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PRECISION MEDICINE: CUSTOMIZED HAEMATOLOGICAL REFERENCE INTERVALS FOR NAKURU COUNTY'S DIVERSE POPULATION

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Abstract

Haematology reference intervals play a crucial role in clinical laboratory systems, serving as the cornerstone for healthcare provision and diagnostic procedures. This paper explores the significance of reference hematological parameters in disease screening, diagnosis, and the detection of blood disorders. The establishment of these reference intervals involves utilizing blood specimens and assigning values obtained from research studies to specific intervals. These intervals encompass the upper and lower reference limits, typically defined at the 95% confidence level. The comprehensive understanding of haematological reference intervals is vital for ensuring accurate and effective healthcare management.

1.0. Introduction

Haematology reference interval values are a part of the clinical laboratory systems which have a worldwide responsibility of providing health care to the populations of which they are derived and also elsewhere in the world (Kratz et al., 2004). A blood specimen is usually used to estimate these haematological reference intervals values. Reference hematological parameters are important for screening and diagnosis of diseases and also in detecting blood disorders (Haileamlak et al., 2012). The laboratory results become more practical when values obtained from research studies are then assigned to interval of values (Mohammad et al., 2011). The term reference intervals refer to the values within the upper and lower reference limit and it also includes the upper and the lower reference limits defined by a certain percentage usually 95% (Zeh et al., 2011).

The use of reference values obtained elsewhere and utilized to manage a different group of people from which it was obtained has been questioned owing to the noted differences from various studies (Lugada et al. 2004). This suggests a need to provide values for a particular population in order to improve patients care (Koram et al., 2007). There are however few clinical laboratories that have established their own reference ranges particularly in Africa and clinician has continued to use the European and American established reference values (Ferre et al., 1999).

The Clinical Laboratory and Standards Institute and the International Federation of Clinical Chemistry both recommend that each laboratory establishes its own reference ranges for each parameter (Clinical Laboratory

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and Standards Institute, 2008: Jagalinec et al., 1998). In establishing reference values the data may come from healthy population such as those visiting hospital clinics for routine checkup or as volunteer blood donors or may be obtained from patients' records with an assumption that the patients were healthy (Ferre et al., 1999). Laboratory reference values including Haematological reference intervals are essential for clinical practice but there is insufficiency data for African populations including Kenya (Alexander et al., 2011). Clinical trials have been taking part in African countries due to increase of the infectious diseases such as tuberculosis, HIV/AIDS and other endemic diseases such as soil helminthes to try to ease the disease burden (Jaoko et al., 2008; UNAIDS 2010). Accurate laboratory reference intervals are very important tools in clinical care and also in clinical trials for drug therapy and adverse effects but are unavailable for most African populations especially when they are required to participate in clinical trials (Zeh et al., 2011).

The reference interval values commonly used for clinical diagnosis and research in sub-Saharan Africa and Asia are from the western countries despite the fact that differences have been noted for these values from one region to another due to age, gender, altitude, ethnicity, environmental exposure and infections (Tugume et al., 1995: Kibaya et al., 2008). Some of the white blood cell parameters such as monocyte and eosinophil levels are higher in African population when compared to the European and the American white populations while neutrophils are lower. This is most probably due to chronic exposure to soil helminths, malaria and schistosomiasis which are endemic in African countries (Zeh et al., 2011, Gill et al., 1995).

Females have indicated higher haematological levels for RBC, Hb and Hct, MCV and MCH with increased values for the adult females as compared to adult males in African populations (Karita et al., 2009, Koram et al., 2007). Age differences were also noted with male adults having higher levels than male adolescents for the red blood cell parameters (Zeh et al., 2011). This concurs with western population for adolescents (Omosa-Manyonyi et al., 2011). Platelet counts have showed increased reference values for adults than the adolescents among the Africans. Gender differences also exist for the platelet values with females having higher values than male which is influenced by hormonal differences and menstrual blood in females (Zeh et al., 2011).

WBC counts, neutrophil counts and lymphocytes have showed lower values in reference intervals than the western values. The WBC counts are increased in females compared to their male counterparts both African and Caucasian populations (Karita et al., 2009, Saathoff et al., 2006). Statistical differences in age have shown that adolescents have higher WBC counts than the adults (Lugada et al., 2004). Higher median levels for monocytes, basophil and eosinophil counts than the western reference values have been shown in East African studies done both in Kenya and Uganda (Lugada et al., 2004; Zeh et al., 2011).

Haematological reference intervals are lacking for most African countries including Kenya and despite this, clinicians have been using the same reference values which have been established from Caucasian populations in patient care and in clinical trials which have proved different (Jaoko et al; 2008). As many people from African continue to participate in many clinical trials it is important to establishment reference intervals to suit such trials. Clinical reference intervals which are not applicable to a particular population may lead to exclusion of people who would otherwise have participated making the process of clinical trials difficulty, very costly, and the results less representative which also applies for the toxicity tables (Eller et al., 2008): Karita et al., 2009).

Previous studies conducted in Kenya on haematological reference intervals both in Kisumu and in Kericho indicated differences in a number of haematological parameters, which suggests the need for the establishment of reference values for specific geographical regions (Zeh et al., 2011). These factors prompted this study in order to obtain reference interval values for Nakuru county population to ensure that the healthy participants who

intend to participate in clinical trials are not left out of such trials and for proper diagnosis and management of haematological diseases within the community.

2.0. Materials and Methods 2.1. Study area and population

The study was conducted in Nakuru County which is one of the forty seven Counties in Kenya. Nakuru County lies at an altitude of 1850m above sea level with a population of approximately 1, 603325 according to 2009 census conducted in Kenya.

The County is located about 165 km from Nairobi and is a major agricultural centre due to its rich volcanic soil which accommodating nearly any kind of farming. It is a cosmopolitan County, with its population originating from all the major tribes of Kenya predominantly the Kikuyus and Kalejins. The study utilized a cross sectional design where blood samples were collected from volunteer donors who were randomly selected from all over Nakuru County and later analyzed in the laboratory for determination of haematological measures. The study population was adolescents (12-18 years, WHO, 2013) and adult (19-55 years, who are eligible for blood donation in Kenya) and also residents of Nakuru County for at least three years with no signs of acute or chronic illness, normal blood pressure, no history of drug taking, non smokers, those who provided informed consent or assent in case of a minor and also those who agreed to participate in the study by signing a written consent.

2.2. Sample collection

Seven milliliters (mls) of blood samples was collected in ethylenediamine tetra acetic acid (EDTA) vacutainer tubes between twelve and two o´clock, transported in cool boxes to the laboratory and analyzed within 4 hours of collection to minimize variations of the hematological parameters. Urine specimens were obtained from all female participants for pregnancy testing for the purpose of exclusion from the study. Stool samples were also collected from all participants to rule out parasitic infections that may cause variations in the blood parameters.

2.3. Laboratory procedures

All samples were analyzed at Rift Valley Provincial General Hospital laboratory which is a level five hospital currently undergoing accreditation. Upon arrival in the laboratory, all samples were analyzed according to the stipulated procedures. Blood was tested for infections by use of rapid test kits as directed by the manufacturers of that kit which included HIV/AIDS, the first testing kit being determine (Alere Medical Co., Ltd, Chiba, JAPAN) and the confirmatory test being the first response (Premier Medical Corporation Private Limited, Gujarat, INDIA); hepatitis B virus, hepatitis C antigen, (EUROMEDI EQUIP LTD, West Harrow U.K); presence of syphilis (Guangzhou Wondfo Biotech Co., LTD. Science city, CHINA) and pregnancy test (EUROMEDI EQUIP LTD, West Harrow U.K). The stool specimen was examined by wet preparation method and all positive samples results to any of these tests were discarded and the samples which were negative were utilized for the study.

Haematological tests was analyzed using automated haematology analyzer (Quinttus, Boule Medical AB, Spånga, Sweden) which works on impendence principle for counting of the WBC, RBC and PLT and their indices.

The instrument automatically counts and gives a printout result of erythrocytic parameters (RBC (10^{12}/L), Hb (g/dL), PCV (%), MCV (fl), MCH (pg), MCHC (g/dL)), and RDW %., thrombocytic indices (PLT (10^9/L,), PDW (fl), MPV (fl)) and leukocytic indices (WBC count (10^9/L), (neutrophils (10^9/L), lymphocytes (10^9/L), eosinophils (10^9/L), basophils (10^9/L), monocytic cells (10^9/L) and WBC differentials in %. An internal quality control was performed on the hematological equipment (Quinttus) every morning before any blood test was done using the quality control samples supplied by the manufacturers for that particular equipment. The analytical sessions in the current study were 22 in total. Quality control results for the analyzed parameters were within the

specific assigned QC range of target value ± 2 standard deviations (SD). In case of any discrepancies a trouble shooting was performed until the testing passed. The results were also compared by using different back up haematology equipment. A blood film was also prepared which was stained with Giemsa method of staining the blood films in order to detect abnormalities of blood cells such as hypochromia), leukaemia, sickle cells, malaria parasites and other blood parasites and for those found positive, participants were referred for further management

2.4. Ethical Considerations

Scientific, ethical approval and authorization of the study was obtained from Kenyatta University (ethics review committee), the National committee of science and technology and the Ministry of health, Nakuru County. Consent to obtain the samples obtained from the participants and for the minors; assent was sought first from the minor and then from the guardian both of whom signed the assent forms (one for the minor and the other one for the parents/guardian). The results and any other information regarding the study were held in total confidentiality both by the investigator and Kenyatta University administration by placing them in lockable cabinets and were only accessed by authorized persons.

2.5. Data Analysis and Presentation

Data generated from the laboratory assays was dual entered and was analyzed statistically using a Statistical Package for Social Sciences (SPSS version 21). The data was grouped according to age and gender with adolescents aging between 13 to18 years and 19 to 55 years for the adults. The measure of the central tendency was the median, where the 2.5 and 97.5 percentiles specified the 95% reference interval for the data. Further a parametric method (ANOVA) was used to establish the reference intervals (Rhoads, 2007b). Comparisons in the hematological measures across the study groups were performed using the ANOVA test (post hoc anlysis). All tests were two-tailed and an alpha-value of 5% was used to determine the statistical inferences.

3.0. Results

The number of the participants recruited in to the study were 627 who included the adults (male, n=252; female, n=134) and adolescents (male, n=128; female, n=113). The erythrocyte median and reference indices (RBC count, $P < 0.0001$; Hb, $P < 0.0001$; HCT, $P < 0.0001$; and MCHC, $P < 0.0001$) were significantly different across the study groups with males having higher values than females for both adults and adolescents. Statistical differences were also observed by age for Hb, RBC, HCT, and MCHC with adult males having higher values than male adolescents ($P < 0.0001$). The female values for both adults and adolescents were however similar. The reference interval values for the absolute monocytes counts were higher in females than male for both adults and adolescents across the study groups and the levels were statistically significance ($p < 0.05$). Age differences were also noted with female adolescents having higher values than the female adults ($P<0.0001$) with no differences noted among the males. The absolute values for WBCs, lympocytes, neutrophils were similar. Females had higher reference values for absolute platelet counts than males for adult and adolescents and the values were statistically significance ($P < 0.0001$). Further analysis indicated statistical significance within study groups between female adolescents and male adolescents ($P < 0.0001$) with females having higher values while the ones for the adults were statistically the similar.

Table 1. Heamatological reference intervals for adolescents and adults in Nakuru County

Characteristics	Adolescents			Adults			P
	Male, n=128	Female, n=113		Male, n=252	Female, n=134		
RBC×10^{12}/L	5.3 (4.0-6.4)	4.8 (3.5-6.1)	0.000	5.5 (5.0 – 5.9)	5.0 (4.6 – 5.5)	.003	<0.0001
Hb, g/dl	15.1 (12.2-18.0)	13.2 (10.7-15.7)	0.000	15.1 (12.1-17.3)	13.1(10.4-15.8)	.146	<0.0001
Hct, %	46.1 (39.6-53.0)	41.6 (29.0-54.8)	0.000	43.9 (32.7-53.3)	43.3 (28.6-43.1)	.001	<0.0001
MCV, fl	85.8 (65.5-106.3)	85.2 (59.6-109.0)	.290	86.1 (76.1-94.5)	85.5 (68.0-104.2)	.225	0.484
MCH, pg	28.7 (23.4-34.0)	30.6 (19.6-30.5)	.338	28.4 (16.6-40.5)	29.1 (18.6-39.6)	.389	0.034
MCHC, %	32.5 (29.4-35.6)	31.9 (23.5-31.9)	0.000	32.7 (29.1 - 35.9)	32.2 (29.2-35.8)	.808	<0.0001
WBC (×10^9 /L)	5.4 (2.8-8.2)	5.0 (2.5-7.7)	.088	5.7(2.6-8.0)	5.0 (2.5-7.9)	.132	0.567
Lymphocytes (×10^9 /L)	2.1 (1.5-3.5)	2.2 (0.9-3.7)	.994	2.1(1.2-3.2)	2.1 (1.0-3.4)	.301	0.562
Neutrophils (×10^9 /L)	2.1 (0.3-4.3)	2.3 (0.5-4.5)	.014	2.1 (0.4-4.2)	2.4 (0.4-4.4)	0.004	0.074
Monocytes (×10^9 /L)	0.4 (0.0-4)	0.4 (0.0-0.9)	.715	0.2 (0.1-0.5)d	0.2(0.2-0.7)	0.034	<0.0001
Eosinophils (×10^9 /L)	0.1 (0.0-0.6)	0.1 (0.0-1.0)	.894	0. 1 (0.0 - 0.3)e	0.1 (0.0-0.2)	.291	0.036
Platelets(×10^9 /L)	228.0 (107.0-405.0)	272.0 (97.0-430.0)	000	296.0 (104.0-436.0)	324.0(96.3433.6)	0.074	.213

Data presented are median and reference value (mean ± 2SD). RBC, red blood cell; HB, haemoglobin; HCT, haematocrit; MCV, mean cell volume; MCH, mean cell haemoglobin; MCHC, mean cell haemoglobin concentration; WBC, white blood cell.

3.2. Comparison of reference ranges between the current and previous studies

Absolute RBC count, HB and HCT tended to be lower in this study than in the U.S based comparison intervals. Similar findings have previously been observed in healthy populations in Uganda, South Africa, Central Africa and Kericho, Kenya. Other RBC parameters such as MCV among others were similar with those from the previous studies. The WBC parameters were lower in this study than those for the western values except for the monocyte count which is slightly elevated. Lower WBC parameters compared to western reference intervals have also been reported in other African populations including Ethiopia, Uganda, Central Africa. In contrast, the monocytes counts in the current study were elevated relative to other African studies and also the U.S.-based studies. The platelet reference values are lower than the US based studies. This has also been reflected in other African studies.

Table 2. Comparison of haematological reference ranges between the current and previous studies

	Current study	Kenya(kibaya 2009)	Ethiopia(Tsegaye, 1999)	Uganda(Eller 2008)	C. Afr(manard 2003)	S. Africa	U. States & European (Kratz 2009)
RBC count $\times 10^{12}$/L							
Male	5.0-5.9	4.3-7.5	4.3-5.9	3.8-6.0	4.5.6.1	3.2-5.8	4.5-5.9
Female	3.4-5.5	6.4-6.3	3.7-5.2	3.7-5.3	3.4-5.4	3.0-5.3	4.0-5.2
HB (g/dl)							
Male	12.1-17.3	8.3-11.3	13.9-16.8	11.1-16.8	12.3-17.3	10.3-16.7	13.5-17.5
Female	10.4-15.8	5.9-10	12.2-16.6	10.1-14.3	9.1-14.9	9.0-15.2	12.0-16.0
HCT (%)							
Male	32.7-53.3	40.0-50.0	41.6-55.1	32.2-47.8	39.0-52.0	30.0-52.5	41.0-53.0
Female	28.6-43.1	30.0-50.0	35.3-48.8	29.6-41.4	28.0-44.0	27.3-47.2	36.0-46.0
Absolute leucocyte counts $\times 10^{9}$/L							
WBC	2.6-8.0	2.8-8.2	3.0-10.2	3.4-8.7	3.4-8.7	3.2-12.6	4.5-11.0
Lympocytes	1.2-3.2	1.1-3.4	1.0-3.5	1.4-4.2	1.4-4..2	1.2-3.7	1.0-4.8
Neutrophils	0.4-4.4	0.9-4.7	1.0-7.1	0.8-3.4	NA	1.0-5.3	1.8-7.7
Monocytes	0.2-0.8	0.1-0.6	0.2-0.7	0.2-0.6	NA	0.2-0.8	0-0.8

Data presented are median and reference value (mean ± 2SD). RBC, red blood cell; HB, haemoglobin; HCT, haematocrit; MCV, mean cell volume; MCH, mean cell haemoglobin; MCHC, mean cell haemoglobin concentration;

WBC, white blood cell

4. Discussion

Haematological reference interval values are important in clinical care and research and therefore appropriate interpretation of these values will aid in the management of the population from which they have been derived (Kibaya et al., 2008; (Tugune et al., 1995; Solberg et al., 2001). The study showed that the reference intervals for

the HB, RBC count, HCTt and (MCHC) in female adults were lower compared to male adults and adolescents but were higher relative to female adolescents and they were statistically significance. The results concure with other similar studies from western and also African countries (Koram et al., 2007; Mwinga et al.,2009). The differences between male and female values are associated with nutritional deficiency with prevalence of iron deficiency anaemia in women probably as a result of menstrual blood loss as well as hormonal influences on haemopoesis where estrogen lowers haemoglobin by hemodilution and testosterone increases the plasma volume in males (Lewis, et al., 2006; Zeh et al., 2012).

Age differences for the RBC, HCT and MCHC was also observed among male participants, with adults having higher levels compared to male adolescents in the current study which are consistence with other African studies (Zeh et al., 2011). Similar results were also reported in a Caucasian adolescents study (Romeo et al., 2009). This difference may be associated the presence androgen hormone which is found in larger amount in older males than in the young males. Increased levels in older males are also associated with an increase in the size and mass of muscle fibers hence an increase in the number of circulating red blood cells (Zeh et al., 2012). The females indicated no age difference for the said parameters which may support the above idea. The MCV showed neither gender nor age related statistical differences unlike other studies which showed statistical differences (Zeh et al., 2011).

The haematological reference intervals for RBC parameters in the current study are higher in comparison to other Kenyan haematological studies. The differences may be attributed to many factors such as methodology, type of study population used and environmental factors among others. The current study for instance investigated helminthes infestations and malaria which causes chronic blood loss while the other tests did not. Also some regions like Kisumu where one study was performed is a malaria endemic zone which accounts for low Hb levels in the population. The Nakuru County where the current study was carried out is a rich agricultural area and therefore a balanced diet may account for the higher RBC values compared to Kericho and Kisumu where food crop farming is not a major occupation. Altitude can also affect these hematologic parameters and has been associated with reduced red blood cell components (Wintrobe et al., 1999) which may account for differences in reference values in the Kenyan studies. These study areas are located in different geographical zones with Kisumu County in lowest altitude hence low values for haemoglobin than Nakuru County.

The results for all RBC parameters were lower in comparison with the commonly used European and the American reference interval values. Studies in Kenya indicated similar observations for the red blood cell parameters

(Kibaya et al., 2008; Zeh et al., 2011), Uganda (Luganda et al., 2004), Ethiopia (Saathoff et al., 2008) and Tanzania (Tsegaye et al., 1999). The reason for these reduced RBC components is attributed to lower dietary iron intake, genetic variants, chronic blood loss, and chronic exposure to endemic parasites, environmental and ethnic factors which were not tested in these studies and has been shown to be common for African populations.

Most WBCs parameters indicated no statistical significance both for gender and age except for the reference intervals for absolute monocytes counts which were higher in females than male adolescent and male adults. The values were however lower than those from Caucasian populations (Zeh et al., 2011; Eller et al., 2008). Age differences were also noted with female adolescents having higher values than the female adults. Previous studies however indicated no gender or age differences (Zeh et al., 2011; Kibaya et al., 2008; Karita et al., 2009). This is purported to be as a result of endemic parasitic infections or exposure to environmental allergens (Abdulkarir 1999; Luganda, et al., 2004). Unlike in other similar African studies Eosinophils reference values were not elevated which may be due to the fact that some parasites such as malaria and hookworms were investigated in

the current study and those participants found infected were excluded from the study. The values differs with other African populations studies which shows increased eosinophil counts in both genders compared to the western values reference intervals (Zeh et al., 2011; Karita et al., 2009).

The results from other studies are attributed to prevalence of parasitic infections such as schistosomiasis, helminthes and malaria African populations (Saathoff et al., 2008; luganda et al., 2004) and the failure to test for the infections in most studies.The current study intervals for the WBC parameters would mean that the study population would be said to have had adverse effects due to the low values of most parameters. The decisions to initiate and continue, or change antiretroviral therapy regimens are determined using the lymphocyte subsets such as CD4 count and therefore correct lymphocyte reference intervals for a particular population will be appropriate to avoid patient mismanagement.

Gender differences have been noted for absolute platelet counts with higher values in females than males which concur with other studies regardless of ethnicity (Tikly et al., 1987; Bain et al., 1996). This has been attributed to hormonal influences (Tikly et al., 1987). The values were however lower when compared to the Western populations which is consistent in several African studies (Bain 1984; Tsegaye et al., 1999). The causes are however not known but factors such as dietary, environmenta, malaria and genetics have been indicated as the probable cause (Ngowi et al., 2009).

5. Conclusion

There was variation among the data sets for haemoglobin, RBC count, HB, HCT, MCH and MCHC across gender and age groups with female indicating lower levels than the males. In addition, adolescents had increased levels than the adult for these parameters. The WBC parameters as well as platelets showed lower levels compared to those on currently used guidelines with adolescents having higher reference values than the adults. Platelet parameters varied across gender and age with females showing higher values than the males for both adults and adolescents. The reference intervals therefore need to be adjusted to suit the local populations for proper client management and for use in clinical trials

Acknowledgement competing interests the authors declare no competing interests.

Authors' contributions

TW,SWK and NM were involved in the study conceptualization, design, data collection, data analysis, manuscript writing and editing. All the authors read and approved the manuscript.

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