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Estimation of Reference Values for Liver Function Tests for Adult Population in North-Rift Valley, Kenya

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Abstract: The aim of this study was to determine age and sex based reference ranges for eight liver function biochemical parameters for the adult population of North Rift Valley region. This was a population based cross-sectional study carried out at Moi Teaching and Referral Hospital in collaboration with the Regional Blood Transfusion Center, North Rift. A total of 400 volunteer blood donors were screened and 367 (211 males and 156 females) free from human immunodeficiency virus, hepatitis B and C virus, and syphilis were used in the analysis. Cobas Integra® 400 plus was used to analyze the eight liver function clinical chemistry parameters. Reference ranges were constructed using nonparametric methods to estimate 2.5 and 97.5 percentiles of distribution as lower and upper reference limits, respectively. Significant age specific differences in the North Rift Valley Kenyan reference ranges were observed for alkaline phosphatase, alanine aminotransferase, gamma glutamyltransferase while significant sex related differences were also observed for total protein, albumin, alkaline phosphatase, alanine and aspartate aminotransferase, gamma glutamyltransferase, total and direct bilirubin. The developed North Rift Valley Kenyan liver function clinical chemistry reference ranges differ from the American values commonly used in Kenyan Hospitals. This study provides adult sex and age specific liver function reference range values to be used in North Rift Valley region. This study recommends adoption of these reference ranges in North Rift valley and determination of similar values for other regions in Kenya.

Key words: Age, adult reference ranges, liver function parameters, sex

INTRODUCTION

Reference values in clinical chemistry are the result of quantitative analysis of a certain analyte obtained from an individual or group of individuals who are selected according to clearly defined criteria (Solberg, 1986). Population - based reference values are obtained from a group of well-defined reference individuals, usually the type of values referred to when the term reference value is used without qualifying words (Solberg, 1987).

In health-related fields, a reference range usually describes the variations of a measurement or value in healthy individuals. It is a basis for a physician or other health professional to interpret a set of results for a particular patient. At present, there are no reference ranges in North rift valley population for the liver function parameters. Liver function tests comprise a variety of individual tests and procedures that can be used to evaluate how well the liver functions. These tests help to determine if the liver is performing its task adequately. In Kenya, many clinical chemistry laboratories are either using the reference values from reagent manufacturers or those published in laboratory textbooks.

These measured laboratory parameters are influenced not only by individual factors such as age, sex, and lifestyle, but also by population and ecological factors such as ethnicity, climate, and altitude; the parameters vary not only between individuals but also between populations (NCCLS, 2000). The aim of this study was therefore to establish reference ranges for eight liver function tests for the adult population of the North Rift Valley region of Kenya and determine possible differences between published and the eight developed local reference ranges.

MATERIALS AND METHODS

Study area: This study was undertaken at Moi Teaching and Referral Hospital (MTRH), Eldoret environs with collaborative arrangement of Regional Blood Transfusion Centre - North Rift. MTRH is situated in a rich farming highland approximately 2100 meters above sea level in North Rift Valley of western Kenya.

Participants: Reference population consisted of healthy volunteer blood donors aged between 18 to 50 years old who had stayed in North Rift valley region for not less

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than six months. Donors came from different parts of North Rift valley region and those who gave written informed consent for this study were interviewed through a questionnaire. Those who did not meet the inclusion criteria were excluded from the study.

Ethical consideration: Ethical approval was obtained from Moi Teaching and Referral Hospital and Moi University Review and Ethical Committee and permission to use the regional blood donor facility granted by the Ministry of Health, Kenya.

Inclusion and exclusion criteria: Healthy males and females between 18 and 50 years who had stayed in North Rift Valley region of Kenya for not less than six months were included in the study. Donor serum samples from people on any form of medication, oral contraceptives, smokers and those with chronic diseases such as tuberculosis, diabetes mellitus, hypertension, chronic renal failure were excluded from the study. All donor serum samples which tested positive for HIV antibody, Hepatitis B surface antigen, Hepatitis C antibody and Syphilis were excluded from the study data set. Also excluded were donor serum samples from pregnant women and male and female blood donors who did not consent to participate in the study.

Initial screening for anti HIV-1 antibody was conducted using Genetic Systems rLAV ELISA (BioRad Laboratories, Redmond, WA). Reactive samples were repeated in duplicates using Vironostika HIV-1 Microelisa Systems (Organon Teknika, Durham, North Carolina). Samples repeatedly reactive by both ELISAs were tested using Genetic Systems Confirmatory Assay 3.0 (BioRad Laboratories, Redmond, WA). Screening for Hepatitis B surface antigen (HBsAg) was performed using the Genetic Systems HBsAg EIA 3.0 (BioRad Laboratories, Redmond, WA). Repeatedly reactive samples were confirmed using the Genetic System Confirmatory Assay 3.0 (BioRad Laboratories, Redmond, WA). Screening for anti-Hepatitis C antibody was performed using the Ortho HCV version 3.0 ELISA Tests System. Repeatedly reactive samples were tested in the Chiron RIBA HCV 3.0 SIA (Chiron Corporation, Emeryville, CA). Serum pregnancy testing was performed on all females using Wampole PreVue HCG cassettes (Wampole Laboratories, Inc Dist., Princeton, NJ). Syphilis testing was performed using the Wampole Laboratories Impact RPR (Wampole Laboratories, Princeton, NJ, USA).

Specimen collection: Blood from suitable blood donors was the specimen of choice and collection was done during the day between the months of August and December 2007. Three hundred milliliters of blood was allowed to flow into the blood bag to clear any anticoagulant along the wall of the pilot tube. Ten millilitres of blood was then sampled from the sampling pot along the pilot line of the blood bag during donation using vacutainer needles and plain vacutainer tubes. Once the specimens were acquired, they were labeled with the donor and study numbers. After bleeding each participant, about five milliliters of blood from the blood bag was collected and used to screen for human immunodeficiency virus (HIV), Hepatitis B surface antigen (HBsAg), Hepatitis C virus (HCV), Syphilis (VDRL) and pregnancy.

Specimen transportation, processing and storage: Specimens were transported from the donation centre to the processing laboratory in ice packed cool boxes within one hour. Once clotted, the blood specimens were centrifuged at 3000 revolutions per minute for two minutes and serum separated immediately into labeled cryovials in duplicate. Serum specimens were then stored at -70^{o}C awaiting laboratory analysis at AMPATH clinical laboratory at MTRH.

Laboratory analysis: Eight liver function tests were determined on the sera specimens: total proteins (TP), albumin (ALB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), Gamma-glutamyl transferase (GGT), total bilirubin (BIL-T) and direct bilirubin (BIL-D). All the assays were performed based on the standard operating procedures (SOPs) written and maintained in the AMPATH modular laboratory using Cobas Integra® 400 plus automatic Chemistry Analyzer (Roche Diagnostics, Mannheim, Germany).

Calibration of tests: Calibrator for automated systems (C.f.a.s) was used. The system performed calibrations automatically.

Quality Assurance (QA)/ Quality Control (QC): To ensure accuracy and precision of the test results, all preanalytical, analytical and post analytical precautions were taken into consideration. Internal QC materials from Roche diagnostics; Precinorm and Precipath which were run daily and external QC materials from American Proficiency Institute (API) which monitors the performance and participation of MTRH and AMPATH laboratories were run twice during the analytical period according to the manufacturers' instructions and QC protocols. The system performed quality controls automatically according to the specifications in the test definition (Ohmann, 1997).

Data management and statistical analysis: Data were double entered into a Microsoft Excel database, compared, and corrected for data entry errors then imported into Statistical Package for Social Sciences (SPSS). The data was visually inspected for extreme values and ten values for single parameters that appeared physiologically impossible removed. Outliers in the remaining data were identified using Box plots, a

procedure proposed by Horns and Pesce (2003). The first quartile (Q_{25}), the median ($Q_{.50}$) and third quartile ($Q_{.75}$) were calculated, that is, the interquartile range (IQR) by subtracting the first quartile from the third quartile ($Q_{.75}$ - $Q_{.25}$). Any data observation which lay more than 1.5 × IQR lower than the first quartile or 1.5 × IQR higher than the third quartile was considered an outlier and manually deleted from the data. The above exclusions and missing results for some parameters led to different sample sizes for each parameter.

Since more than half of the measured parameters did not follow a Gaussian probability curve according to Kolmogorov-Smirnov and Shapiro-Wilk tests for normality, non parametric statistical methods were therefore used as per the CLSI guideline (NCCLS, 2000).

Non-parametrically, reference ranges, means and medians were directly obtained from the analyzed data separately for both males and females at 95% confidence limit (2.5^{th} and 97.5^{th} percentiles) (Horns and Pesce, 2003). P-values for the difference between male and female participants were estimated using the Mann-Whitney test where $p<0.05$ were considered significantly different. Comparison of reference ranges for different age groups for each sex was by means comparison using One-Way-ANOVA and Dunnetts Multiple Comparisons test since all age categories did not have a minimum sample size of 120 required by CLSI (NCCLS, 2000); $p<0.05$ was considered significantly different.

RESULTS

Establishment of reference ranges for adult males and females: Out of the 400 participants recruited for the study, only 367 were involved in the study; 211 males and 156 females. Of those whose data were excluded, 11(33%) were HIV positive, 6(18%) HBsAg positive, 5(15%) HCV positive, 2(6%) VDRL positive, 2(6%) were lipeamic, 3(9%) icteric, and 4(12%) were hemolyzed. Reference ranges for eight liver function biochemical parameters were established for males and females with an age range of 18 to 50 years with median age of 25 and 27 for males and for females, respectively. The reference values were constructed using 2.5^{th} and 97.5^{th} percentiles as lower and upper limits at 95% confidence interval in accordance with CLSI (NCCLS, 2000) guideline for determining reference intervals. The medians for males and females were statistically compared using Mann-Whitney test. $p<0.05$ was considered statistically different.

Table 1 shows combined or sex specific reference ranges for each parameter based on the p-values for the difference between male and female participants. The table also indicate the number of combined and sex specific participants used for determining the reference values for each parameter which were all above the minimum sample size (N = 120) suggested by CLSI (NCCLS, 2000). All the liver function tests (LFTs) (TP, ALB, ALT, AST, ALP, GGT, BIL-D and BIL-T) showed significant sex differences ($p<0.05$).

Reference range values among different age groups in healthy adult North rift valley Kenyan population: The different age groups were categorized as: Category 1 (18-28 years), Category 2 (29-39 years), and Category 3 (40-50 years). Reference range differences between males and females for the measured analytes were estimated by comparing the mean of each age category using One-Way-ANOVA and Dunnetts Multiple Comparisons test; p-values less than 0.05 were considered statistically significant.

Table 2 shows analytes that comprise liver function tests. In age category 1, all the measured analytes showed significant sex differences as indicated by $p<0.05$. In age category 2, analytes ALB, BIL-D, ALT and AST showed significant sex differences as indicated by $p<0.05$. In age category 3, analytes ALB, BIL-D, AST, and GGT showed significant sex differences as indicated by $p<0.05$. Males had greater reference values for all the measured analytes in all age categories compared to females. Significant differences between age groups 1 and 2 shown by superscript a (^{a}) within females for liver function tests were seen with ALT and GGT while within males they were seen in ALP and ALT. Difference between group 1 and 3 was only observed with males for GGT among all the liver function tests as shown by superscript b (^{b}).

Comparison of North-Rift valley population reference values of the measured analytes with those found in literature: Table 3 compares reference range values for liver function tests with the literature values. Comparisons were based on the lower and upper reference limits and interval values of each analyte. TP values for north rift were greater than those for all the comparison sites and all the studies showed insignificant sex difference except in Uganda. ALB values for North Rift were in agreement with the Ugandan one but slightly greater than for other areas. The ALP values for this study were higher than those for Roche with lower limits in better agreement with those from other areas while the upper limit was lower than that from other sites. Male ALT values were comparable with those from Mbeya and Kampala but were lower than those from Kericho, compared to Roche; the North Rift ALT values were higher while female upper limit values for North Rift were lower than those from all the others. North Rift AST values were in better agreement with the Kericho ones. Bilirubin values for the current study were higher than for Roche and Kuwait but almost twice those from other literature areas. Upper GGT limits compared well with the Ugandan values, were higher than those for Roche but were markedly lower than

Table 1: The established reference ranges for TP, ALB, ALP, ALT, AST, GGT, BILD and BIL-T for male and female adults from North rift valley region-Kenya

				Percentiles				Difference between M & F	
Analyte (unit)	Sex	N	Median	2.5th	97.5th	Reference value	IV	z-value	Sig*
TP (g/L)	M&F	361	78	67	92	67-92	25	-0.436	0.003*
	F	207	79	66	89	66-89	23		
	M	154	79	67	93	67-93	26		
ALB (g/L)	M&F	364	44	38	50	38-50	12	-5.52	<0.001*
	F	208	43	38	48	38-48	10		
	M	156	45	38	51	38-51	13		
ALP (U/L)	M&F	348	81	43	143	43-143	100	-4.913	<0.001*
	F	148	74	43	126	43-126	83		
	M	200	87	45	147	45-147	83		
ALT (U/L)	M&F	361	15	7	39	7-39	32	-6.502	<0.001*
	F	153	13	6	27	6-27	21		
	M	207	17	9	42	9-42	33		
AST (U/L)	M&F	361	22	13	44	13-44	31	-9.502	<0.001*
	F	152	19	12	33	12-33	21		
	M	209	25	16	47	16-47	31		
GGT (U/L)	M&F	353	19	7	66	7-66	59	-0.745	<0.001*
	F	149	17	7	49	7-49	42		
	M	204	20	6	69	6-69	63		
BIL-D (µmol/L)	M&F	347	1.7	0.2	4.8	0.2-4.8	4.6	-5.507	<0.001*
	F	146	1.4	0.2	3.7	0.2-3.7	3.5		
	M	201	2.0	0.5	4.9	0.5-4.9	4.4		
BIL-T (µmol/L)	M&F	357	9.8	4.5	28.0	4.5-28.0	23.5	-5.439	<0.001*
	F	156	8.3	3.4	27.0	3.4-27.0	23.6		
	M	201	8.3	4.9	29.7	4.9-29.7	24.8		

Results are expressed as median value of the measured analyte for the number of subjects shown in the column labeled N; *: represents significant sex difference where p<0.05 by Mann-Whitney test; Sig: significance; M: male; F: female; IV: Interval Value

Table 2: Comparison of reference ranges for male and female in different age groups for TP, ALB, BIL-D, BIL-T, ALP, ALT, AST and GGT.

Analyte (Unit)	Sex	N	Category I 18-28 years	N	Category II 29-39 years	N	Category III 40-50 years
TP (g/L)	M	134	79.00±6.55*	50	80.08±5.71	23	80.08±6.00
	F	89	76.84±5.74	44	78.07±5.04	21	77.56±4.61
ALB (g/L)	M	135	44.43±3.17*	50	45.61±3.06*	23	44.76±2.65*
	F	91	42.96±3.14	44	43.10±2.22	21	42.64±2.21
BIL-D (µmol/L)	M	127	2.28±1.28*	51	2.05±1.12*	23	2.14±1.19*
	F	84	1.60±0.89	42	1.46±0.76	20	1.37±0.91
BIL-T (µmol/L)	M	129	13.15±6.47*	50	12.03±5.20	22	12.46±6.13
	F	91	10.06±5.17	44	11.68±16.70	21	9.55±6.27
ALP (U/L)	M	127	92.93±25.69*	51	82.26±22.14[a]	22	83.20±20.63
	F	86	75.45±21.39	44	76.70±22.41	21	80.20±23.49
ALT (U/L)	M	133	17.78±7.83*	51	21.71±9.55[a]*	23	18.91±6.69
	F	89	12.11±4.40	44	16.55±5.67[a]	20	15.44±6.76
AST (U/L)	M	133	26.42±6.74*	53	27.31±10.38*	23	23.97±7.42*
	F	88	19.77±4.62	43	20.56±4.65	18	18.70±4.70
GGT (U/L)	M	133	22.02±13.52*	49	28.78±18.53	22	33.95±18.36[b]*
	F	89	16.69±7.51	41	25.51±14.34[a]	19	23.05±11.15

Results are expressed as Mean ± standard deviation (SD) of the number of subjects shown in columns labeled N; *: significant sex difference in each age category where p<0.05 by t-test: [a]: significant specific sex difference between age category 1 and 2 where p<0.05 by One-Way ANOVA and Dunnetts Multiple Comparison test; [b]: represents significant specific sex difference between age category 1 and 3 where p<0.05 by One-Way ANOVA and Dunnetts Multiple Comparison test

the Tanzanian limit. During the entire analytical period, everyday control value result and the standard deviation (SD) from the control target value were noted (Table 4). All the daily QC runs were within ±2SD from the target values.

DISCUSSION

Reference values for adult males and females in North Rift Valley region Kenyans have not previously been established. Although the number of males (211) was more than those of females (156), each group exceeded the minimum of 120 participants per subgroup for nonparametric estimates required for 95% reference interval determination as recommended by CLSI (NCCLS, 2000). The lower proportion of females is likely due to physiological factors such as pregnancy, lactation and menstruation, therefore less frequent participation in blood donation. The rigorous screening process employed by the blood bank presumably resulted in blood collection from overall healthy adults. The results for reference values for each parameter under study were obtained using similar analytical methods and unit of measure as those in the literature. Emphasis was laid on external and internal quality control methods which ensured accuracy and precision (Gahutu and Wane, 2006).

Table 3: Comparison of established reference values for TP, ALB, ALP, ALT, AST, GGT, BIL-D and BIL-T for North-Rift valley population with those in literature

Analyte (unit)	Sex	NorthRift, Kenya	Roche, America	Kericho, Kenya	Mbeya, Tanzania	Kampala, Uganda	Kuwait
TP (g/L)	M&F	67-92	64-83		66.3-85.5	66-89*	64-79
	M					65-89	
	F					68-90	
ALB (g/L)	M&F	38-50*	35-50	37-49*	37-50	38-53*	35-47
	M	38-51		35.8-48.1		39-54	
	F	38-48		34.4-47.5		37-52	
ALP (U/L)	M&F					44-151	40-87
	M	45-147	40-129		45-170	42-159	
	F	43-126	35-104		45-155	47-160	
ALT (U/L)	M&F						10-49
	M	9-42	0- 41	11-54	7-45	7-43	
	F	6-27	0- 32	9-47	9 -55	5-39	
AST (U/L)	M&F						14-38
	M	16-47	0- 38	15-45	15 -53	13-36	
	F	12-33	0- 31	13-38	14-35	11-29	
GGT (U/L)	M&F					8.5-69*	
	M	6-69	8-61		9-121	9-71	
	F	7-49	5-36		7-52	8-41	
BIL-D (µmol/L)	M&F	0.2-4.8*	0.3-4.0	1.1-8.8	0.7-8.2	0.3-6.8	
	M	0.5-4.9				1.7-8.6	
	F	0.2-3.7				0-6.84	
BIL-T (µmol/L)	M&F	3.4-27.0*	0- 17.1	4.9-39.9	5.2-41	6.8-42.8	4-17
	M	4.9-29.7				6.8 -44.5	
	F	3.4-27.0				5.1-32.5	

*: significant sex difference $p<0.05$ but combined values indicated for comparison with other studies; Kericho: reference values by Kibaya *et al*. (2008); Mbeya: reference values by Saathoff *et al*. (2008); Kampala: reference values by Eller *et al*. (2008); Kuwait: values by Olusi and Al-Awadhi (2002); Roche: values by Roche diagnostics (2005)

Table 4: The quality control (QC) report for TP, ALB, ALP, ALT, AST,BIL-D and BIL-T under study

		Assigned QC report			Study QC report		
Analyte (unit)	Qctype	Mean	SD	%CV	Mean	SD	% CV
TP (g/L)	PPU	49.7	2.0	4.02	48.6	1.2	2.52
	PNU	67.0	2.7	4.03	66.5	1.6	2.35
ALB (g/L)	PPU	31.3	1.90	6.07	29.95	1.06	3.60
	PNU	48.8	2.90	5.94	48.85	1.75	3.73
ALP (U/L)	PPU	228	14.0	6.14	226.8	5.1	2.23
	PNU	83.4	5.0	6.00	83.8	2.6	3.16
ALT (U/L)	PPU	137	8.0	5.84	143.1	2.5	1.75
	PNU	48.4	2.9	5.99	49.3	2.0	4.09
AST (U/L)	PPU	142	9.0	6.34	145.5	1.9	1.32
	PNU	43	2.6	6.05	44.8	1.3	2.99
GGT (U/L)	PPU	234	14	6.0	228.4	15	6.6
	PNU	47.7	2.9	6.1	47.1	3.1	6.6
BIL-D (µmol/L)	PPU	36.60	2.90	7.92	36.32	0.75	2.06
	PNU	8.55	0.68	7.95	8.52	0.29	3.35
BIL-T (µmol/L)	PPU	97.3	5.8	5.96	93.5	3.1	3.27
	PNU	22.2	1.3	5.86	21.7	0.9	4.26

The significantly higher values of the reference ranges for ALP, ALT, AST, GGT, TP, ALB, BIL-D and BIL-T in males compared to females indicates sex differences in these clinical chemistry parameters. Sex differences in AST, ALT, and ALP have been known to exist due to differences in muscle mass which affects AST and ALT and bone mass which influences ALP. Similar findings have been reported in black populations of Kampala, Uganda; Kericho, Kenya; Mbeya, Tanzania; Rwanda and white USA populations (Roche diagnostics, 2005; Gahutu and Wane, 2006; Saathoff *et al*., 2008; Eller *et al*., 2008; Kibaya *et al.,* 2008). The differences by sex noted for GGT could be due to extra production from the prostate gland in males as compared to females who have no prostate gland, a result that agrees with those reported in other East African states (Saathoff *et al*., 2008; Eller *et al*., 2008). Sex differences in the BIL-T and BIL-D values could be partly due to influence of sex hormones. These findings are in agreement with those of similar studies done in Uganda (Eller *et al*., 2008). Manolio *et al*. (1992) reported higher reference range values for ALT, GGT, ALP and BIL-T in both white and black males than for black and white females, respectively.

The significant sex differences in the reference range values for TP and ALB could be attributed to the sample size; however, this difference may not have clinical

significance. The sex difference in the reference range values for serum TP observed in this study are in contrast to that reported for the American population where males and females have common reference range values but agrees with the findings of the Rwandan study (Roche diagnostics, 2005; Gahutu and Wane, 2006).

The observed significant increase of some liver function analytes and decrease of others in one or both sexes as age progressed is an indication that these analytes are age dependent. The increase in serum reference range for ALT could be explained by loss of liver cell integrity with advancement in age and is in agreement with studies carried out in India and Kuwait (Olusi and Al-Awadhi, 2002; Furruqh *et al*., 2004). The increase in serum reference range for GGT in males and females with progression of age could be due to the decrease of renal and hepatic integrity with advancing age; similar results have been reported by Manolio *et al*. (1992).

The decrease in serum ALP could be due to reduced bone growth as age advances, a finding that is in agreement with that of Manolio *et al*. (1992) but contrasts that of Furruqh *et al*. (2004) who reported an increase of serum ALP with advancement in age.

The observed variation in reference range values developed in this study compared to reference range values for the same parameters from other locations suggest variations in analytical methods in addition to ethnic composition and ecological parameters as stated by Saathoff *et al*. (2008). The higher reference range value for TP, GGT and ALP, compared to those of other locations could be due to genetic factors, dietary and environmental factors. Manolio *et al*. (1992) reported a higher reference values for TP, GGT, AST and ALP in blacks than in whites. Ichihara *et al*. (2008) reported differences in reference range values for TP between Asia cities.

The differences in the reference range value for AST compared to those determined from other literature sites could be explained by differences in genetic factors and muscular exertion; these results agree with those reported in studies in six Asian cities and Ghana (Ichihara *et al*., 2008; Koram *et al*., 2007).

Generally, physiological functions have been shown to vary with population due to differences in diet, genetics, physical, environmental and socioeconomic conditions (Koram *et al*., 2007). The reference values for most liver function tests determined in this study vary from those of American population currently used to interpret laboratory results for North Rift valley and other populations, indicating that there is need to use sex and age established reference values that are applicable to specific populations rather than take a set of reference values determined for one population and apply it to another population.

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