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Establishing Population Reference Intervals of Some Electrolytes, Urea and Creatinine for Adults in Ogbomoso, South Western Nigeria.

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Abstract: *A robust population reference interval is the backbone of laboratory report and the baseline of good interpretation of laboratory results in a well articulate clinical laboratory practice. Due to the difficulty in generating population reference interval many laboratories use manufacturers' values which at times have the shortcomings of been alien to the population.*

One hundred and twenty four healthy workers of the institution aged 18-50years were recruited into the study. A questionnaire was used to collect their demographic data after written consent was taken. Sodium, potassium, chloride were assayed by direct electrochemical method on SFRI ISE6000, urea using enzymatic endpoint method and creatinine through enzymatic kinetic method on the plasma using Randox Kits.

The reference intervals for the analytes derived in this study from mid-95 centile are: sodium (120-149 mmol/L), potassium (2.9-5.1 mmol/L), chloride (88-120 mmol/L), urea (1.7 -6.2 mmol/L), creatinine (50-135µmol/L).

The reference intervals derived in this study is generally lower than the manufacturers' range but seem to compare well with reports of similar study in area with same geographical, socio-economical and dietary characteristics.

I. Introduction

Interpretation of clinical laboratory data is a comparative decision making process whereby values of analytes are compared with reference values taking into account avoidable and controllable factors other than the effect of the pathology on such analytes[1, 2]. Clinical care requires accurate laboratory reference intervals for appropriate assessment of patients, monitoring disease progression, as well as reporting adverse events. Laboratories are usually encouraged to establish their own reference intervals from the local population or validate the use of those obtained from a different settings[3]. Despite this, clinicians and researchers in Africa have continued to use reference values of European or North American populations.

Individual reference values are said to be the best. As the individual transcend through all the physiology and developmental milestone in a healthy state values of biochemical constituents are documented and it is against these, that pathological values are compared. The population reference intervals become imperative due to the inability of getting individual reference intervals in most population. More often these vary according to population, ethnicity, race, among others and aside of avoidable and controllable factors[4].

The reference interval of a given biochemical constituent of clinical interest can be defined as the concentration of the constituent found in a group of clinically healthy persons. These values are taken to be between 2.5 and 97.5 percentile of the said population following strict quality assurance programme and standard statistical methods[5, 6]. Population reference intervals are established according to the recommendation of the Expert Panel on Theory of Reference Value (EPTR) [2] and of International Federation of Clinical Chemistry (IFCC) [5, 6]. Establishing reference values is, however, time-and effort-consuming and requires a lot of funds [7]. These issues and the importance of reference values in clinical chemistry made laboratories to adopt manufacturers' values which are synonymous to kits reference interval or method related reference interval. In a survey by the American College of Pathologist in 2001, 78% of the laboratories adopted manufacturers' values for reference intervals. Another survey in 2007 revealed that about 50% of the laboratories studied use

population reference intervals but of these 50%, about half derived their reference intervals using ≥100 sample size [8].

Different populations have different genetic make-up, dietary habits, life style, socio-economic and many other environmental and biological factors which can affect the analytical outcome[3]. Ladoke Akintola University of Technology Teaching Hospital (LTH), Ogbomoso is a new tertiary health institution in Nigeria. In view of the absence of reference intervals in this locality, we embarked on this study to establish population reference intervals of sodium, potassium, chloride, urea and creatinine.

II. Materials And Methods

The study population consisted of 124 adults aged 18-50 yrs residing in Ogbomoso, Oyo State, South-western Nigeria. The participants were recruited consecutively by a direct priori selection. Participants with hypertension, diabetes mellitus, kidney disease, liver disease and those on medication for any illness were excluded. Also excluded were those with history of smoking, alcohol intake, excessive exercise, pregnant women, and recent history of fever, trauma or blood transfusion. A structured questionnaire was used to obtain information such as age, gender, educational status, occupation, cigarette smoking, alcohol intake, physical activity, dietary habits, and medical history. Physical examination and urinalysis were subsequently done on the subjects. A written consent was taken from each participant.

The weight (kilograms) of each participant was taken in light clothing with the shoes off to the nearest 0.1kg, and height (meters) was measured with the shoes off using a stadiometer to the nearest 0.1cm. Body mass index (BMI) was calculated from the formula: weight (kg)/height^2 (m^2). Each participant was allowed 5 minutes rest before blood pressure measurement at sitting position.

5mL of blood was collected from each subject through an aseptic cubital venepuncture at sitting position and after a 10 minutes rest period into lithium heparinized tube. This was centrifuged at 3000 rpm using a bench top centrifuge within 30 minutes of collection and plasma separated into plain aliquot bottle and frozen at -20^{0}C before analysis. Analysis was done in batches within a week of specimen collection.

Analtical Methods:

Na^+, K^+, Cl^-, was analyzed using direct electrochemical methods using SFRI ISE 6000 analyzer. Urea was analyzed using enzymatic endpoint assay (urease-Berthelot method) with commercially available RANDOX kits where urea is hydrolysed to ammonia in the presence of urease. The ammonia is then measured photometrically by Berthelot's reaction. Creatinine was analyzed using enzymatic kinetic methods with RANDOX kits whereby creatinine in an alkaline solution react with picric acid to form a coloured complex which is directly proportional to the creatinine concentration. The entire enzymatic assay was read using a semi-automatic chemistry analyzer HA1900.

Quality Control Procedures:

Commercial control materials (Randox brand) in the normal, low and pathologic ranges were ran in each batch analysis. Mean, SD and CVs were calculated and seen to be within acceptable quality goals of the methods for each analyte.

Statistical Analysis:

Continuous variables were summarized as means ± SD while categorical variables were expressed as proportions. Comparison of two continuous variables was done using the students't' test. The analytes assumed a normal Guassian distribution and a parametic statistic was used. The mean, median and the percentile values of the analytes were calculated and upper and lower reference values were taken for the 97.5 percentile and 2.5 percentile respectively. All statistical analyses were done using the Statistical Package for Social Sciences (SPSS) software, IBM SPSS Statistics version 20.

III. Results

All the analytes maintain normal Gaussian distribution as depicted in Figures 1, 2 and 3. All the subjects were normotensive and their urinary glucose and protein were negative. There were 124 healthy subjects aged 18 to 50 years, among who 24(19.3%) were ≤ 20years, 37(29.8%) were between 21 to 30years, 55(44.4%) were between 31 to 40years and 8(6.5%) between 41 to 50years old. 12(9.7%) of the subjects were obese, 33(26.6%) were overweight, 5(4%) were underweight while the rest 74(59.7%) have normal BMI.

Table 1 shows the mean ± SD of the population characteristics of the subjects. The mean± SD of age (30.38± 6.32),height(1.63±0.07),weight(64.5±12.76),SBP(118.95±10.97),DPB(74±8.29),BMI(24.32±4.42),sodium(135. 72±7.91),potassium(4±0.47),Chloride(102.13±8.55), urea(3.14±1.19), creatinine(82.93±22.78) .

Table 2 shows reference intervals derived in this study for sodium(120-149mmol/L), potassium(2.9-5.1mmol/L),chloride(88-120mmol/L), urea(1.7-6.2mmol/L) and creatinine(50-135 µmol/L) with the methods used for assay. Results obtained are generally lower than most standard references quoted in Caucasians.

Table 3: Depicts the mean ± SD of the subjects according to their gender. Forty four (35.5%) subjects are male while eighty (65.5%) are female. There were no significant gender difference in age, height, BP, sodium, chloride, and urea. Significant difference in terms of weight, BMI and potassium was noticed in both sexes.

Figure I: Histogram showing the statistical distribution of sodium**.**

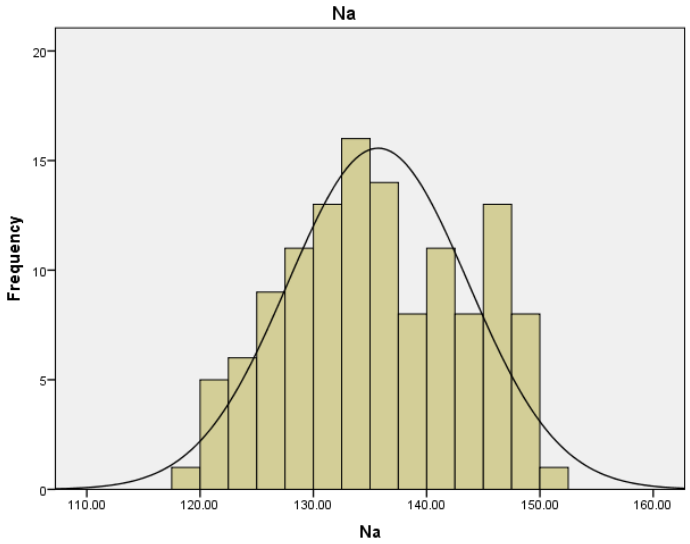

Figure II : Histogram illustrating the statistical distribution of potassium.

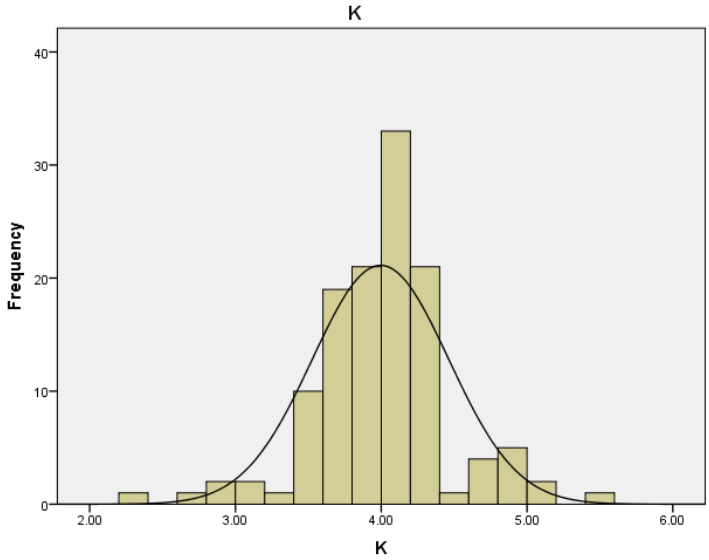

Figure III : Histogram illustrating the statistical distribution of chloride.

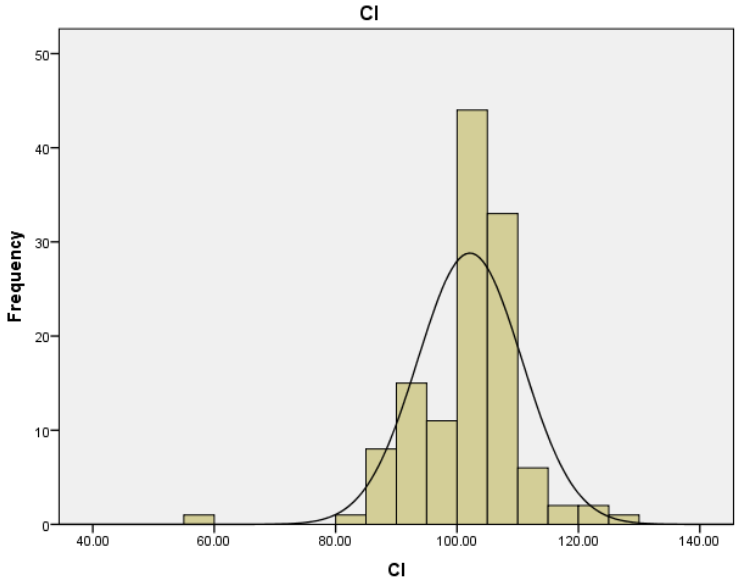

Table 1: Characteristics of Study Population.

n=124	Minimum	Maximum	Mean ± SD
Age(years)	17	54	30.38± 6.32
Height(m)	1.47	1.8	1.63± 0.07
Weight(kg)	36	112	64.5± 12.76
SBP(mmHg)	95	140	118.95± 10.97
DBP(mmHg)	53	90	74± 8.29
BMI	16.2	41.1	24.32± 4.42
Na^+(mmol/L)	118.40	150.20	135.72± 7.91
K^+(mmol/L)	2.3	5.48	4.00± 0.47
Cl^-(mmol/L)	58.4	127.40	102.13± 8.55
Urea(mmol/L)	1.6	7.2	3.14± 1.19
Creatinine(µmol/L)	46.5	140.9	82.93± 22.78

Table 2: Reference Interval of some electrolytes, urea and creatinine (2.5^{th}-97.5^{th} centiles) in comparism with adopted values.

Analytes	Method used	Reference intervals	Adopted Reference intervals
Na^+(mmol/L)	Direct ISE	120-149	136-146
K^+(mmol/L)	Direct ISE	2.9-5.1	3.6-5.2
Cl^-(mmol/L)	Direct ISE	88-120	99-111
Urea(mmol/L)	Enzymatic, endpoint	1.7-6.2	1.7-9.1
Creatinine(µmol/L)	Enzymatic, kinetic	50-135	44-97

Table 3: Baseline characteristics of the study population

Variables	Mean Values ± SD			p-values
	Male (n = 44)	Female (n = 80)	Total (N = 124)	
Age(years)	31.48±5.75	29.49±6.02	30.13±5.98	.076
Height(m)	1.64±0.07	1.62±0.07	1.63±0.07	.207
Weight(kg)	68.74±14.45	62.38±11.15	64.63±12.73	.007*
BMI	25.60±5.14	23.68±3.82	24.64±4.48	.019*
SBP(mmHg)	121.09±8.45	117.59±11.83	118.83±10.93	.088
DBP(mmHg)	73.59±7.79	74.18±8.62	73.97±8.31	.710
Sodium(mmol/L)	136.63±8.07	135.21±7.88	135.72±7.95	.344
Potassium(mmol/L)	3.87±0.46	4.07±0.46	4.00±0.47	.021*
Chloride(mmol/L)	100.72±9.71	102.88±7.86	102.11±8.58	.180
Urea(mmol/L)	3.21±1.13	3.08±1.23	3.13±1.19	.564
Creatinine(µmol/L)	84.21±21.54	82.29±23.67	82.98±22.86	.656

*Statistically significant

IV. Discussion

It is difficult and expensive establishing reference intervals for clinical laboratories. Due to these reasons laboratories, most especially the smaller ones adopt manufacturers' values which are usually obtained in kit inserts. This provides no detailed information about the reference populations. In studies done in Asia a decade ago possible bias associated to differences in physical activity and climatic influences was avoided by choosen the participants among the hospital staff[11,12]. In this study the volunteers were choosen from the staff working in the hospital.

The reference interval derived in this study differs a little from the convectional ones which were the kits reference interval or adapted ones from Caucasian studies. The differences experienced might not be unconnected to various factors influencing reference interval most especially methodology, racial difference, diet and geographical location. The life style as well as diet of a particular group of people might be factors playing crucial role in these existing differences [13].

11.2% of the study population have lower potassium level than 3.6mmol/L, 49.6% have sodium <135mmol/L and 20% has chloride <95mmol/L. However this result is similar to result reported in Abeokuta[14], a town in south western Nigeria whose geographical location and other demographic characteristics are comparable. This is also true for studies carried out in the eastern part of Africa[15], buttressing the fact there is necessity to derive population reference interval. However the story is different in a study in Kenya that discovers a comparable reference interval in some biochemical analytes[16]. Most of the other studies also found difference in gender values in some biochemical analytes most especially creatinine, which is due to muscle built variation of both gender, but in this study it is not statistically significant.

Despite the study having double advantage as been direct priori method of carrying out reference interval study and the use of reference methods in assaying the samples the limitation of this study is not conducting a thorough clinical examination in selecting healthy subjects. Aside from this the subjects from the little clinical examination were healthy.

V. Conclusion:

We can conclude from this study that there exist some differences in reference interval for various populations and thus individual clinical laboratories should put effort in deriving their population reference interval other than relying on adapted values.

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