reported[15] (**Table 2**). This has been confirmed in a recent study.[41] Low excretion of urinary testosterone at HA seems to be an effect of low catabolism. This suggests that the high availability of serum testosterone after hCG stimulation may be due to reduction in conversion to oestradiol or to the elevated conversion of androstenedione or DHEAS to testosterone.

At 4340 m, testosterone levels and testosterone/DHEAS are high, whereas serum DHEAS levels are low in men with EE at all times after stimulation with 1000 IU of hCG compared to those without EE living at the same altitude.[41] At HA, the group with the highest score ($\geqslant 10$) in CMS showed higher chronological age, serum testosterone levels and T/E_2 ratios, but lower pulse oxygen saturation (SpO_2) levels than the group with CMS scores of $\leqslant 4$. Some symptoms of CMS such as sleep disorders and paraesthesia are more related to high serum testosterone levels then with elevated Hb levels; cyanosis is more related to high Hb values than high serum testosterone levels. In conclusion, high serum testosterone levels are associated with high CMS scores.[97]

High androgen levels could be due to low aromatase activity or an elevated conversion rate from precursors to testosterone. This has been studied utilizing an aromatase enzyme inhibitor, letrozole ($5\,mg\,day^{-1}$), administered for a 5-day period in men at HA and at sea level. Men with erythrocytosis had lower basal serum testosterone/

Table 2 Percent response of serum testosterone to hCG (1000 IU im) in adult men natives from Lima (150 m), Cusco (3500 m) and Cerro de Pasco (4340 m)[15]

Altitude (m)	*Basal (%)*	*24 h post-hCG*	*48 h post-hCG*	*72 h post-hCG*
Lima(150 m)	100	118	126	157
Cusco (3500 m)	100	108	143	154
Cerro de Pasco (4340 m)	100	123	184*	157

Abbreviations: hCG, human chorionic gonadotropin; im, intramuscular injection; m, meters.
*Response significantly higher than at 150 m.

androstenedione ratios than men at sea level and men with EE (Hb>21 g dl^{-1}) at HA. Men at HA with EE had higher testosterone/DHEAS ratios than men with erythrocytosis and than those at sea level before and after letrozole administration. After letrozole administration, both groups of men at HA (with erythrocytosis or with EE) showed lower aromatase activities than those at sea level. In conclusion, higher serum testosterone levels in men with EE were associated with an increased conversion rate from DHEAS to testosterone rather than with lower aromatase activity.[106] The enzyme participating in this conversion is 17beta-HSD.[107] This suggests that a higher activity of this enzyme could explain the elevated levels of serum testosterone in subjects with EE at HA.

In summary, higher serum testosterone levels in men with EE are associated with greater conversion of DHEAS to testosterone.

Testosterone in women and adaptation to altitude

CMS is less frequent in women,[108] most likely due to the protective effect of oestrogens.[35] After menopause, when oestrogen production is dramatically reduced, the risk of CMS in women increases.[34] In addition, serum testosterone concentrations are greater in women living at HA than in those residing at sea level. Serum concentrations of DHEA, DHEAS and androstenedione are lower in women living at HA than in those living at sea level. The DHEAS/DHEA ratio is significantly greater, and the androstenedione/testosterone ratio is lower in samples of women living at HA. Among women above the age of 50 years, a greater decline in serum concentrations of DHEA has been observed in those living at HA than in those living at sea level. Among women between 60 and 70 years of age, serum concentrations of DHEA at HA are 47% of the concentrations in women of the same age living at sea level. The decay of DHEAS at sea level and at HA occurs from the age of 40 years. The decline is faster at HA than at sea level, and in women aged 60–70 years, serum values of DHEAS at HA are at 56% of the values of those at sea level. In the same age group, serum concentrations of androstenedione among those natives at HA are 27% of the values at sea level. At sea level and at HA, the serum testosterone/oestradiol ratio increases with age ($P<0.0034$ and $P<0.0001$, respectively).[109]

These data suggest that in women as well as in men[106] living at HA, there is a greater conversion of DHEAS to testosterone, indicating a higher activity of 17beta-HSDs. We demonstrated in Cerro de Pasco (altitude 4340 m) that serum testosterone/oestradiol values become higher as haematocrit/Hb increases,[110] suggesting that the effects of higher testosterone or testosterone/oestradiol levels impact both men and women at HA. Moreover, in women, high Hb/haematocrit levels are associated with elevated testosterone/DHEAS ratios,[15] confirming the data observed for men at HA.

Our hypothesis is that testosterone is increased at HA as a result of hypoxia and that the elevated serum testosterone levels subsequently cause EE. This idea is based on the fact that data from acute exposure to HA and from natives at HA with EE both demonstrate increased testosterone levels. Moreover, the level of plasma testosterone in hypoxic rats is higher than that in normoxic rats. Enhanced testosterone production has been observed in rat Leydig cells treated with hCG, 8-Br-cAMP or forskolin under both normoxic and hypoxic conditions. Intermittent hypoxia results in a further increase of testosterone production in response to testosterone precursors. The activity of 17beta-HSD is stimulated by the treatment of intermittent hypoxia *in vitro*.[111]

SUMMARY

According to our data, native men at HA are not adequately adapted if they have elevated testosterone levels. This seems to be related to the increased conversion of DHEAS into testosterone.[106,109] Further analyses of men at HA with erythrocytosis show higher serum androstenedione levels and a lower testosterone/androstenedione ratio than men with EE, suggesting reduced 17beta-HSD activity.[106] Lower 17beta-HSD activity through Δ4-steroid production[112] in men with erythrocytosis at HA may protect against elevated serum testosterone levels and prevent EE. The greater conversion of DHEAS into testosterone indicates increased 17beta-HSD activity through the Δ5-pathway.[106] Women with elevated testosterone levels are more likely to have EE.

In summary, elevated serum testosterone seems to be responsible for, or at least associated with, chronic mountain disease.

FINAL REMARKS

Populations living at HA in Peru represent an important model to study adaptation to HA. Human beings have lived in the Peruvian Andes since 12 000 years BC, a length of time in which adaptation could have occurred, but the Spaniard conquest in the middle of the eighteenth century may have altered this pattern. At present, there are various situations (human biodiversity) in which people live at HA with high or low degrees of adaptation associated with low or high Hb levels,[11] respectively. Antiquity could be an important component of adaptation to life at HA in Peru, and testosterone seems to be a hormone participating in this process.

COMPETING FINANCIAL INTERESTS

The author has nothing to disclose and declares no conflict of interest.

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1 Hero M, Wickman S, Hanhijärvi R, Siimes MA, Dunkel L. Pubertal upregulation of erythropoiesis in boys is determined primarily by androgen. *J Pediatr* 2005; **146**: 245–52.
2 Pasha MA, Newman JH. High-altitude disorders: pulmonary hypertension: pulmonary vascular disease: the global perspective. *Chest* 2010; **137**(6 Suppl): 13S–9S.

3 Beall CM, Decker MJ, Brittenham GM, Kushner I, Gebremedhin A *et al*. An Ethiopian pattern of human adaptation to high-altitude hypoxia. *Proc Natl Acad Sci USA* 2002; **99**: 17215–8.
4 Hartinger S, Tapia V, Carrillo C, Bejarano L, Gonzales GF. Birth weight at high altitudes in Peru. *Internat J Gynecol Obstet* 2006; **93**: 275–81.
5 Wu TY, Wang X, Wei C, Cheng H, Wang X *et al*. Hemoglobin levels in Qinghai–Tibet: different effects of gender for Tibetans *vs*. Han. *J Appl Physiol* 2005; **98**: 598–604.
6 Hubbe M, Neves WA, Harvati K. Testing evolutionary and dispersion scenarios for the settlement of the new world. *PLoS ONE* 2010; **5**: e11105.
7 Bonavia D. Peru. Man and History. From the Origin to Century XV. 1st ed. Lima: Edubanco; 1991.
8 Martinez-Laso J, Siles N, Moscoso J, Zamora J, Serrano-Vela JI *et al*. Origin of Bolivian Quechua Amerindians: their relationship with other American Indians and Asians according to HLA genes. *Eur J Med Genet* 2006; **49**: 169–85.
9 Rupert JL, Hochachka PW. Genetic approaches to understanding human adaptation to altitude in the Andes. *J Exp Biol* 2001; **204**: 3151–60.
10 Shinoda K, Adachi N, Guillen S, Shimada I. Mitochondrial DNA analysis of ancient Peruvian highlanders. *Am J Phys Anthropol* 2006; **131**: 98–107.
11 Gonzales GF, Tapia V. Association of high altitude-induced hypoxemia to lipid profile and glycemia in men and women living at 4,100 m in the Peruvian Central Andes. *Endocrinol Nutr* 2012; **59**: 521–2.
12 McCormick SD, Bradshaw D. Hormonal control of salt and water balance in vertebrates. *Gen Comp Endocrinol* 2006; **147**: 3–8.
13 Vitzthum VJ. The ecology and evolutionary endocrinology of reproduction in the human female. *Am J Phys Anthropol* 2009; **140**(Suppl 49): 95–136.
14 Zafón C. [Evolutionary endocrinology: a pending matter]. *Endocrinol Nutr* 2012; **59**: 62–8. Spanish.
15 Gonzales GF. [Hemoglobin and testosterone: importance on high altitude acclimatization and adaptation]. *Rev Peru Med Exp Salud Publica* 2011; **28**: 92–100. Spanish.
16 Gonzales GF, Tapia V, Gasco M, Rubio J, Gonzales-Castañeda C. High serum zinc and serum testosterone levels were associated with excessive erythrocytosis in men at high altitudes. *Endocrine* 2011; **40**: 472–80.
17 Beall CM, Laskowski D, Erzurum SC. Nitric oxide in adaptation to altitude. *Free Radic Biol Med* 2012; **52**: 1123–34.
18 Hoit BD, Dalton ND, Gebremedhin A, Janocha A, Zimmerman PA *et al*. Elevated pulmonary artery pressure among Amhara highlanders in Ethiopia. *Am J Hum Biol* 2011; **23**: 168–76.
19 Beall CM, Cavalleri GL, Deng L, Elston RC, Gao Y *et al*. Natural selection on EPAS1 (HIF2alpha) associated with low hemoglobin concentration in Tibetan highlanders. *Proc Natl Acad Sci USA* 2010; **107**: 11459–64.
20 Gonzales GF, Salirrosas A. Arterial oxygen saturation in healthy newborns delivered at term in Cerro de Pasco (4340 m) and Lima (150 m). *Reprod Biol Endocrinol* 2005; **3**: 46.
21 Gonzales GF, Villena AE. Low pulse oxygen saturation in post-menopausal women at high altitude is related to high serum testosterone/estradiol ratio. *Int J Gyn Obstet* 2000; **71**: 147–54.
22 McAuliffe F, Kametas N, Krampl E, Ernsting J, Nicolaides K. Blood gases in pregnancy at sea level and at high altitude. *BJOG* 2001; **108**: 980–5.
23 Hurtado A, Gonzales GF. Pulse oxygen saturation in healthy newborns at term in Cusco, Peru. *Int J Gynaecol Obstet* 2006; **95**: 155–6.
24 Brutsaert TD, Parra EJ, Shriver MD, Gamboa A, Rivera-Ch M *et al*. Ancestry explains the blunted ventilatory response to sustained hypoxia and lower exercise ventilation of Quechua altitude natives. *Am J Physiol Regul Integr Comp Physiol* 2005; **289**: R225–34.
25 Kryger MH, Grover RF. Chronic mountain sickness. *Sem Resp Med* 1983; **5**: 164–8.
26 Whitelaw W. Mechanisms of sleep apnea at altitude. *Adv Exp Med Biol* 2006; **588**: 57–63.
27 Pei T, Li X, Tao F, Xu H, You H *et al*. Burden of disease resulting from chronic mountain sickness among young Chinese male immigrants in Tibet. *BMC Public Health* 2012; **12**: 401.
28 Monge CC, Arregui A, León-Velarde F. Pathophysiology and epidemiology of chronic mountain sickness. *Int J Sports Med* 1992; **13**: S79–81.
29 Pei SX, Chen XJ, Si Ren BZ, Liu YH, Cheng XS *et al*. Chronic mountain sickness in Tibet. *Q J Med* 1989; **266**: 555–74.
30 Moore LG, Niermeyer S, Zamudio S. Human adaptation to high altitude: regional and life-cycle perspectives. *Am J Phys Anthropol* 1998; Suppl 27: 25–64.
31 Wang B, Zhang YB, Zhang F, Lin H, Wang X *et al*. On the origin of Tibetans and their genetic basis in adapting high-altitude environments. *PLoS ONE* 2011; **6**: e17002.
32 Spicuzza L, Casiraghi N, Gamboa A, Keyl C, Schneider A *et al*. Sleep-related hypoxaemia and excessive erythrocytosis in Andean high-altitude natives. *Eur Respir J* 2004; **23**: 41–6.
33 Monge CC, Leon-Velarde F, Arregui A. Increasing prevalence of excessive erythrocytosis with age among healthy high-altitude miners. *N Engl J Med* 1989; **321**: 1271.
34 Leon-Velarde F, Ramos MA, Hernandez JA, de Idiaquez D, Munoz LS *et al*. The role of menopause in the development of chronic mountain sickness. *Am J Physiol* 1997; **272**: R90–4.
35 Ou LC, Sardella GL, Leiter JC, Brinck-Johnsen T, Smith RP. Role of sex hormones in development of chronic mountain sickness in rats. *J Appl Physiol* 1994; **77**: 427–33.
36 Kouchiyama S, Masuyama S, Shinozaki T, Kurono T, Sakuma T *et al*. Prediction of the degree of nocturnal oxygen desaturation in sleep apnea syndrome by estimating the testosterone level. *Nippon Kyobu Shikkan Gakkai Zasshi* 1989; **27**: 941–5.
37 Beall CM, Worthman CM, Stallings J, Strohl KP, Brittenham GM *et al*. Salivary testosterone concentration of Aymara men native to 3600 m. *Ann Hum Biol* 1992; **19**: 67–78.
38 León-Velarde F, Rivera-Chira M, Monge-C C. Gender differences in the physiopathological sequence which leads to chronic mountain sickness. In: Ohno H, Kobayashi T, Masuyama S, Nakashima M, editors. Progress in Mountain Medicine at High Altitude. Tokorosawa: Japanese Society of Mountain Medicine; 1998. p143–8.
39 Yan JH, Li ZQ, Ji LH, Chai KX, Ge RL. [Changes of serum angiogenesis in patients with chronic mountain sickness]. *Zhongguo Ying Yong Sheng Li Xue Za Zhi* 2009; **25**: 457–60. Chinese.
40 Bailey DM, Rimoldi SF, Rexhaj E, Pratali L, Salmòn CS *et al*. Oxidative-nitrosative stress and systemic vascular function in highlanders with and without exaggerated hypoxemia. *Chest*; e-pub ahead of print 20 August 2012; doi:10.1378/chest.12-0728.
41 Gonzales GF, Gasco M, Tapia V, Gonzales-Castañeda C. High serum testosterone levels are associated with excessive erythrocytosis of chronic mountain sickness in men. *Am J Physiol Endocrinol Metab* 2009; **296**: E1319–25.
42 León-Velarde F, Villafuerte FC, Richalet JP. Chronic mountain sickness and the heart. *Prog Cardiovasc Dis* 2010; **52**: 540–9.
43 Behan M, Wenninger JM. Sex steroidal hormones and respiratory control. *Respir Physiol Neurobiol* 2008; **164**: 213–21.
44 Tatsumi K. [Gender difference in the respiratory functions of the upper airway]. *Masui* 2009; **58**: 16–24. Japanese.
45 Krishnan V, Collop NA. Gender differences in sleep disorders. *Curr Opin Pulm Med* 2006; **12**: 383–9.
46 Liu PY, Yee B, Wishart SM, Jimenez M, Jung DG *et al*. The short-term effects of high dose testosterone on sleep, breathing, and function in older men. *J Clin Endocrinol Metab* 2003; **88**: 3605–13.
47 Netzer NC, Eliasson AH, Strohl KP. Women with sleep apnea have lower levels of sex hormones. *Sleep Breath* 2003; **7**: 25–9.
48 Yang HP, Kang JH, Su HY, Tzeng CR, Liu WM *et al*. Apnea-hypopnea index in nonobese women with polycystic ovary syndrome. *Int J Gynaecol Obstet* 2009; **105**: 226–9.
49 Wenninger JM, Olson EB Jr, Cotter CJ, Thomas CF, Behan M. Hypoxic and hypercapnic ventilatory responses in aging male *vs* aging female rats. *J Appl Physiol* 2009; **106**: 1522–8.
50 Preston ME, Jensen D, Janssen I, Fisher JT. Effect of menopause on the chemical control of breathing and its relationship with acid-base status. *Am J Physiol Regul Integr Comp Physiol* 2009; **296**: R722–7.
51 Tatsumi K, Pickett CK, Jacoby CR, Weil JV, Moore LG. Role of endogenous female hormones in hypoxic chemosensitivity. *J Appl Physiol* 1997; **83**: 1706–10.
52 Cistulli PA, Barnes DJ, Grunstein RR, Sullivan CE. Effect of short-term hormone replacement in the treatment of obstructive sleep apnoea in postmenopausal women. *Thorax* 1994; **4**: 699–702.
53 León-Velarde F, Rivera-Chira M, Tapia R, Huicho L, Monge-CC. Relationship of ovarian hormones to hypoxemia in women residents of 4,300 m. *Am J Physiol Regul Integr Comp Physiol* 2001; **280**: R488–93.
54 Townsend EA, Miller VM, Prakash YS. Sex differences and sex steroids in lung health and disease. *Endocr Rev* 2012; **33**: 1–47.
55 Canguven O, Albayrak S. Do low testosterone levels contribute to the pathogenesis of asthma? *Med Hypotheses* 2011; **76**: 585–8.
56 Mikkonen L, Pihlajamaa P, Sahu B, Zhang FP, Jänne OA. Androgen receptor and androgen-dependent gene expression in lung. *Mol Cell Endocrinol* 2010; **317**: 14–24.
57 Moore LG, Asmus I, Curran L. Chronic Mountain Sickness: Gender and Geographic Variation. In: Ohno H, Kobayashi T, Masuyama S, Nakashima M, editors. Progress in Mountain Medicine at High Altitude. Tokorosawa: Japanese Society of Mountain Medicine; 1998. p114–9.
58 Shahani S, Braga-Basaria M, Maggio M, Basaria S. Androgens and erythropoiesis: Past and present. *J Endocrinol Invest* 2009; **32**: 704–16.
59 Peschle C, Rappaport IA, Sasso G, Condorelli M, Gordon AS. The role of estrogen in the regulation of erythropoietin production. *Endocrinol* 1973; **92**: 358–62.
60 Golfam M, Samant R, Eapen L, Malone S. Effects of radiation and total androgen blockade on serum hemoglobin, testosterone, and erythropoietin in patients with localized prostate cancer. *Curr Oncol* 2012; **19**: e258–63.
61 Ip FF, di Pierro I, Brown R, Cunningham I, Handelsman DJ *et al*. Trough serum testosterone predicts the development of polycythemia in hypogonadal men treated for up to 21 years with subcutaneous testosterone pellets. *Eur J Endocrinol* 2010; **162**: 385–90.
62 Coviello AD, Kaplan B, Lakshman KM, Chen T, Singh AB *et al*. Effects of graded doses of testosterone on erythropoiesis in healthy young and older men. *J Clin Endocrinol Metab* 2008; **93**: 914–9.
63 Morita H, Ikeda T, Kajita K, Fujioka K, Mori I *et al*. Effect of royal jelly ingestion for six months on healthy volunteers. *Nutr J* 2012; **11**: 77.
64 Bhasin S, Travison TG, Storer TW, Lakshman K, Kaushik M *et al*. Effect of testosterone supplementation with and without a dual 5α-reductase inhibitor on fat-free mass in men with suppressed testosterone production: a randomized controlled trial. *JAMA* 2012; **307**: 931–9.
65 Rochira V, Zirilli L, Madeo B, Maffei L, Carani C. Testosterone action on erythropoiesis does not require its aromatization to estrogen: Insights from the testosterone and estrogen treatment of two aromatase-deficient men. *J Steroid Biochem Mol Biol* 2009; **113**: 189–94.
66 Zitzmann M. Effects of testosterone replacement and its pharmacogenetics on physical performance and metabolism. *Asian J Androl* 2008; **10**: 364–72.

67 Perretta M. Molecular action of erythropoietin on RNA synthesis: 30 years of study. *Arch Biol Med Exp (Santiago)* 1988; **21**: 203–17.
68 Kim SW, Hwang JH, Cheon JM, Park NS, Park SE *et al*. Direct and indirect effects of androgens on survival of hematopoietic progenitor cells *in vitro*. *J Korean Med Sci* 2005; **20**: 409–16.
69 Mantalaris A, Panoskaltsis N, Sakai Y, Bourne P, Chang C *et al*. Localization of androgen receptor expression in human bone marrow. *J Pathol* 2001; **193**: 361–6.
70 Ray R, Novotny NM, Crisostomo PR, Lahm T, Abarbanell A *et al*. Sex steroids and stem cell function. *Mol Med* 2008; **14**: 493–501.
71 Bachman E, Feng R, Travison T, Li M, Olbina G *et al*. Testosterone suppresses hepcidin in men: a potential mechanism for testosterone-induced erythrocytosis. *J Clin Endocrinol Metab* 2010; **95**: 4743–7.
72 Luque-Ramirez M, Alvarez-Blasco F, Alpanes M, Escobar-Morreale HF. Role of decreased circulating hepcidin concentrations in the iron excess of women with the polycystic ovary syndrome. *J Clin Endocrinol Metab* 2011; **96**: 846–52.
73 Qiao B, Sugianto P, Fung E, Del-Castillo-Rueda A, Moran-Jimenez MJ *et al*. Hepcidin-induced endocytosis of ferroportin is dependent on ferroportin ubiquitination. *Cell Metab* 2012; **15**: 918–24.
74 Means RT Jr. Hepcidin and iron regulation in health and disease. *Am J Med Sci* 2013; **345**: 57–60.
75 Hentze MW, Muckenthaler MU, Andrews NC. Balancing acts: molecular control of mammalian iron metabolism. *Cell* 2004; **117**: 285–97.
76 Mok K, Mlodnicka AE, Hentze MW, Muckenthaler M, Schumacher A. The molecular circuitry regulating the switch between iron deficiency and overload in mice. *J Biol Chem* 2006; **281**: 7946–51.
77 Yoon D, Ponka P, Prchal JT. Hypoxia. 5. Hypoxia and hematopoiesis. *Am J Physiol Cell Physiol* 2011; **300**: C1215–22.
78 Beaumont C, Karim Z. [Iron metabolism: state of the art]. *Rev Med Interne* 2013; **34**: 17–25. French.
79 Nemeth E. Iron regulation and erythropoiesis. *Curr Opin Hematol* 2008; **15**: 169–75.
80 Smith TG, Robbins PA, Ratcliffe PJ. The human side of hypoxia-inducible factor. *Br J Haematol* 2008; **141**: 325–34.
81 León-Velarde F, Gamboa A, Chuquiza JA, Esteba WA, Rivera-Chira M *et al*. Hematological parameters in high altitude residents living at 4355, 4660 and 5500 meters above sea level. *High Alt Med Biol* 2000; **1**: 97–104.
82 Peñaloza D, Arias-Stella J. The heart and pulmonary circulation at high altitudes. Healthy highlanders and chronic mountain sickness. *Circulation* 2007; **115**: 1132–46.
83 Wu TY. Chronic mountain sickness on the Qinghai–Tibetan plateau. *Chin Med J* 2005; **118**: 161–8.
84 Talbot NP, Lakhal S, Smith TG, Privat C, Nickol AH *et al*. Regulation of hepcidin expression at high altitude. *Blood* 2012; **119**: 857–60.
85 Soliz J. Erythropoietin and respiratory control at adulthood and during early postnatal life. *Respir Physiol Neurobiol* 2013; **185**: 87–93.
86 Mackenzie RW, Watt PW, Maxwell NS. Acute normobaric hypoxia stimulates erythropoietin release. *High Alt Med Biol* 2008; **9**: 28–37.
87 Gunga HC, Kirsch KA, Roecker L, Kohlberg E, Tiedemann J *et al*. Erythropoietin regulations in human under different environmental and experimental conditions. *Resp Physiol Neurobiol* 2007; **158**: 287–97.
88 Li P, Huang J, Tian HJ, Huang QY, Jiang CH *et al*. Regulation of bone marrow hematopoietic stem cell is involved in high-altitude erythrocytosis. *Exp Hematol* 2011; **39**: 37–46.
89 Chang CC, Chiu PF, Chen HL, Chang TL, Chang YJ *et al*. Simvastatin downregulates the expression of hepcidin and erythropoietin in HepG2 cells. *Hemodial Int* 2013; **17**: 116–21.
90 Gonzales GF, Chung FA, Miranda S, Valdez LB, Zaobornyj T *et al*. Heart mitochondrial nitric oxide synthase is upregulated in male rats exposed to high altitude (4,340 m). *Am J Physiol Heart Circ Physiol* 2005; **288**: H2568–73.
91 Madrid E, Reyes JG, Hernández B, García JM, San Martín S *et al*. Effect of normobaric hypoxia on the testis in a murine model. *Andrologia*; e-pub ahead of print 11 September 2012; doi:10.1111/and.12019.
92 Barnholt KE, Hoffman AR, Rock PB, Muza SR, Fulco CS *et al*. Endocrine responses to acute and chronic high-altitude exposure (4,300 meters): modulating effects of caloric restriction. *Am J Physiol Endocrinol Metab* 2006; **290**: E1078–88.
93 Liang JF. [Experimental study on changes of sexual hormones in senior males living on high altitude]. *Zhonghua Nan Ke Xue* 2003; **9**: 286–7. Chinese.
94 Reeves JT, Leon-Velarde F. Chronic mountain sickness: recent studies of the relationship between hemoglobin concentration and oxygen transport. *High Alt Med Biol* 2004; **5**: 147–55.
95 Keyl C, Schneider A, Gamboa A, Spicuzza L, Casiraghi N *et al*. Autonomic cardiovascular function in high-altitude Andean natives with chronic mountain sickness. *J Appl Physiol* 2003; **94**: 213–9.
96 Goldenberg F, Richalet JP, Onnen I, Antezana AM. Sleep apneas and high altitude newcomers. *Int J Sports Med* 1992; **13**(Suppl 1): S34–6.
97 Gonzales GF, Tapia V, Gasco M, Gonzales-Castañeda C. Serum testosterone levels and score of chronic mountain sickness in Peruvian men natives at 4340 m. *Andrologia* 2011; **43**: 189–95.
98 Tatsumi K, Hannhart B, Pickett CK, Weil JV, Moore LG. Effects of testosterone on hypoxic ventilatory and carotid body neural responsiveness. *Am J Respir Crit Care Med* 1994; **149**: 1248–53.
99 Nelson NR, Bird IM, Behan M. Testosterone restores respiratory long term facilitation in old male rats by an aromatase-dependent mechanism. *J Physiol* 2011; **589**: 409–21.
100 Liu C, Cao Y, Malhotra A, Ling L. Sleep fragmentation attenuates the hypercapnic (but not hypoxic) ventilatory responses *via* adenosine A_1 receptors in awake rats. *Respir Physiol Neurobiol* 2011; **175**: 29–36.
101 Koos BJ. Adenosine A_{2a} receptors and O_2 sensing in development. *Am J Physiol Regul Integr Comp Physiol* 2011; **301**: R601–22.
102 Ramírez G, Herrera R, Pineda D, Bittle PA, Rabb HA *et al*. The effects of high altitude on hypothalamic-pituitary secretory dynamics in men. *Clinical Endocrinol* 1995; **43**: 11–8.
103 Garmendia F, Castillo O, Valdivia H, Ugarte N, Garmendia A. [Sensibilidad hipófiso-testicular del nativo normal de altura a la administración de hormona liberadora de gonadotropinas]. *Arch Biol And* 1984; **13**: 207–11. Spanish.
104 Richalet JP, Letournel M, Souberbielle JC. Effects of high-altitude hypoxia on the hormonal response to hypothalamic factors. *Am J Physiol Regul Integr Comp Physiol* 2010; **299**: R1685–92.
105 Guerra-Garcia R, Velasquez A, Coyotupa J. A test of endocrine gonadal function in men: urinary testosterone after the injection of hCG. II. A different response at high altitude natives. *J Clin Endocrinol Metab* 1969; **29**: 179–82.
106 Gonzales GF, Tapia V, Gasco M, Gonzales-Castañeda C. Aromatase activity after a short-course of letrozole administration in adult men at sea level and at high altitude (with or without excessive erythrocytosis). *Horm Metab Res* 2012; **44**: 140–5.
107 Mindnich R, Haller F, Halbach F, Moeller G, Hrabé de Angelis M *et al*. Androgen metabolism *via* 17 beta-hydroxysteroid dehydrogenase type 3 in mammalian and non-mammalian vertebrates: comparison of the human and the zebrafish enzyme. *J Mol Endocrinol* 2005; **35**: 305–16.
108 Arregui A, Leon-Velarde F, Valcarcel M. Salud y Minería: El riesgo del mal de montaña crónico entre mineros de Cerro de Pasco. Lima: ADEC-ATC/Mosca Azul; 1990.
109 Gonzales GF, Góñez C, Villena A. Adrenopause or decline of serum adrenal androgens with age in women at sea level and at high altitude. *J Endocrinol* 2002; **173**: 95–101.
110 Gonzales GF, Tapia V. Hemoglobin, hematocrit and adaptation to high altitude: relationship with hormone changes and multigenerational period of residence. *Rev Med* 2007; **15**: 80–93.
111 Hwang GS, Chen ST, Chen TJ, Wang SW. Effects of hypoxia on testosterone release in rat Leydig cells. *Am J Physiol Endocrinol Metab* 2009; **297**: E1039–45.
112 Scott HH, Mason JI, Sharpe RM. Steroidogenesis in the fetal testis and its susceptibility to disruption by exogenous compounds. *Endocr Rev* 2009; **30**: 883–925.