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BRIEF REPORT

REVISED Effect of acute altitude exposure on physiological parameters and glucose metabolism in healthy lowland Peruvians [version 2; peer review: 2 approved]

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Abstract

Background: High altitude exposure triggers a series of physiological changes to maintain homeostasis. Although longer-term (days to years) acclimatization processes are well studied, less is known about the physiological changes upon rapid ascent. We took advantage of Peru's geography to measure the first physiological changes following rapid transport from a low to a high-altitude environment among lowlanders.

Methods: Blood glucose, insulin, C-peptide, and salivary cortisol among healthy lowland Peruvians were measured before and after glucose ingestion at 40 m and upon arrival at 3470 m. Resting heart rate, blood oxygen saturation, and blood pressure were also monitored.

Results: At high altitude, we find a significant (p<0.05) increase in heart rate and a decrease in blood oxygen saturation and salivary cortisol. Additionally, baseline levels of blood glucose, plasma C-peptide, and cortisol were reduced (p<0.05). Blood glucose, plasma insulin, and plasma C-peptide returned to baseline or below faster at high altitude after glucose ingestion.

Conclusions: Although many overlapping environmental and physiological factors are present in the high-altitude environment, the first steps of acclimatization in this population appear to be caused by increased energy expenditure and glucose metabolism to maintain

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Approval Status ✔ ✔

	1	2
version 2 (revision) 08 Nov 2023		✔ view
version 1 21 Jun 2023	✔ view	? view

1. **Takayuki Nishimura**, Kyushu University, Fukuoka, Japan

2. **Robert K Szymczak**, Medical University of Gdańsk, Gdańsk, Poland

Any reports and responses or comments on the article can be found at the end of the article.

oxygen homeostasis until the longer-term acclimatization mechanisms become more significant.

Keywords
altitude sickness, hypoxia, insulin, C-peptide, cortisol

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Author roles: Fernandez - Rodriguez LJ: Conceptualization, Funding Acquisition, Writing – Original Draft Preparation, Writing – Review & Editing; **Bardales-Zuta VH**: Formal Analysis, Investigation, Writing – Review & Editing; **Vásquez-Tirado GA**: Writing – Review & Editing; **Avalos Alvarado C**: Data Curation, Resources; **Schaefer EJ**: Data Curation, Resources; **Hilario-Vargas J**: Writing – Review & Editing

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REVISED **Amendments from Version 1**

A correlation analysis was done for the changes in oxygen saturation, blood glucose, C-peptide, insulin and cortisol with each participant representing a datapoint. The analysis revealed that there was no correlation between parameters. For instance, we found that the change in oxygen saturation did not predict the change in blood glucose for the participants tested. Additionally, it was observed that low-altitude values for blood parameters did not predict their corresponding high-altitude values.

The resting initial values for these parameters were also tested pairwise to search for correlations at each altitude. Some moderate correlations were found between glucose, c-peptide, and insulin, but cortisol had only weak correlation (r squared < 0.3) against the other parameters.

We also expanded the discussion by about 400 words to better discuss the physiological changes observed upon arrival at high altitude, especially blood pressure, glucose metabolism, and cortisol. A paragraph was added to discuss the results of the correlation analysis. Also, we have added eight new references.

An error in Table 1 (BMI) was corrected.

An error in the Figure 1 legend was corrected.

Any further responses from the reviewers can be found at the end of the article

Introduction

Humans have been traveling between low and high altitudes since prehistory. Today, it has been estimated that approximately 40 million lowlanders visit a high-altitude environment, which is marked by increased wind velocity, solar radiation, topographic variation, and temperature variability, as well as lower humidity, average temperature, and atmospheric pressure (Luks *et al.* 2021). To maintain homeostasis at high altitude, the human body has developed short-term, mid-term, and long-term coping mechanisms.

The altitude acclimatization process has already been studied extensively, providing insight into various altitude-coping physiological processes and to better treat and prevent altitude sickness (Parati *et al*. 2018, Narvaez-Guerra *et al.* 2018, Torlasco *et al.* 2020, Luks *et al.* 2021). These studies reveal that the acclimatization process involves both persistent and transient physiological changes. However, we are unaware of any published reports that describe the very first physiological changes (<1 h) upon arrival in a real high-altitude environment. One study that analysed physiological changes in a hypobaric chamber suggested that immediate physiological changes may differ from longer-term acclimatization (Woolcott *et al.* 2015), leading us to hypothesize that short-term physiological compensation to high altitude may differ from longer-term acclimatization mechanisms.

Therefore, to better understand the first steps of altitude acclimatization, we measured blood pressure, heart rate, oxygen saturation, and pulse rate in 15 young healthy lowland participants near sea level and immediately after rapidly ascending to 3470 meters above sea level (masl). Furthermore, blood glucose, plasma c-reactive peptide, plasma insulin, and salivary cortisol were measured as a fasting baseline and after ingestion of a glucose bolus at both low and high altitude. These parameters have been previously measured in mid- to longer- term altitude studies allowing for direct comparison between shorter and longer-term altitude acclimatization (Woolcott *et al.* 2015, Parati *et al*. 2018, Narvaez-Guerra *et al.* 2018, Torlasco *et al.* 2020, Luks *et al.* 2021). We hypothesized that there may be physiological differences between immediate and longer-term altitude acclimatisation.

Methods

This study was approved by the Research Office of Universidad Privada Antenor Orrego (UPAO), resolution number 0372-2014-R-UPAO. Research office approval requires ethical review of the project. Physiology and endocrinology students of UPAO were invited to participate voluntarily in the study and provided written informed consent. As this is a convenience sample study, caution should be taken in applying these results to the general population. This research was not preregistered at an independent registry. Neither participation nor non-participation had any effect on the academic records of the students. Potential participants were excluded if they had conditions that affected the cardiovascular system, glucose metabolism or the hypothalamic-pituitary-adrenal axis, used tobacco or caffeine, regularly participated in strenuous activity, took drugs that affected the hypothalamic-pituitary-adrenal axis (such as steroids, corticosteroids, growth hormone, thyroid hormone, vasopressin, or dopamine) or if they travelled to high altitude locations less than a year before the study. Only participants for which an entire dataset was generated was included in the study. Participants self-reported their genders.

At the UPAO physiology laboratory in Trujillo, Peru (40 masl), fasting (>8 h) participants were subjected to blood oxygen saturation, resting pulse rate, weight, height, waist-hip ratio and fasting blood glucose, plasma insulin, plasma C-peptide and salivary cortisol measurements. The participants then drank an aqueous solution containing 70 g of anhydrous glucose (Dropaksa, Trujillo), dissolved in 300 mL of water. Blood glucose, plasma insulin, plasma C-peptide, and salivary cortisol measurements were taken 30, 60, 90, and 120 min after drinking the glucose solution.

Several days later, fasting (>8 h) participants travelled together from Trujillo to Salpo, Perú (3470 masl) and the same tests were completed upon arrival, except for the anthropometric measurements. Blood samples were centrifuged and cooled. Plasma and saliva were processed in the UPAO physiology laboratories and at the National University of Trujillo; blood glucose was measured on-site.

The tests occurred at approximately 9:00 AM at both locations. As much as possible, the participants maintained their daily schedules and wake-up times for both study days. All data acquisition took place in December 2014.

Procedures

All equipment was used and calibrated according to the manufacturer's instructions at high and low altitude, where applicable. Blood pressure, oxygen saturation, and pulse rate were measured with a digital blood pressure monitor CH-452 Lot 906 (Citizen Systems Japan Co., Ltd) and a pulse oximeter MF-415 (More Fitness), respectively. Since both monitors also measure pulse rate, the average reading was used. Blood glucose was measured using the Accu-Chek glucose meter (Roche), which was appropriately calibrated at both study locations. Plasma C-peptide, plasma insulin, and salivary cortisol were tested with kits from Gateways Medical (Catalogue Numbers: 80-CPTHU-E01.1, 80-INSHU-E01, 11-CORHU-E01- SLV) according to manufacturer instructions. An ELISA plate reader (Bio-Rad Laboratories Inc.) was also used to process the samples.

Statistics

A two-sample t-test with Bonferroni correction was applied to search for differences between men and women participants for all data sets taken. To compare corresponding data taken in Trujillo vs. Salpo and baseline vs. timepoint results, a Shapiro-Wilk test was performed to test for normality. If the data set was normally distributed, a paired t-test was performed, if not, a Wilcoxon test was used to account for statistical bias. A result was considered significant if $p<0.05$.

Table 1. Anthropometric measurements of participants. Anthropometric measurements of study participants taken in Trujillo, significant differences between men and women are indicated with an asterisk. Values are means ± SD; (n=15).

	Women	Men	Combined
Age (years)	19.4±1.7	19.0±0.8	19.3±1.5
Weight (kg)	53.6±5.0	63.6±9.4	56.3±9.17
Height (cm)	155±2.3	169±5.3	159.1±7.1*
BMI (kg/m^2)	22.2±1.9	22.1±1.9	22.2±1.9
Waist (cm)	70.3±3.8	78.2±7.5	72.4±5.6
Hip (cm)	86.0±5.6	89.2±12.2	86.9±6.8
Waist-Hip ratio	0.82±0.07	0.88±0.04	0.84±0.07

Table 2. Physiological measurements of participants. Oxygen saturation (O_2SAT), pulse rate, systolic (SBP) and diastolic (DBP) blood pressure measurements of study participants in Trujillo and Salpo. Values are means ± SD. In the rightmost column, the *p*-value of the paired t-test is listed, which indicates whether a statistically significant difference was found between Trujillo and Salpo.

	Trujillo	Salpo	*p*
O_2SAT (%)	98.8±0.5	88.1±3.7	<0.0001
Pulse rate, min^{-1}	77.3±11	91.8±10	<0.0001
SBP (mmHg)	110±11	113±12	0.47
DBP (mmHg)	75.0±9.7	76.9±6.6	0.34

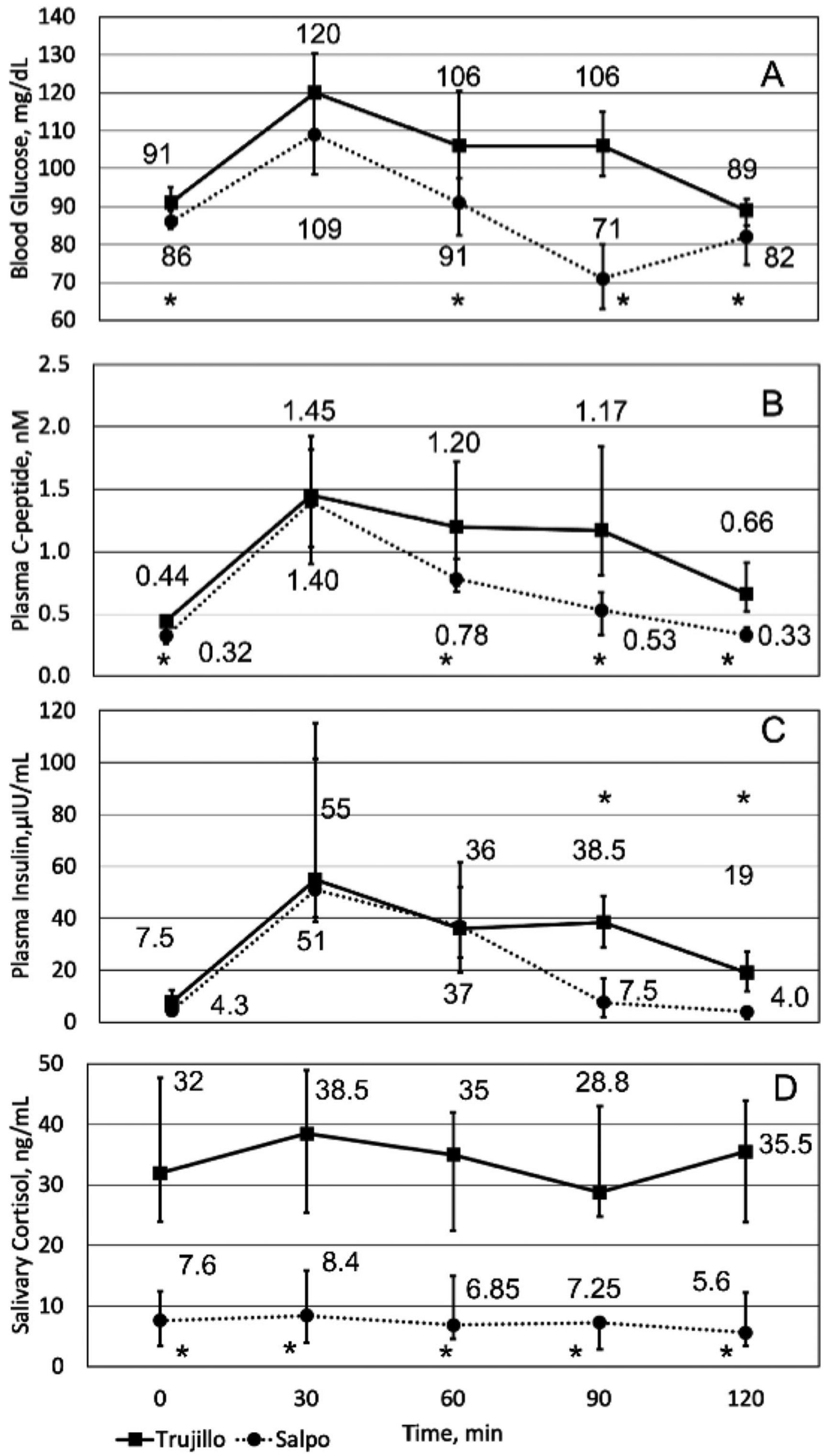

Figure 1. **Glucose tolerance at different elevations.** Median blood glucose (A), plasma C-peptide (B), plasma insulin (C), and salivary cortisol (D) for Trujillo (squares, solid line) and Salpo (circles, dotted line) before (0 min) and after (30-120 min) ingestion of 70 g of glucose. Whiskers represent the interquartile range of the 15 participants. Significant differences (*p*<0.05) between Trujillo and Salpo are indicated with asterisks.

Results

Of the 254 medical students enrolled in UPAO at the time, 71 were asked to participate in the study. Of these, 15 participants (11 females and 4 males) between 17 and 23 years of age met the acceptance criteria and completed the study. Table 1 reports the anthropometric data of the study participants taken in Trujillo. The only statistically significant difference found between sexes using a two-sample t-test with Bonferroni correction was height, $p<0.0001$, with men taller than women.

Table 2 and Figure 1 (0-minute time point) record the physiological baseline measurements in Trujillo and Salpo. Oxygen saturation, blood glucose, plasma C-peptide, and salivary cortisol were significantly lower in Salpo than in Trujillo, while heart rate was higher in Salpo ($p=0.02$ for C-peptide; $p<0.004$ for other measurements).

The baseline and sequential measurements taken after consuming 70 g glucose reveal significant differences in glucose metabolism after rapid ascent (Figure 1). Insulin, glucose, and C-peptide levels rose to approximately the same concentrations in both locations but decreased more quickly in Salpo, resulting in statistically significant lower values between datasets. Throughout the time course, salivary cortisol was significantly lower in Salpo ($p<0.0008$).

During the time course some notable differences occurred (Figure 1): (1) blood glucose at 90 and 120 minutes was lower than baseline in Salpo ($p<0.002$), while it was above or indistinguishable from baseline in Trujillo; (2) C-peptide remained significantly above baseline throughout the time course in Trujillo ($p<0.004$), but was indistinguishable from baseline at 120 minutes in Salpo; (3) insulin became indistinguishable from baseline after 90 minutes in Salpo, but remained above baseline throughout the entire time course in Trujillo ($p<0.0008$); and (4) salivary cortisol did not show statistically significant changes throughout the time course for both Trujillo and Salpo. Statistical analysis using the t-test or the Wilcoxon test gave nearly identical results regardless of normality.

Baseline results for O_2SAT, Glucose, C-peptide, insulin, and cortisol from each participant were tested for correlation. We considered correlations $r^2<0.3$ to be weak. Only weak correlations were observed between Trujillo and Salpo for each parameter, so low-altitude values could not predict high altitude values per participant. Furthermore, the degree of change of each parameter for each participant does not correlate with the degree of change of any other parameter. When each of the parameter pairs are compared at a study location, only two moderate correlations were found. At high altitude, blood glucose (mg/dL) predicted C-peptide (pM), R^2=.44, $F(1,13)$=10.04, p=.007. β=19.56, p=.007, α=-1369.61, p=1.975. At low altitude, C-peptide predicted insulin, R^2=.57, $F(1,13)$=17.17, p=.001. β=.033, p=.001, α=-4.59, p=1.779.

Discussion

Eight physiological parameters were measured in 15 healthy Peruvian students at low-altitude Trujillo (40 masl) and high-altitude Salpo (3470 masl), taking advantage of Peru's geography, where high altitude regions are accessible from the coast approximately 3 hours by road. Unlike other studies that take initial measurements after a stepwise ascent or within the first days of arrival, this study tested unacclimatized lowlanders within an hour of arrival at high altitude, thus allowing greater understanding of the first physiological changes associated with rapid ascent to a real high-altitude environment from sea level. Furthermore, the participants were driven to Salpo, which controls for physical exertion. To control for daily variations in certain physiological parameters, measurements were taken at approximately the same time of day and participants maintained their daily routine as much as possible. Since only height was statistically different between men and women for all parameters tested, male and female participants were treated as one group.

Combining the results (Table 2, Figure 1), we can outline the physiological changes that take place immediately upon arrival at high altitude and propose the underlying mechanisms. One of the main challenges in comparing these results with other studies is that activity level, genetics, altitude change, and time of sojourn all have effects on physiological response, sometimes causing parameters to decrease and later increase (Braun 2008, Woods *et al.* 2012, Woolcott *et al*. 2015, von Wolff *et al.* 2018, Heggie 2019, Luks *et al.* 2021). This underlies the importance in testing different populations at different altitudes for different time periods to elucidate a clear picture of the altitude response for different physiological parameters.

This notion is supported by our data which indicates that individual responses to altitude are somewhat different, given that no strong correlations were observed for the same parameter taken at different altitudes and the changes in these parameters. The only exception was between C-peptide and insulin (low altitude), and C-peptide and glucose (high altitude), which are all associated in the same pathway, as the production of active insulin results in C-peptide release, and increased insulin stimulates the elimination of glucose from the blood (Fu *et al.* 2013).

Upon initial exposure to altitude, the main physiological challenge is compensating for a decrease in partial oxygen pressure. This stimulates the sympathetic nervous system and peripheral chemoreceptors, increasing heart and breathing (respiratory) rates to maintain acceptable blood oxygen levels (Luks *et al*. 2021). This effect and its mechanism have been studied previously, revealing that taking β-blockers, which inhibit the sympathetic nervous system, cause a decrease in heart rate at high altitude (Boissou *et al.* 1989). In this study, there was an insignificant small increase in blood pressure. Several other studies have shown similar slight increases with varying degrees of significance (Savonitto *et al.* 1993, Bilo *et al*. 2019). It is likely that the youth of the subjects, short sojourn, and lack of underlying high blood pressure contributed to this nonsignificant change. Additionally, an increase in cardiac output can at least be partially offset by a decrease in peripheral vascular resistance due to hypoxia-caused vasodilation (Vogel and Harris 1967).

Postprandial glucose elimination at high altitude was more efficient, resulting in a statistically significant decrease at baseline and after 60 minutes post glucose ingestion. Insulin and C-peptide levels were no different 30 minutes after glucose ingestion, but then tapered off more rapidly at high altitude. Taken together, it appears that glucose sensitivity improved at high altitude, as glucose clearance occurred more rapidly with a similar insulin response. This result closely resembles a finding using prompt *simulated* altitude exposure (Woolcott *et al.* 2015). A likely explanation is that an increase in respiration causes an increase in energy demand, which is largely fulfilled by glucose clearance and limitation of fatty acid oxidation, but alterations to energy metabolism remain and depend on length of stay and degree of altitude (Stock *et al.* 1978, Braun 2008, Murray 2016).

The relationship between altitude and cortisol is nonlinear. Acute exposure to altitudes around 3000-5000 masl causes a decrease in cortisol, while altitudes in excess of 5000 masl cause an increase when compared to cortisol measured at sea level (Woods *et al.* 2012, Woolcott *et al.* 2015, von Wolff, *et al.* 2018). The results of this study corroborate these findings, as salivary cortisol in Salpo (3470 masl) was less than that observed in Trujillo. The lower salivary cortisol may partly explain the lower baseline glucose, improved glucose tolerance, and no significant increase in blood pressure in Salpo. Since cortisol is also associated with mid- and long-term stress, we cannot rule out that the lower cortisol observed here may be a result of the short respite from their academic studies the students experienced on their day in Salpo, but this is not easily controlled because a high-altitude town differs greatly from a large provincial city. However, this observation is likely to be relevant for other high-altitude travellers because such trips are often made for recreation.

The physiological changes observed here are likely transient and only last several hours, as other studies involving longer-term altitude exposure have shown that within the first day or two the body compensates with above normal glycemia in response to sympathetic stimulation and increased cortisol, which then decreases after the first week at high altitude. Longer-term sojourns tend to improve glucose tolerance beyond the corresponding low-altitude values, which may be explained by increased insulin sensitivity. Indeed, high-altitude residents tend to have healthier glycemia and glucose tolerance than lowlanders. However, other factors associated with people living at altitude, such as degree of physical activity, food availability, and genetics and ethnicity, are also important in explaining physiological differences between highlanders and lowlanders (Braun 2008, Woods *et al.* 2012, Woolcott *et al.* 2015, Parati *et al.* 2018, Narvaez-Guerra *et al.* 2018, von Wolff *et al.* 2018, Koufakis *et al.* 2019, Heggie 2019, Torlasco *et al.* 2020, Luks *et al.* 2021, Stock *et al.* 1978). Therefore, additional work, likely with more participants that better reflect the demographics of high-altitude visitors, will be necessary to confirm these results.

Nonetheless, these findings may be important in understanding the first stages of altitude sickness. This work may also be useful for people with type-1 diabetes or other people with glucose-metabolism disorders who visit high altitude due to the lower insulin levels observed among participants upon arrival, higher insulin levels within a few days of arrival, which then decrease (Richards and Hillebrandt 2013).

The present study captured the earliest effects of high altitude among healthy volunteers, with longer-term processes associated with altitude acclimatization becoming more important hours and days after arrival. These early changes seem to centre around increased glycolysis to maintain oxygen homeostasis without high glycemia or elevated cortisol. When the results of other high-altitude studies are combined with these results, a complex set of physiological changes occur – the degree and direction of which depend on activity level, genetics, the altitude change and time of sojourn.

Data availability statement

Figshare: Trujillo-Salpo Dataset. DOI: 10.6084/m9.figshare.22685278.v1 (Fernandez 2023a).

This project contains the following underlying data:

- dataset060123.txt (Supplementary dataset for the article "Effect of acute altitude exposure on physiological parameters and glucose metabolism in healthy lowland Peruvians".)

Reporting guidelines

Figshare: STROBE checklist for "Effect of acute altitude exposure on physiological parameters and glucose metabolism in healthy lowland Peruvians". DOI: 10.6084/m9.figshare.22687624.v1 (Fernandez 2023b).

Acknowledgments

The authors wish to thank the technical staff of the physiology laboratory of Universidad Privada Antenor Orrego.

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Current Peer Review Status: ✔ ✔

Version 2

Reviewer Report 16 November 2023

https://doi.org/10.5256/f1000research.158350.r221703

✔ **Robert K Szymczak**
Department of Emergency Medicine, Faculty of Health Sciences, Medical University of Gdańsk, Gdańsk, Poland

No further improvements are needed.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Emergency medicine, high altitude medicine

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 10 October 2023

https://doi.org/10.5256/f1000research.147395.r205874

? **Robert K Szymczak**
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The main goal of the presented article is to expand knowledge about the first steps of altitude acclimatization - during the first hours of acute high altitude exposure of not acclimatized lowlanders. The research included measurements of blood glucose, insulin, C-peptide and salivary cortisol at sea level and at altitude of 3470m before and after glucose ingestion. The study found that baseline levels of glucose, C-peptide and cortisol were reduced at high altitude. Another result was that the blood glucose, plasma insulin and C-peptide returned to baseline or below faster at high altitude than at sea level after ingestion of glucose. Authors concluded that above results can be explained by increased energy expenditure and glucose metabolism to maintain oxygen homeostasis at high altitude.

In my opinion, the article is publishable, but needs minor improvements in the discussion section.

Authors should expand discussion section and compare their results to those presented by other authors. There are few works in which cortisol levels, similarly to results presented in the manuscript, were lower at high altitude in comparison to seal level:

- Woods et al. The cortisol response to hypobaric hypoxia at rest and post-exercise, Horm Metab Res, 2012 Apr;44(4):302-5. doi: 10.1055/s-0032-1304322.
- Von Wolff et al. Adrenal, thyroid and gonadal axes are affected at high altitude, Endocr Connect, 2018 Oct 1;7(10):1081-1089. doi: 10.1530/EC-18-0242.

There are also works in which glucose and insulin levels at high altitude were analyzed, were similarly to results of the presented manuscript, the baseline levels of blood glucose and plasma insulin were decreased at high altitude.

- Stock at al. Effects of exercise, altitude, and food on blood hormone and metabolite levels, J Appl Physiol Respir Environ Exerc Physiol 1978 Sep;45(3):350-4. doi: 10.1152/jappl.1978.45.3.350.

Table 1. Value of BMI for Men has a wrong value 222.1. It has to be changed.

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Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: emergency medicine, high altitude medicine

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 30 Oct 2023

Lissett Fernández

The authors expanded the discussion by approximately 400 words and included the suggested references regarding cortisol and glucose levels at high altitude.

The error in Table 1 was corrected.

Competing Interests: The authors have no competing interests in replying to this peer review report.

Reviewer Report 31 August 2023

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This paper is overall well written and there are no particular problems. Short-term adaptation to high altitudes is an important issue and is also relevant to prevention of AMS. There is few studies that tested glucose metabolism in high-altitude, and this study provides important findings. However, it may be better to perform a more detailed analysis, for example, a correlation analysis of the relationship between glucose metabolic function and SpO2 and cortisol. Decreasing cortisol in high altitude is interesting but difficult to understand. Please refer this article, it may help your study.

Bouissou, P. et al. Effect of beta-adrenoceptor blockade on renin-aldosterone and alpha-ANF during exercise at altitude. J. Appl. Physiol. 67, 141–146 (1989).

Minor point; the BMI description for men in Table 1 is incorrect.

References

1. Bouissou P, Richalet JP, Galen FX, Lartigue M, et al.: Effect of beta-adrenoceptor blockade on renin-aldosterone and alpha-ANF during exercise at altitude.*J Appl Physiol (1985)*. 1989; **67** (1): 141-6 PubMed Abstract | Publisher Full Text

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Anthropology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 30 Oct 2023

Lissett Fernández

A correlation analysis between the parameters mentioned was completed and included in the updated manuscript. The correlation was done for the changes in oxygen saturation, blood glucose, C-peptide, insulin and cortisol with each participant representing a datapoint. The analysis revealed that there was no correlation between parameters. For instance, we found that the change in oxygen saturation did not predict the change in blood glucose for the participants tested. Furthermore, low-altitude values for blood parameters did not predict their corresponding high-altitude values.

The resting initial values for blood oxygenation, glucose, c-peptide, insulin, and cortisol were also tested pairwise to search for correlations. Some moderate correlations were found between glucose, c-peptide, and insulin, but cortisol had only weak correlation (r squared < 0.25) against the other parameters.

We also expanded the discussion by approximately 400 words, included a reference to the mentioned paper and corrected the error in Table 1.

Competing Interests: The authors have no competing interests in replying to this peer review report.