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RESEARCH ARTICLE

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The establishment of biological reference intervals of nontraditional glycemic markers in a Chinese population

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Background: We established the reference intervals for glycated albumin (GA), fructosamine (FA), and 1,5-anhydroglucitol (1,5-AG) in a Chinese healthy population.

Methods: This study enrolled a total of 458 eligible reference individuals, consisted of 226 men and 232 women, aged from 20~79 years (median age 43 years), who attending routine healthy checks. We stratified the subjects according to gender (males and females) and age (20-39, 40-59, and 60-79 years), and combined statistical methods with Lahti algorithm, as well as appropriate clinical consideration, to judge whether partitioning for data was needed.

Results: Glycated albumin levels between males and females were statistically different ($P<.001$), but the absolute difference between the upper reference limits was only 0.31%, which was too small to be clinically relevant. GA levels across the three age groups were statistically different ($P<.001$), and Lahti algorithm suggested partitioning for 20-59 and 60-79 years, which reference intervals were 10.38%-13.89% and 10.23%-14.79%, respectively. 1,5-AG levels in males were significant higher than females ($P<.001$), and absolute difference was 51 μmol/L (8.5 μg/mL) in mean level. Thus, partitioning for gender was needed. Reference intervals for 1,5-AG were 107-367 μmol/L for males and 79-306 μmol/L for females. The absolute difference of the lower reference limits for FA was only 7 μmol/L between males and females. FA levels across the three age groups were not statistically different ($P>.05$). The reference interval for FA was 220-298 μmol/L.

Conclusion: New reference intervals for nontraditional glycemic markers were established based on a Chinese population.

KEYWORDS
1,5-anhydroglucitol, fructosamine, glycated albumin, reference intervals

1 | INTRODUCTION

With the development of techniques and detecting methods, glycemic markers are not limited to glucose and hemoglobin A_{1c} (HbA1c). New nontraditional glycemic markers are of interest for researchers and widely used in clinical practice.

HbA1c is used as the gold standard index for assessment of glycemic control in diabetes treatment and has been recommended as a diagnosis marker for diabetes, which represents long-term glycemic control state (2-3 months). Nonetheless, HbA1c may not accurately reflect glycemic status in some conditions,[1,2] such as anemia, pregnancy, liver cirrhosis, variant hemoglobin, and neonatal diabetes mellitus. All these conditions influence the concentration of HbA1c, which may lead to an error of diagnosis or in management of diabetes. Furthermore, HbA1c does not represent rapid changes of glycemic control and postprandial glucose.[2]

In the status of HbA1c invalid, nontraditional glycemic markers, such as 1,5-anhydroglucitol (1,5-AG), fructosamine (FA), and

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glycated albumin (GA), may be more suitable for clinical practice.[3-6] FA is formed through a nonenzymatic reaction that blood glucose and serum proteins bind together to form keto-amines. GA, formed in a similar mechanism as FA, is specific to albumin. Both FA and GA reflect endogenous glucose exposure over the prior 2-3 weeks,[2] which have a greater susceptibility compared to HbA1c in glycemic excursion, enabling physician to assess the treatment regimen in time.[7]

1,5-AG is freely filtered by glomeruli and reabsorbed in the proximal tubule, which as a marker of recent glycemic control (1-2 weeks). During the status of hyperglycemia, tubular reabsorption is inhibited by glucose, urinary excretion of 1,5-AG is accelerated, and the serum concentration of 1,5-AG correspondingly drops.[6,8]

However, those glycemic markers, unlike traditional clinical chemical indexes that have recognized reference intervals based on different region and ethnic background, are newly applied in clinical practice, whose reference intervals mainly derived from the data provided by the manufacturers have not reached a consensus.

Due to the different selection criteria for manufacturers, reference intervals used in other populations may lead to an inconsistency in clinical practice. For instance, 1,5-AG levels were significantly higher in Asian and African subjects compared with Caucasians[9]; the 1,5-AG levels are lower in subjects of Japan than in US subjects.[10] Recently, Chen et al.[11] established the adult FA reference intervals based on a Beijing population and reported that there was no gender difference in the level of FA, but elder persons significantly higher than younger one. This study aimed to establish the reference intervals for 1,5-AG, FA, and GA in a Chinese healthy population.

2 | MATERIALS AND METHODS

2.1 | Study population

This study enrolled eligible reference individuals attending routine healthy checks from October to December in 2015 in The First Affiliated Hospital of Anhui Medical University, one of third-level Grade A hospital with 3000 beds in China. Clinical and demographic data were collected from electronic medical records, including data on ultrasonography, history of disease, data on height, weight, and blood pressure. BMI was calculated as weight in kilograms divided by the square of height in meters. Laboratory tests were directly extracted from laboratory information system, as part of healthy checks. Residual serum samples were collected and stored in −80°C refrigerator. We measured 1,5-AG, GA, and FA in stored serum samples simultaneously. High stability of these tests in stored serum samples has been demonstrated by previous literatures.[12-14]

The exclusion criteria of this study were required to meet the following criteria: (i) history of diabetes mellitus; (ii) history liver disease, kidney disease, metabolic disorders, or cardiovascular disease; (iii) pregnancy; (iv) abnormal ultrasonography in liver, gallbladder, pancreas, and bilateral renal reached the level of clinical decisions; and (v) the tests conducted and their cutoff thresholds for subject exclusion were shown in Table 1. A total of 458 subjects were included in the present study, consisted of 226 men and 232 women, aged from 20~79 years (median age 43 years). The study protocol was approved by the Ethics Committee of The First Affiliated Hospital of Anhui Medical University.

TABLE 1 Laboratory tests and corresponding thresholds used as exclusion criteria

Laboratory	Threshold[a]
Fasting blood glucose	<3.89 mmol/L or >6.11 mmol/L
Albumin	<35 g/L
Alanine aminotransferase	<9 U/L or >50 U/L (males) <7 U/L or >40 U/L (females)
Aspartate aminotransferase	<15 U/L or >40 U/L (males) <13 U/L or >35 U/L (females)
Serum creatinine	<53 μmol/L or >106 μmol/L (males) <44 μmol/L or >97 μmol/L (females)
Blood urea nitrogen	<3.20 mmol/L or >7.10 mmol/L
Uric acid	<208 μmol/L or >428 μmol/L (males) <155 μmol/L or >357 μmol/L (females)
Triglycerides	<0.56 mmol/L or >1.70 mmol/L
Cholesterol	<2.86 mmol/L or >5.98 mmol/L
Hepatitis B surface antigen	Positive

[a]The test values that exceeded the lower or upper limit of the reference intervals of those tests in our laboratory were defined as the exclusion criteria of those test.

2.2 | Laboratory measurements

Serum GA (Asahi Kasei Pharma, Tokyo, Japan) and 1,5-AG (Medical system, Ningbo, China) concentrations were measured using enzymatic assays, whereas the level of FA was measured using a colorimetric method (Roche Diagnostics GmbH, Mannheim, Germany). Serum GA was determined by an enzymatic method using albumin-specific proteinase, ketoamine oxidase, and albumin assay reagent. GA values were expressed as the percentage of glycated albumin in total serum albumin. The interassay coefficient variations were as follows: 2.5% (1,5-AG, mean 94 μmol/L), 1.7% (GA, mean 12.7%), and 3.80% (FA, mean 471 μmol/L). All serum measurements were performed on Roche Modular DPP biochemistry autoanalyzer (Roche Diagnostics GmbH). All blood samples were obtained in the morning following an overnight fasting for at least 8 hours.

2.3 | Statistical analysis

Continuous data were checked for normal distribution by the Kolmogorov-Smirnov normality test. Normally distributed data are expressed as mean±SD, while skewed data are expressed as the median (interquartile range, IQR). Student's *t* test and Mann-Whitney *U* test were applied to examine the difference between two groups. Analysis of variance (ANOVA) followed by post hoc analysis using Bonferroni correction was used to compare variables across multiple groups, while Kruskal-Wallis test for groups with skewed data. Lahti

algorithm[15,16] was used to judge the corresponding lower and upper reference limits of subgroups in gender and age whether partitioning of reference intervals was required. Reference intervals of GA, 1,5-AG, and FA were expressed as 2.5th to 97.5th percentile. Values of $P<.05$ were considered statistically significant. Statistical analyses were performed using SPSS for Windows, version 20.0 (SPSS, Inc., Chicago, IL, USA).

3 | RESULTS

3.1 | Clinical and biochemical characteristics

The clinical and biochemical characteristics of the 458 subjects were shown in Table 2. The distribution of GA, 1,5-AG, and FA in this study was Gaussian-distributed. Previous studies[6,17,18] have shown the partitioning was required for gender and age. So, we stratified the subjects according to gender (male and female) and age (20-39, 40-59, and 60-79 years).

3.2 | GA

GA concentrations between males and females were statistically different (Student's *t* test, $t=-4.726$; $P<.001$), but Lahti algorithm just obtained a marginal value for the upper reference limit, which may be used as an important clinical decision (in the diagnosis or monitoring of hyperglycemic conditions), but the absolute difference between the upper reference limits was only 0.31% (Table 3). Thus, we recommended those two groups were merged.

GA concentrations across the three age groups were statistically different (analysis of variance; ANOVA, $F=8.226$; $P<.001$), and the Lahti algorithm suggested partitioning for two of three comparisons (Table 4). So, we recommended the reference interval of GA needs partitioning at the age of 60 years. The reference intervals were shown in Table 5.

3.3 | 1,5-AG

1,5-AG concentrations in males were higher than females (*t* test, $t=9.373$; $P<.001$), and the Lahti algorithm suggested a partitioning value for the upper reference limit and a marginal value for the lower reference limit (Table 3). The absolute difference was 51 μmol/L (8.5 μg/mL) in mean level, which should be taken into clinical consideration. Thus, the partitioning for gender was needed.

There was no statistically significant difference for 1,5-AG across the three age groups (ANOVA, $F=0.206$; $P=.814$), and the Lahti algorithm suggested no need for partitioning of reference interval (Table 4). Thus, all data were merged.

1,5-AG concentrations across the three age groups were statistically different (ANOVA, $F=18.484$; $P<.001$). Lahti algorithm suggested nonpartitioning for the lower reference limit and partitioning for the upper reference limits (Table 4). The lower reference limit for 1,5-AG is used as decision limit. In spite of the suggested partitioning for the upper reference limits, we do not recommend partitioning for age group in females. The obtained reference intervals were shown in Table 5.

3.4 | FA

FA concentrations between males and females were statistically different (*t* test, $t=-5.752$; $P<.001$), but Lahti algorithm just gave a marginal value for the lower reference limit, which seldom used as decision limit and the absolute difference between lower reference limits was only 7 μmol/L (Table 3). Thus, we combined males with females to calculate reference interval.

FA concentrations across the three age groups were not statistically different (ANOVA, $F=0.969$; $P=.38$), and the Lahti algorithm suggested no need for partitioning (Table 4). Thus, all data merged to calculate the reference interval (Table 5).

4 | DISCUSSION

This study aimed to establish the reference intervals of GA, FA, and 1,5-AG in a Chinese population, simultaneously. 1,5-AG, FA, and GA are nontraditional glycemic markers of hyperglycemia, which are of increasing interest in research and clinical practice. We combined statistical methods with Lahti algorithm, as well as appropriate clinical consideration, to judge whether partitioning for data was needed.

To prevent the onset and progression of diabetic chronic complications is the main purpose of diabetic treatment. Previous studies have shown postprandial hyperglycemia is closely related to the development of diabetic complications.[19,20] HbA1c as a traditional glycemic marker mainly reflects mean plasma glucose level, but does not reflect postprandial plasma glucose well. Furthermore, it does not reflect glycemic control accurately under conditions with rapid changes in glycemic control.

Recently, it has been reported that GA reflects not only mean plasma glucose level but also postprandial plasma glucose as well as glycemic excursion.[21] An investigation of patients with diabetes based on continuous glucose monitoring (CGM) data also gave the evidence of GA as a glycemic marker has a close relationship with glycemic excursion compared with HbA1c.[22] In this study, we observed GA levels were statistical significant in gender and age groups, similar to previous literatures.[17,18] However, those studies gave the reference intervals just relied on the statistical significant of subgroup comparison to define the partitioning of subgroups. We used Lahti algorithm to judge whether partitioning was needed. For gender group, Lahti model just obtained a marginal value for the upper reference limits. Lahti et al. suggested the decision whether need for partitioning should be made using nonstatistical judgment if marginal value obtained. The nonstatistical considerations are as follows: (i) the upper reference limit of GA in the diagnosis or monitoring of hyperglycemic conditions may be used as a decision limit, (ii) but the absolute difference between upper limits was only 0.31%, which was too small to be clinically relevant (Table 3). Overall, in spite of the supposed gender dependence, we do

TABLE 2 Clinical and biochemical characteristics of study population

	Total	Male	Female	*P*-value
N	458	226	232	—
Age, y	43 (31, 53)	43 (31, 52)	43 (32, 55)	.440
BMI, kg/m^2	22.9 (20.9, 25.1)	23.1 (20.9, 25.1)	22.7 (20.8, 25.0)	.418
SBP, mm Hg	126±16	126±17	126±16	.975
DBP, mm Hg	75±11	75±11	75±11	.922
FPG, mmol/L	5.21±0.41	5.21±0.42	5.21±0.41	.968
ALB, g/L	49.1±2.8	49.5±2.0	48.7±2.6	<.001
ALT, U/L	17 (13, 22)	20 (16, 27)	14 (11, 18)	<.001
AST, U/L	21 (18, 24)	22 (19, 25)	20 (17, 23)	<.001
BUN, mmol/L	5.03±0.96	5.13±0.95	4.91±0.95	.011
sCr, μmol/L	61 (51, 72)	72 (64, 78)	51 (48, 57)	<.001
UA, μmol/L	287±58	324±47	250±42	<.001
TG, mmol/L	0.96 (0.77, 1.18)	1.02 (0.84, 1.28)	0.90 (0.72, 1.09)	<.001
CHOL, mmol/L	4.58±0.62	4.56±0.62	4.60±0.63	.580
AFP, ng/mL	2.8 (1.9, 4.0)	3.0 (2.0, 4.3)	2.7 (1.7, 3.8)	.031
CEA, ng/mL	1.2 (0.7, 1.9)	1.3 (0.7, 1.9)	1.2 (0.7, 1.9)	.819

Normally distributed data are expressed as mean±SD, while skewed data are expressed as the median (interquartile range).
BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; sCr, serum creatinine; UA, uric acid; TG, triglycerides; CHOL, cholesterol; AFP, alpha-fetoprotein; CEA, carcinoembryonic antigen.

TABLE 3 Application of partitioning criteria to glycemic markers in gender

	Data for subgroup distributions		Lahti-distances partitioning criteria	
Case	Subgroup1 (male)	Subgroup2 (female)	D (SD)	Conclusion for one end
GA (%)				
Lower limit	10.35	10.44	0.105	Nonpartitioning
Upper limit	14.07	14.26	0.360	Marginal
Mean±SD	11.95±0.90	12.34±0.86$^{\#}$	—	—
FA (μmol/L)				
Lower limit	219.7	226.7	0.390	Marginal
Upper limit	297.3	301.4	0.223	Nonpartitioning
Mean±SD	253.3±19.2	263.3±18.0$^{\#}$	—	—
1,5-AG (μmol/L)				
Lower limit	106.7	79.1	0.502	Marginal
Upper limit	366.8	306.1	1.093	Partitioning
Mean±SD	226.3±60.7	175.2±55.8$^{\#}$	—	—

Compared with man: $^{\#}P$<.001. 1,5-AG (μmol/L)≈6×1,5-AG (μg/mL).
The ratio of the distance between reference limit of subgroups and the smaller SD of each subgroup, D. The results are compared with others using Lahti algorithm to judge the need for partitioning: Marginal (the subgroup reference limits at each end of the distribution between 0.25SD to 0.75SD); nonpartitioning, no need of partitioning (the subgroup reference limits at each end of the distribution between <0.25SD); partitioning, need of partitioning (the subgroup reference limits at each end of the distribution between >0.75SD).
1,5-AG, 1,5-anhydroglucitol; GA, glycated albumin; FA, fructosamine; SD, standard deviations.

not suggest partitioning for gender. For age group, relied on Lahti algorithm, we combined age between 20 and 39 years with age between 40 and 59 years and suggested a partitioning at the age of 60 years to calculate the reference interval for GA. Overall, reference intervals for GA were 10.38%-13.89% for 20-59 years and 10.23%-14.79% for 60-79 years. The reference interval provided by the manufacturer is 11%-16%, which derived from the guideline for diabetic treatment drawn up by The Japan Diabetes Society. Different from this reference interval, we recommended a partitioning at the age of 60 years, and the lower and upper reference limits are slightly lower than the

TABLE 4 Application of partitioning criteria to glycemic markers in age

	Data for subgroup distributions			Lahti-distances partitioning criteria					
				D (SD)			Conclusion for one end		
Case	Subgroup1 (20-39 y)	Subgroup2 (40-59 y)	Subgroup3 (60-79 y)	1 vs 2	2 vs 3	1 vs 3	1 vs 2	2 vs 3	1 vs 3
GA (%)									
Lower limit	10.29	10.38	10.22	0.108	0.178	0.084	Nonpartitioning	Nonpartitioning	Nonpartitioning
Upper limit	13.80	14.27	15.18	0.566	1.011	1.663	Marginal	Partitioning	Partitioning
Mean±SD#	11.98±0.83	12.20±0.90	12.41±0.99						
FA (μmol/L)									
Lower limit	217.0	221.5	221.4	0.234	0.005	0.229	Nonpartitioning	Nonpartitioning	Nonpartitioning
Upper limit	298.0	301.5	301.4	0.182	0.005	0.177	Nonpartitioning	Nonpartitioning	Nonpartitioning
Mean±SD*	257.1±19.3	258.5±19.2	260.6±19.2						
1,5-AG (μmol/L) male									
Lower limit	107.3	114.7	87	0.132	0.450	0.363	Nonpartitioning	Marginal	Marginal
Upper limit	347.6	378.5	372.5	0.552	0.098	0.445	Marginal	Nonpartitioning	Marginal
Mean±SD#	228.9±56.0	225.5±61.5	221.8±70.6						
Female									
Lower limit	80.3	71.4	80.1	0.213	0.163	0.005	Nonpartitioning	Nonpartitioning	Nonpartitioning
Upper limit	242.9	295.9	346.8	1.271	0.951	2.492	Partitioning	Partitioning	Partitioning
Mean±SD*	156.8±41.7	174.0±53.5	213.0±70.6						

Compared variables across three age groups: #$P<.001$, *$P>.05$. 1,5-AG (μmol/L)≈6×1,5-AG (μg/mL).

The ratio of the distance between reference limit of subgroups and the smaller SD of each subgroup, D. The results are compared with others using Lahti algorithm to judge the need for partitioning: Marginal (the subgroup reference limits at each end of the distribution between 0.25SD to 0.75SD); nonpartitioning, no need for partitioning (the subgroup reference limits at each end of the distribution <0.25SD); partitioning, need for partitioning (the subgroup reference limits at each end of the distribution >0.75SD).

SD, Standard deviations; 1,5-AG, 1,5-anhydroglucitol; GA, glycated albumin; FA, fructosamine; 1 VS 2, subgroup1 vs subgroup 2; 2 VS 3, subgroup2 vs subgroup3; 1 VS 3, subgroup1 vs subgroup3.

TABLE 5 Reference intervals for the three glycemic markers that were evaluated

	GA, %		1,5-AG, μmol/L (μg/mL)	FA, μmol/L
	20-59 y	60-79 y	20-79 y	20-79 y
Male	10.38-13.89	10.23-14.79	107-367 (17.8-61.2)	220-298
Female			79-306 (13.2-51.0)	

1,5-AG (μmol/L)≈6×1,5-AG (μg/mL).
1,5-AG, 1,5-anhydroglucitol; GA, glycated albumin; FA, fructosamine.

intervals recommended by manufacturer. The reason may be related to our strictly enrolled criteria, the values of laboratory results within reference intervals.

Studies have shown 1,5-AG reflects postprandial hyperglycemia as well as glycemic excursions better than HbA1c or FA in patients with diabetes under moderately controlled state (HbA1c 6.5%-8.0%).[23,24] Furthermore, 1,5-AG has a high sensitivity in monitoring and dosing adjustment of treatment for patients with diabetes.[25,26] Our data suggested the level of 1,5-AG in females was lower than males (Table 2). The absolute difference was 51 μmol/L (8.5 μg/mL) in mean level, which was too great to be clinically relevant. So, the gender group required partitioning between males and females. For males, Lahti algorithm did not recommended partitioning in age group, even 1,5-AG levels across the three groups were statistically different (Table 4). For females, 1,5-AG levels across the three groups were statistically different. Lahti algorithm suggested need of partitioning for the upper reference limits, but no need of partitioning for the lower reference. In other hand, tubular reabsorption is inhibited by glucose accelerated in urinary excretion of 1,5-AG correspondingly dropped in the serum concentrations of 1,5-AG in hyperglycemic conditions. That is, the lower reference limit is used as decision limit. Overall, we did not suggest partitioning of age groups. The reference intervals for 1,5-AG were 107-367 μmol/L (17.8-61.2 μg/mL) for males and 79-306 μmol/L (13.2-51.0 μg/mL) for females. Yamanouchi et al. recommended 14 μg/mL as the lower limit for normal 1,5-AG levels, which are well accepted, whereas this result was the cutoff for the diagnosis of diabetes and in their study, the gender difference was not considered.[27] Other researchers obtained the reference intervals in US population were 10.2-33.8 μg/mL for males and 5.9-31.8 μg/mL for females, and reference intervals in Japan for males and females were 12.2-41.0 μg/mL and 9.5-33.5 μg/mL.[10,28]

Studies have shown that FA, GA, and 1,5-AG as nontraditional glycemic markers may be useful in identifying persons at risk for diabetes and were associated with development of diabetes.[29] In this study, we obtained the reference interval of FA was 220-298 μmol/L, which was similar to the study published by Kruse-Jarres et al.[30] for adults without diabetes (205-285 μmol/L). However, the lower and upper reference limits of our study were higher than Kruse-Jarres et al., approximately 15 μmol/L, which may be related to the discrepancy of population. Chen et al.[11] reported that the levels of FA in the age 20-65 years (249.88±18.39 μmol/L) were significantly lower than the age 65-85 years (264.63±23.05 μmol/L), which we does not detect the difference in those age group.

In this study, we enrolled eligible reference individuals to establish reference range for nontraditional glycemic markers. Furthermore, the methods we used were better standardized and more precise,[7] enzymatic method for GA and dye nitroblue tetrazolium (NBT) assay for FA. The methods have a low biological variation in clinical practice,[31], and the coefficient of variations for GA, FA, and 1,5-AG in this study met the requirement of instrument. However, it should note that American Diabetes Association (ADA) Expert Committee in 2003 reported reduced lower FPG cut point to define impaired fasting glucose (IFG) from 6.1 to 5.6 mmol/L. However, this change in the definition of IFG had not been adopted by the World Health Organization and many other diabetes organizations.[1] So, in this study, we also considered the normal reference range of FPG in healthy adult was 3.89-6.11 mmol/L.

There were several limitations to this study. Firstly, sample size in each age and gender group might be limitation of the study. Secondly, this study was a single-center research, and the results which we obtained that were used in other centers should be verified.

In conclusion, new reference intervals for nontraditional glycemic markers were established based on a Chinese healthy population. However, before the reference intervals of those glycemic markers reach consensus, it is difficult to use those biomarkers for diagnosis or monitoring of DM and it is unlikely that those biomarkers will be inserted in the future international guidelines. So multicenter investigations based on different region and ethnic background should be conducted in the future.

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AUTHOR CONTRIBUTIONS

Qiang Zhou and De-Bao Shi contributed equally to this work and should be considered cofirst authors.

ETHICAL STANDARD

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Declaration of Helsinki 2008.

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