International Journal of Gerontology 15 (2021) 160–164
https://doi.org/10.6890/IJGE.202104_15(2).0014

International Journal of Gerontology

journal homepage: http://www.sgecm.org.tw/ijge/

Original Article

Aging at High Altitude: A Study of the Combined Effect of Aging and Altitude on Hemoglobin and Red Cell Parameters

Husain Alkhaldy [a,b], Zuhier Awan [c,d], Saeed Al Amoudi [d], Muhammad Saboor [e,f] *

[a] *Department of Internal Medicine, College of Medicine, King Khalid University, Abha, Saudi Arabia,* [b] *Research Centre for Advanced Materials Science, King Khalid University, Abha, Saudi Arabia,* [c] *Department of Clinical Biochemistry, Faculty of Medicine, King Abdulaziz University, Saudi Arabia,* [d] *Department of Clinical Pathology, Al-Borg Medical Laboratories, Saudi Arabia,* [e] *Department of Medical Laboratory Technology, Faculty of Applied Medical Science, Jazan University, Jazan, Saudi Arabia,* [f] *Medical Research Center, Jazan University, Jazan, Saudi Arabia*

ARTICLE INFO

Accepted 17 December 2020

Keywords:
high altitude,
aging,
hemoglobin,
red cells

SUMMARY

Background: Age and high altitude affect hematological parameters. The purpose of this study was to evaluate the combined effect of age and altitude on hemoglobin (Hb) and red cell parameters.
Methods: In this cross-sectional comparative study, a large data set of complete blood counts, of both genders were retrospectively reviewed. Data were collected from two geographical areas; a moderately high-altitude, Abha city, 2270 meters above sea level, and a coastal Jeddah city, Saudi Arabia. Data were stratified into two age groups for both cities i.e. 12–60 years and 61–100 years. For all CBC parameters, descriptive analysis and multivariate regression analysis was carried out.
Results: Hemoglobin levels of males and females at Abha was high as compared to their counterparts at Jeddah. At both cities, females maintained their hemoglobin concentration and showed slightly increase after menopause while males showed gradual decline in their hemoglobin concentration with aging.
Overall, Hb levels had highly significant negative linear relationship ($p < 0.01$) with age ($r = -0.015$) and gender ($r = -0.182$) while positive liner relationship with altitude ($r = 0.071$). While comparing Hb in both cities, Jeddah population had more negative linear relationship ($r = -0.011$) with age than the Abha population ($r = -0.014$) suggesting that altitude effect on hemoglobin level remains robust despite aging.
Conclusion: Hemoglobin levels are affected by independent variables i.e. age, gender and altitude. Hemoglobin concentration declines with aging, however the positive effect of altitude on hemoglobin concentration remains robust in both genders even at older age groups (80–100).

1. Introduction

Aging is a natural process associated with progressive decline in the physiological organs reserve. Hematopoietic system is among those extensively studied and changes with aging has been defined. Although genetic in nature, aging is influenced by other factors including environmental factors. For example, hypoxia, whether intermittent or sustained has been linked to accelerate aging process due to vital importance of oxygen at the cellular levels.[1] Thus, aging at high altitude might represent a special phenomenon of a double hit to the hematopoietic system.

Many structural changes associated with aging have direct consequences on the hematopoietic system. Clonal hematopoiesis, resulting from accumulating somatic mutations, is a direct age related phenomenon.[2] Aging is also associated with inflammation which through the cytokines storm effects hematopoiesis.[3] Changes like decreased cellularity of the bone marrow and associated reduction in the peripheral blood elements is largely benign.[4] Aging of other body organs, like endocrine system does affect the hematopoietic system.[5] Hemoglobin concentration is known to decrease with aging. This effect is more pronounced in men, possibly due to loss of testosterone drive.[5] Anemia of aging is usually mild. Nonetheless, anemia has been found to be associated with mortality and exacerbation of severity of other illnesses like cardiovascular disease.[6] According to the World Health Organization (WHO) criteria for anemia (hemoglobin < 12 g/dL in women and < 13 g/dL in men), individuals with ≥ 65 years of age have more than 10% prevalence of anemia while in later life (≥ 85 years), the prevalence could be high enough up to 20% or more.[7] Traditional etiologies of anemia are also more common with aging like iron deficiency and anemia associated with chronic diseases. Vitamin B_{12} deficiency is reported to be higher in elderly which could explain the reported higher prevalence of macrocytosis in this age group.[8]

Thus, studying the effects of aging and altitude, singly and combined are important as both factors should be taken in consideration when a practitioner interpret the blood tests commonly requested and used to define illness and base on subsequent management. It is established fact that Hb and red cell parameters are significantly affected by geographical location, ethnicity, race and reference range of one population could not be universally applied. Furthermore, very scanty and outdated data is available reporting

* Corresponding author. Department of Medical Laboratory Technology, Faculty of Applied Medical Science, Jazan University, Saudi Arabia.
E-mail address: msaboor@jazanu.edu.sa (M. Saboor)

the Hb concentrations in this area. Hence, this study was conducted with the purpose of evaluating the combined effect of age and altitude on Hb and red cell parameters.

2. Material and methods

In this cross-sectional comparative study, we retrospectively reviewed large data set of complete blood counts (CBCs) for mainly self-referred subjects done at a commercial clinical laboratory. These tests were done largely for health checkups or follow up of chronic diseases. Data were collected from two geographical areas: a moderately high-altitude, Abha city, (2,270 meters above sea level) from southwestern highland Saudi Arabia and sea level, Jeddah city, western Saudi Arabia. People of both genders were included as study population. This study was approved by the Institutional Review Board, King Khalid University, Abha, Saudi Arabia. (ECM#2020-0905). For the current study, being retrospective in nature, informed consent was waived off by the Institutional Review Board.

Subjects screened for inclusion were also tested for liver function tests, kidney functions tests, thyroid functions test, lipid profiles, and fasting blood sugar or Hb A1c. Subjects with abnormalities in the biochemical tests including liver, kidney, thyroid function tests or diabetes mellitus were excluded. For CBC, the following exclusion criteria were applied.

- Hemoglobin: for male population at Abha < 14.0 g/dl while < 13.0 g/dl of Jeddah population, for females of Abha and Jeddah < 13.0 and < 12.0 g/dl respectively. These cut off values were based on the WHO recommendations for definitions of anemia at different altitudes.[9]
- Mean cell volume (MCV): < 70 or > 95 fl for both genders.
- Red cell distribution width (RDW): > 16% for both genders.
- Total leukocyte count: < 3.5 or >11.5 × 10^9/L for both genders.
- Absolute neutrophil count: < 1 or > 7 × 10^9/L for both genders.
- Platelet count: < 150 or > 400 × 10^9/L for both genders.

For CBC analysis, venous blood samples were collected into liquid K3EDTA tubes and were processed within two hours of collection. The lab analysis follows unified standards in all branches using Sysmex automated analyzers (Sysmex corporation, Kobe, Japan) for complete blood counts.

CBCs were first filtered for abnormal results after excluding all abnormal CBC results and outliers, the normal CBCs were analyzed to study the trend with aging. For comparison of hemoglobin data were stratified into five age groups for both high altitude and sea level. Adolescents (12–18 years), younger adults aged 18–40 years, middle aged 41–60 years, older adults 61–80 years and elderly 81–100 years old. For the evaluation of effect of age and altitude of both genders data were divided in to two groups i.e. 12–60 years and more than 60 years.

2.1. Data analysis

The participants' data were de-identified for any personal information before importing to excel datasheet. After extraction, data were revised, coded, and fed into statistical software IBM SPSS version 22 (SPSS, Inc. Chicago, IL). Outliers and abnormal results were excluded from the final analysis. Statistical analysis was done using two-tailed tests. Descriptive analysis based on frequency and percent distribution was done for participants' residence area, age, and gender. Normal distribution assessment was applied for all scale parameters. Multivariate regression analysis was done to evaluate the effect of age, gender, and altitude on red cell parameters. p value of < 0.05 was considered statistically significant.

3. Results

In this study a total of 69,244 CBC results of males and female of Abha and Jeddah were included in the final data analysis. Comparing the mean (±SD) Hb among different age groups at both locations and genders showed slight increasing trend that declined with aging as shown in Figure 1. When red cell parameters of Abha male and female population were compared with Jeddah participants, all parameters showed statistically significant difference as shown in Table 1.

Overall, Hb levels had highly significant negative linear relationship ($p < 0.01$) with age ($r = -0.015$) and gender (-0.182) while

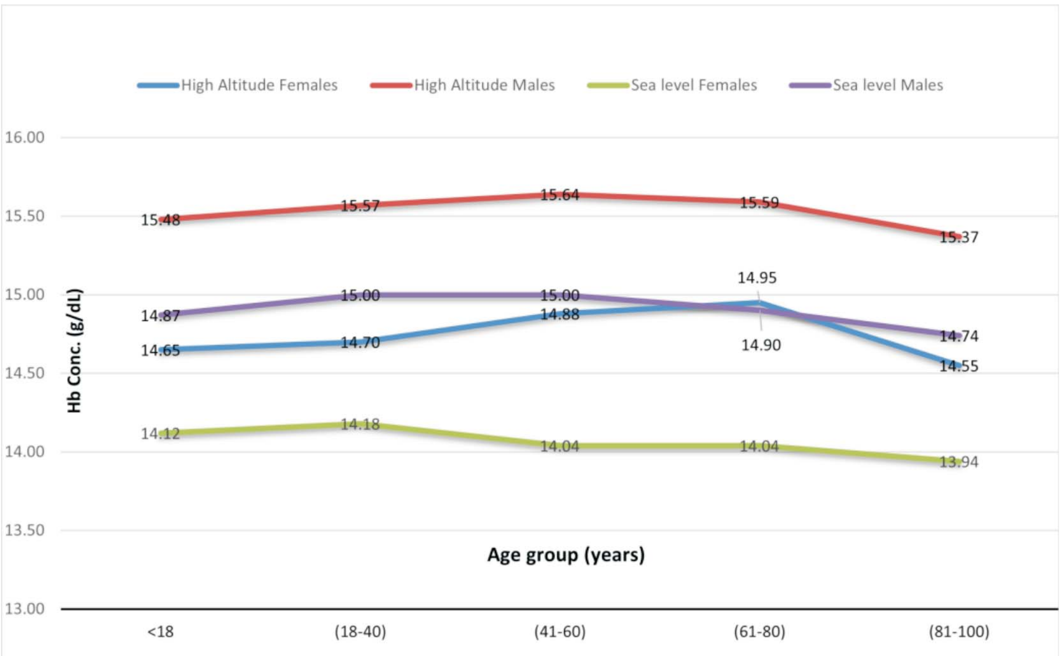

Figure 1. Mean hemoglobin concentrations (g/dL) among male and female participants of Abha city (altitude) and Jeddah city (sea level).

positive liner relationship with altitude (r = 0.071) as shown in Table 2. While comparing Hb in both cities, Jeddah population had more negative linear relationship (r = -0.011) with age than the Abha population (r = -0.014). Similarly, Hb levels also showed more negative linear relationship (r = -0.200) with gender in Jeddah population as compared to Abha population (r = -0.057). From the correlation of Hb in both cities it can be stated as the Hb level increases with an increase in altitude and this increment is maintained despite aging. Correlation of red cell count also showed overall negative correlation with age and gender while very strong positive correlation with altitude as shown in Table 2. Mean cell volume showed overall positive correlation with age while negative correlation with gender and altitude. Strong positive correlation of RDW was associated with age, gender and altitude.

Table 3 demonstrates the multivariate linear regression analysis of hematological parameters of the studied population. Hb level of an individual had statistically highly significant (p < 0.01) relation with the independent variables i.e. age, gender and altitude as shown in Table 3. Regression analysis shows that the Hb levels decrease with aging and increase with altitude. Females had low Hb levels and showed marked increase in their Hb levels at altitude as compared to males. Overall, 4.0% (Adjusted R2 = 0.040) variance among Hb levels were caused by the independent variables age, gender and altitude. All other parameters also showed similar trends as shown in Table 3. Table 4 shows the effect of age and gender on red cell parameters in Abha and Jeddah population separately.

4. Discussion

Several factors affect the hematological parameters in geriatric population including, but not limited to gender, life style, altitude, population, race, ethnicity and genetic adaptations.[9] This study considered two major factors, age and high altitude that directly alters hematological parameters.

Results of this study show that Hb level in geriatrics at high altitude had strong positive correlation as compared to individuals

Table 1
Comparison of red cell parameters among male and female participants of Abha and Jeddah.

Age group (years)	Male				Female			
	18–60 years		> 61 years		18–60 years		> 61 years	
Location	Abha (n = 2,329)	Jeddah (n = 25,550)	Abha (n = 382)	Jeddah (n = 5,157)	Abha (n = 3,345)	Jeddah (n = 28,127)	Abha (n = 351)	Jeddah (n = 4,003)
Hemoglobin (g/dL)	15.56 ± 1.18	14.95 ± 1.11*	14.74 ± 1.47	14.49 ± 1.27*	14.73 ± 1.39	13.85 ± 1.34*	14.5 ± 1.44	13.92 ± 1.26*
Hematocrit (%)	44.90 ± 3.45	43.70 ± 3.12*	42.45 ± 3.91	42.6 ± 3.52*	42.61 ± 3.56	40.89 ± 4.33*	41.90 ± 3.65	41.28 ± 3.47*
Red cell count ($\times 10^{12}$/L)	5.30 ± 0.5	5.13 ± 0.47*	5.27 ± 0.50	5.04 ± 0.47*	5.25 ± 0.51	4.96 ± 0.48*	5.19 ± 0.51	4.88 ± 0.48*
MCV (f)	80.25 ± 4.43	83.86 ± 4.56*	80.62 ± 4.59	84.70 ± 4.67*	80.03 ± 4.59	83.89 ± 4.61*	80.80 ± 4.68	84.67 ± 4.77*
MCH (pg)	27.92 ± 1.68	28.60 ± 1.77*	27.99 ± 1.62	28.82 ± 1.79*	27.86 ± 1.72	28.47 ± 1.77*	28.04 ± 1.77	28.54 ± 1.75*
MCHC (g/dL)	34.79 ± 1.24	34.12 ± 1.32*	34.71 ± 1.35	34.02 ± 1.32*	34.81 ± 1.31	33.95 ± 1.36*	34.67 ± 1.41	33.72 ± 1.35*
RDW (%)	13.74 ± 0.85	13.43 ± 0.88*	13.67 ± 0.86	13.55 ± 0.89*	13.76 ± 0.88	13.54 ± 0.88*	13.8 ± 0.86	13.64 ± 0.89*

Hb, hemoglobin; HCT, hematocrit; RBC, red cell count; MCV, mean cell volume; MCH, mean cell hemoglobin; MCHC, mean cell hemoglobin concentration; RDW, red cell distribution width.
Data are shown as mean ± SD.
* p values < 0.05.

Table 2
Correlation of red cell parameters among all participants.

Variables	Abha		Jeddah		Combined (Abha and Jeddah)		
	Age	Gender	Age	Gender	Age	Gender	Altitude
Hb	-0.014*	-0.057*	-0.011*	-0.200*	-0.015*	-0.182*	0.071*
HCT	0.003*	-0.067*	0.004*	-0.186*	0.004*	-0.174*	0.000*
RBC	-0.026*	-0.049*	0.000*	-0.164*	-0.026*	-0.049*	0.138*
MCV	0.054*	-0.022*	0.007*	-0.001*	0.083*	-0.012*	-0.233*
MCH	0.025*	-0.016*	0.045*	-0.044*	-0.066*	0.000*	-0.059*
MCHC	-0.046*	0.008*	-0.035*	-0.066*	-0.083*	0.000*	0.199*
RDW	-0.008*	0.018*	0.034*	0.054*	0.027*	0.054*	0.080*

* p ≤ 0.05.

Table 3
Results of multivariate linear regression (with step-wise forward selection) among total population.

Variable	Regression coefficients (standard error)				Adjusted R2	F(P)
	Constant	Age	Gender	Altitude		
Hemoglobin	14.92	-0.034	-0.189	0.077	0.040	0.000*
Hematocrit	44.31	-0.018	-0.177	0.006	0.031	0.000*
Red cell count	5.12	-0.057	-0.160	0.142	0.045	0.000*
Mean cell volume	86.72	-0.073	-0.200	-0.233	0.059	0.000*
Mean cell hemoglobin	28.05	0.006	-0.293	0.0001	0.10	0.000*
Mean cell hemoglobin concentration	34.17	-0.004	-0.273	0.001	0.048	0.000*
Red cell distribution width	13.01	0.080	0.055	0.037	0.006	0.000*

Independent variables age, gender and altitude showed 4.0%, 3.1%, 4.50%, 5.40%, 1.0%, 4.8% and 0.6% overall variance with hemoglobin, hematocrit, red cell count, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration and red cell distribution width.
* Statistically significant p < 0.05.

Table 4
Results of multivariate linear regression (with step-wise forward selection) among Abha and Jeddah population.

Variable	Abha					Jeddah				
	Regression coefficients (standard error)			Adjusted R^2	F(P)	Regression coefficients (standard error)			Adjusted R^2	F(P)
	Constant	Age	Gender			Constant	Age	Gender		
Hb	14.97	-0.001	-0.057	0.003	0.000	15.18	-0.036	-0.204	0.040	0.000
HCT	43.07	0.004	-0.067	0.004	0.000	44.52	-0.019	-0.188	0.035	0.000
RBC	5.41	-0.033	-0.053	0.002	0.000	5.27	-0.002	-0.203	0.031	0.000
MCV	79.48	0.007	0.008	0.003	0.000	82.80	0.008	0.078	0.006	0.000
MCH	27.77	0.025	-0.192	0.000	0.000	28.55	0.039	0.040	0.020	0.000
MCHC	34.96	-0.046	-0.079	0.002	0.000	34.48	-0.044	-0.072	0.004	0.000
RDW	13.98	0.001	0.115	0.002	0.000	13.23	0.041	0.059	0.003	0.000

Hemoglobin and red cell parameters in Jeddah's participants were found to be more effected as compared to Ahba population as shown by the adjusted R^2 and F values.

at sea level while strong negative correlation with age. This finding is accordance with previous published reports.[10,11] Hemoglobin levels in Abha population was found to be increased as compared to Jeddah population in both genders. Increased Hb and erythrocytosis at high altitude could be explained on the basis of a complex and well-organized mechanism. Hypoxia induced erythropoiesis occurs through a series of well-integrated yet complex mechanism through interplay of hypoxia-inducible factor (HIF) and erythropoietin. Hypoxia-inducible factor (HIF) is a heterodimer composed of α and β. Erythropoietin gene contains hypoxia-responsive elements (HREs). In hypoxia, the α-β heterodimer of HIF binds with HREs and stimulates the synthesis of erythropoietin (EPO). Release of erythropoietin leads to the proliferation, differentiation and maturation of erythroid precursors leading to erythrocytosis and increased Hb.[12–14]

Elevated Hb level at high altitude is not limited to adult population. A study conducted in Abha in 1996, reported the increased concentration of Hb in newborns in Abha as compared to newborn at low altitude (Riyadh and Jeddah).[15] While in another study comparing Hb levels in children between low altitude (Mohyel and surrounding villages located at 500 m above sea level) and high altitude (Alsoda and the villages around Sabit Allia, located at 2,800–3,150 m above sea level) the same differences were noted being increased in highlanders and decreased in lowlanders.[16] Studies suggest a genetic adaptation towards relatively lower Hb in people living at high altitude. It has been found that native highlanders and long-term residents at high altitude has significant differences in their Hb level. This finding is supported by the difference between Hb level of Tibetan as compared to Han Chinese who moved to Tibet. The scientific justification of low Hb in Tibetan people is the presence of missense mutations in EGLN1 gene that encodes PHD2. PHD2 synthesized by mutated EGLN1 gene leads to reduced levels of HIF-2α that causes low levels of erythropoietin and consequently decreased erythropoiesis. Tibetan people do not present with erythrocytosis even living at high altitude as compared to Han Chinese or other highlanders.[14]

Effect of altitude on the red cell parameters also depends on the extent of height. It has been reported that, although, median values of red cells, Hb and hematocrit noted at altitude of 1869 m (Erzurum, Turkey) were slightly high, the difference was statistically insignificant.[17]

In the current study, MCV also showed differences in both genders at high altitude and sea level. Increase in the MCV was observed in all groups. Increase in the MCV was more pronounced in geriatrics at sea levels as compared to highlanders. Increased MCV with increasing age has also been reported by others.[18] One of the possible reasons of high MCV may be vitamin B_{12} deficiency that occurs in more than 20% elderly individuals.[8] However, it is to be noted that many a times, vitamin B_{12} deficiency remains undetected with potential to develop clinical consequences. Myelodysplastic syndrome, one of the causes of macrocytic anemia, is most common in geriatrics, which may not present with the classical features but with unexplained anemia.[19] Interestingly, value of MCV was high in Jeddah population as compared to Abha, that needs further exploration. Possible explanations may include a higher prevalence of occult iron deficiency at altitude compared to sea level that may be driven by hypoxia associated erythrocytosis and hyperactive bone marrow. The serum ferritin was not assessed in this study. Although overt microcytosis (< 70 fl) were excluded, occult iron deficiency might still exerts some effect on the MCV which could explain some of the intergroup difference in this study.

RDW values also showed differences in male and female groups at high altitude as well as sea levels. Although, there was statistically significant difference in the RDW values of Abha and Jeddah population, the values of both groups did not cross the upper limit of the established normal limit. This finding is in contrast of one study that reported increased RDW with aging.[20] In addition to MCV, other factors found in geriatric population have also shown association with increased RDW e.g. aging, nutritional deficiencies, oxidative stress due to chronic disorders and inflammation.[21]

Findings of this study show that mean values of Hb declined in male group both at high altitude and sea levels with aging. Decline in the level of Hb and red cell count with aging is also reported in other studies.[9,18,20] In addition to other factors, geriatrics have reduced hematopoietic activity. Elders have reduced bone marrow cellularity as compared to children and adults.[22] Stem cells can divide finitely leading to their decreased replicative capability with aging.[18,23,24] Defects in the proliferation of progenitor cells is another factor of lower hematopoietic activity in elders. It is interesting to note that, although, the number of erythroid and myeloid progenitors declines in both genders the reduction is more pronounced in males as compared to females.[18] This finding is also supported by the observations of the current study as shown in Table 4. It has also been reported that hormonal stimulation of the bone marrow hematopoietic tissues diminishes in old age.[5] In addition to other vital roles, testosterone also promotes erythropoiesis.[22] It has been found that low level of testosterone leads to reduced levels of Hb. Two possible mechanism have been presumed regarding the stimulation of erythropoiesis by testosterone i.e. the production of hematopoietic growth factors and/or increased availability of iron. It has been postulated that testosterone act on polychromatophilic erythroblasts in the bone marrow resulting in their multiplication and maturation. Administration of testosterone suppresses hepcidin that leads to increased iron absorption promoting erythropoiesis.[19] Additionally, in older age, the requirement of oxygen decreases due to reduced body mass and less physical activity, this also contributes in decline of Hb in geriatric population.[18] In females, in addition to the above possible mechanisms, other reasons of low Hb may be decreased iron stores, reduced muscle mass and low metabolic activity.[20,25]

In our study, we used the cut off values for inclusion, i.e. exclusion of anemia patients, that was derived from WHO recommendations.[9] For an altitude of 2,270 meters a 1 g/dL (10 g/L) were used as per the WHO recommendations (14 g/dL for males and 13 g/dL for females). However, the mean hemoglobin difference between the same gender at either altitude was ranging from 0.5 to 0.6 g/dL (Figure 1, Table 1). Since, adaptation to altitude is different among different regions and populations, the generalizability of WHO was shown not to be linear and has been questioned.[26] Our study was meant to compare the trend with aging at two different altitude, hence, we do not think this difference in inclusion will affect the conclusion of the study. Nonetheless, it is important to establish reference ranges based on local population studies for both young and old population.

4.1. Limitation of the study

A major limitation of the study was the retrospective laboratory records review with no demographic and clinical information. However, the strict exclusion criteria are believed to minimize the bias of the study.

5. Conclusion

Hemoglobin and red cell parameters are greatly affected by aging and altitude. While sex difference appears to diminish with aging, altitude difference persists, which suggest that for defining anemia, the Hb cut off values in geriatrics shall be better defined according to the local population.

Acknowledgments

The authors extend their appreciation to the Research Center for Advanced Materials (RCAMS) at King Khalid University, Abha, Saudi Arabia for supporting this work through the research group program under grant number RCAMS/KKU/001/20. The authors also thanks to Dr. Rama Mohan Chandika, Faculty of Applied Medical Sciences, Jazan University, Saudi Arabia for statistical analysis.

Financial and non-financial conflicts of interests

The authors declare that they have no competing interests.

References

1. Yeo EJ. Hypoxia and aging. *Exp Mol Med*. 2019;51(6):1–15.
2. Jaiswal S, Ebert BL. Clonal hematopoiesis in human aging and disease. *Science*. 2019;366(6465):eaan4673.
3. Kovtonyuk LV, Fritsch K, Feng X, et al. Inflamm-aging of hematopoiesis, hematopoietic stem cells, and the bone marrow microenvironment. *Front Immunol*. 2016;7:502.
4. Geiger H, de Haan G, Florian MC. The ageing haematopoietic stem cell compartment. *Nat Rev Immunol*. 2013;13(5):376–389.
5. Roy CN, Snyder PJ, Stephens-Shields AJ, et al. Association of testosterone levels with anemia in older men: A controlled clinical trial. *JAMA Intern Med*. 2017;177(4):480.
6. Zakai NA, Katz R, Hirsch C, et al. A prospective study of anemia status, hemoglobin concentration, and mortality in an elderly cohort: The cardiovascular health study. *Arch Intern Med*. 2005;165(19):2214–2220.
7. Goodnough LT, Schrier SL. Evaluation and management of anemia in the elderly. *Am J Hematol*. 2014;89(1):88–96.
8. Wong CW. Vitamin B12 deficiency in the elderly: Is it worth screening? *Hong Kong Med J*. 2015;21(2):155–164.
9. World Health Organization. *Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity*. Geneva, Switzerland: World Health Organization; 2011. Available at https://apps.who.int/iris/handle/10665/85839. Accessed March 6, 2021.
10. Al-Hashem FH. Pattern of haemoglobin among high and low altitude children of southwestern saudi arabia. *J Family Community Med*. 2006; 13(1):35–40.
11. Kaya H, Kiki İ, Akarsu E, et al. Hematological values of healthy adult population living at moderate altitude (1869 m, Erzurum, Turkey). *Turk J Haematol*. 2000;17(3):123–128.
12. Mahlknecht U, Kaiser S. Age-related changes in peripheral blood counts in humans. *Exp Ther Med*. 2010;1(6):1019–1025.
13. Sharma D, Suri V, Pannu A, et al. Patterns of geriatric: A hospital-based observational study in North India. *J Family Med Prim Care*. 2019;8:976–980.
14. Nah EH, Kim S, Cho S, et al. Complete blood count reference intervals and patterns of changes across pediatric, adult, and geriatric ages in Korea. *Ann Lab Med*. 2018;38(6):503–511.
15. Lippi G, Mattiuzzi C, Cervellin G. Learning more and spending less with neglected laboratory parameters: The paradigmatic case of red blood cell distribution width. *Acta Biomed*. 2016;87(3):323–328.
16. Berkahn L, Keating A. Hematopoiesis in the elderly. *Hematology*. 2004; 9(3):159–163.
17. Wagner W, Bork S, Horn P, et al. Aging and replicative senescence have related effects on human stem and progenitor cells. *PLoS One*. 2009; 4(6):e5846.
18. Mandala WL, Gondwe EN, Maclennan JM, et al. Age- and sex-related changes in hematological parameters in healthy Malawians. *J Blood Med*. 2017;8:123–130.
19. Waterstrat A, Van Zant G. Effects of aging on hematopoietic stem and progenitor cells. *Curr Opin Immunol*. 2009;21(4):408–413.
20. Al-Sweedan SA, Alhaj M. The effect of low altitude on blood count parameters. *Hematol Oncol Stem Cell Ther*. 2012;5(3):158–161.
21. Gonzales GF. Serum testosterone levels and excessive erythrocytosis during the process of adaptation to high altitudes. *Asian J Androl*. 2013; 15(3):368–374.
22. Khan MU, Amir SED, Aggerwal S. Hemoglobin levels and blood groups in persons living at a high altitude. *Ann Saudi Med*. 1989;9(5):458–462.
23. Heinicke K, Prommer N, Cajigal J, et al. Long-term exposure to intermittent hypoxia results in increased hemoglobin mass, reduced plasma volume, and elevated erythropoietin plasma levels in man. *Eur J Appl Physiol*. 2003;88(6):535–543.
24. Yang M, Su H, Soga T, et al. Prolyl hydroxylase domain enzymes: important regulators of cancer metabolism. *Hypoxia (Auckl)*. 2014;2:127–142.
25. Bassuni W, Asindi AA, Mustafa FS, et al. Hemoglobin and hematocrit values of Saudi newborns in the high altitude of ABHA, Saudi Arabia. *Ann Saudi Med*. 1996;16(5):527–529.
26. Gassmann M, Mairbäurl H, Livshits L, et al. The increase in hemoglobin concentration with altitude varies among human populations. *Ann N Y Acad Sci*. 2019;1450(1):204–220.