The Establishment of Adult Reference Intervals on Fructosamine in Beijing

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Background: Fructosamine (FRA) is widely used for diabetes monitor and control as a glycemic marker, especially in patients in whom the measurement of HbA1c may be biased or even unreliable. However, the FRA reference intervals based on Asian population features still keep seldom reported. The objective of this study was to establish the adult FRA reference intervals in Beijing, China. **Methods:** A total of 1,497 healthy subjects were separated into three groups by gender and age. Subsequently, FRA levels in the collected serum samples from the reference individuals were tested by automatic chemical analyzer. The obtained data were statistically analyzed with SPSS. **Results:** The serum FRA level in female group was slightly higher than that in male group without statistical significance. Meanwhile, further analysis indicated that the FRA level

gradually increased along with the growth of the age. Compared with the age 20–45 group ($248.83 \pm 17.64 \mu\text{mol/l}$) or the age 46–65 group ($251.95 \pm 19.63 \mu\text{mol/l}$), the FRA level of the age >65 group ($264.63 \pm 23.05 \mu\text{mol/l}$) was statistically significantly increased ($P < 0.01$). To better analyze the difference, the age 20–45 group and the age 46–65 group were combined into an age 20–65 group ($249.88 \pm 18.39 \mu\text{mol/l}$). In comparison to the age >65 group, the FRA level of age 20–65 group was significantly decreased ($P < 0.01$). **Conclusion:** A novel FRA reference interval of the local healthy population in Beijing was established. The data demonstrated that there was no gender difference in FRA level, however, which was significantly increased in elder persons. J. Clin. Lab. Anal. 30:1051–1055, 2016. © 2016 Wiley Periodicals, Inc.

Key words: diabetes; fructosamine; glycated albumin; glycated hemoglobin A1c; glycemic marker; reference interval

INTRODUCTION

Fructosamine (FRA) indicates the level of blood glucose concentration over the past 2 or 3 weeks, which is widely used for diabetes monitoring and control as a glycemic biomarker (1, 2). Most of FRA detection reagent kits were from American and European manufacturers in clinical laboratories in China currently. At the mean time, the FRA reference intervals were established according to the features of American and European populations. However, due to the obvious differences of race, local lifestyle, nutritional habits, and geographical environment among Asian, American, and European populations, the FRA reference intervals provided at present were probably not appropriate to Asian population. Therefore, it is necessary to establish a FRA reference interval based on local residents for clinical diagnosis, treatment, and control for diabetes. The objective of the study was to

establish an adult FRA reference interval of Chinese in Beijing area.

MATERIALS AND METHODS

Instrument and Reagents

Roche Cobas 8000 automatic chemical analyzer, FRA reagent kits, calibrators, and internal quality

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control materials were purchased from Roche Diagnostics Company (Mannheim, Germany).

Subjects

A total of 1,497 healthy individuals aged 20–85 years (median age 42), including 399 men and 1098 women, were enrolled in this study.

Following the guideline for the diagnosis and classification of diabetes from World Health Organization (WHO, 1998) and C28-A2 guideline from Clinical and Laboratory Standards Institute (CLSI) (3), the exclusion criteria included diabetes mellitus, impaired glucose tolerance (IGT), hypoproteinemia, hypoalbuminemia, cardiovascular diseases, renal disease, endocrine disorders, liver obstruction, alcohol consumption, use of oral contraceptive, strenuous exercise or heavy manual labor, and women in pregnancy or lactation. In addition, all of these healthy individuals enrolled in this study were normal body weight indexes (BMI) and fasting plasma glucose (FPG) concentrations.

Sample Preparation and Analysis

Venous fasting blood specimens were collected and rapidly centrifuged at 1500 g for 10 min. FRA, FPG, and albumin levels in serum samples were subsequently tested with automatic chemical analyzer within 2 hr after separation.

Statistical Analysis

The statistical analysis of the data in this study was performed by SPSS. The data are presented as group mean $\pm$ SD. Differences between groups were assessed by one-way analysis of variance and followed by least-significant difference (LSD) test. A *P*-value of 0.05 was significant.

RESULTS

Distribution of Serum FRA Level in Healthy Adults

The FRA level in serum was ranged from 184.0 to 366 $\mu\text{mol/l}$ in 1,497 healthy individuals. Male and female accounted for 27% (399 subjects) and 73% (1098 subjects), respectively (Fig. 1A). Moreover, cases in age 20- to 45-year group, age 46- to 65-year group, and age >65-year group were up to 60% (891 subjects), 30% (453 subjects), and 10% (153 subjects), respectively (Fig. 1B). All data of serum FRA concentration approximately accorded with normal distribution (Fig. 1C).

Difference of Serum FRA Level on Gender in Healthy Adults

Samples adopted in this study were divided into two groups according to gender. The serum FRA level in female group was $252.45 \pm 19.46 \mu\text{mol/l}$, slightly higher than that in male group ($248.46 \pm 19.07 \mu\text{mol/l}$).

Fig. 1. Distribution of serum FRA level in healthy adults. (A) Distribution of subjects in female or male group. (B) Distribution of subjects in different age groups. (C) Histogram of serum FRA concentration in healthy adults.

However, the difference between the genders was not statistically significant ($P > 0.05$, Fig. 2 and Table 1).

Difference of Serum FRA Level on Age in Healthy Adults

Subsequently, 1,497 subjects were separated into three groups: age 20–45 group, age 45–65 group, and age >65 group. The serum FRA concentrations in three groups were then determined, respectively (Table 1). The results showed that compared with the age 20–45 group ($248.83 \pm 17.64 \mu\text{mol/l}$) or the age 46–65 group ($251.95 \pm 19.63 \mu\text{mol/l}$), the FRA level of the age >65 group ($264.63 \pm 23.05 \mu\text{mol/l}$) was increased statistically significant differences ($P < 0.01$). Nevertheless, the difference of the results between the age 20–45 group and the age 46–65 group was not statistically significant (Fig. 3A). To better observe the difference, the age 20–45 group and the age 46–65 group were combined into a group of age 20–65

($249.88 \pm 18.39 \mu\text{mol/l}$). The serum FRA level of age 20–65 group was significantly decreased compared with that of age >65 group ($P < 0.01$; Table 1; Fig. 3B).

DISCUSSION

Diabetes is one of the most severe and common endocrine human disorders (4, 5). Due to its high global prevalence and huge damage, frequently life-threatening complications including chronic pain, acute infectious diseases, retinopathy, neuropathy and cardiovascular disease, and diabetes must be regarded as a serious and increasing global health burden (5–7). An early diagnosis of diabetes and a strict glucose control are crucial for preventing or delaying the onset of these serious, even life-threatening, complications (5).

The current diagnostic and prognostic strategies in diabetes depend on the clinical laboratory examination, which is mainly based on two tests, plasma (or capillary) glucose and glycated hemoglobin A1c (HbA1c). However, the measurement of glucose and HbA1c may be biased due to the rapid changes of glucose homeostasis, red blood cell disorders, renal disease, etc. (8, 9). Compared with glucose and HbA1c, serum FRA measurement shows many advantages: (a) FRA can accurately reflect short-term changes in glycemia that corresponds to the half-life of albumin. (b) The patients in whom the HbA1c values are falsely low level ongoing hemolytic anemia associated with Myelodysplastic syndrome. FRA is an alternate indicator of glycemic control that has proven utility in situations when HbA1c is less accurate (10, 11). (c) HbA1c levels must be interpreted with caution in patients with hematologic diseases that change RBC survival lifetime. Nevertheless, FRA is unaffected by disorders of red blood cells or hemoglobin, and this test is useful in patients with blood loss or hemolytic anemia (10, 12). (d) FRA may be reliably measured irrespective of fasting or non-fasting status (1). (e) FRA, but not HbA1c, provides a significantly better parameter for estimating glycemic control and is associated with morbidity (hospitalizations and infections) in diabetic patients on hemodialysis (13, 14). (f) FRA enables intervention, improves diabetes control, and provides a more accurate indicator for ongoing glycemic control (10). These advantages suggested that FRA may be a more alternative marker of glycemic control for diabetes prevention.

The clinical laboratory should make sure the accurate results, and their appropriate reference ranges before the tests were used. To the determination of reference intervals, separate intervals were generally needed for different subclasses, preferentially by gender or age class (3). Our study revealed that the FRA level was not significantly different in gender (Fig. 2),

Fig. 2. Serum FRA level in gender group. The serum FRA level in female group was slightly higher than that in male group, but without statistical difference ($P > 0.05$).

TABLE 1. Serum FRA level and percentile in adult ($\mu\text{mol/l}$)

	N	Mean $\pm$ SD	2.5%	97.5%
Gender				
Male	399	248.46 ± 19.07	214.00	286.00
Female	1098	252.45 ± 19.46	217.00	292.00
Age (years)				
20–45	891	$248.83 \pm 17.64^{**}$	215.00	283.70
46–65	453	$251.95 \pm 19.63^{##}$	214.00	292.00
>65	153	264.63 ± 23.05	225.55	325.25
20–65	1344	$249.88 \pm 18.39^{\Delta\Delta}$	215.00	287.00
Total	1,497	251.39 ± 19.43	215.45	290.00
Published ^a	555		205.00	285.00

^{**} $P < 0.01$, age 20–45 group vs. age >65 group. ^{##} $P < 0.01$, age 46–65 group vs. age >65 group. ^{$\Delta\Delta$} $P < 0.01$, age 20–65 group vs. age >65 group.

^aThe published reference intervals on FRA by the manufacturer.

Fig. 3. Difference of serum FRA level among the different age groups. (A) The serum FRA level in age >65 group, age 20–45 group, and age 46–65 group. (B) Difference of serum FRA level between age >65 group and age 20–65 group. Differences between groups were assessed by one-way analysis of variance and followed by least-significant difference (LSD) test. ** $P < 0.01$.

and the small differences between both genders probably have no influence on the interpretation of clinical results.

In comparison to the gender factor, the dependency of FRA level on age might be of more significance. Further analysis in this study indicated that the FRA level gradually increased with the growth of age, which in the population of aged 65 and older was significantly higher than that in the age 20–65 population (Fig. 3). Moreover, the new FRA confidence interval on the age >65 group (225–325 μmol/l) was obviously higher than the FRA reference interval published by the manufacturer (205–285 μmol/l). However, the local FRA reference intervals of the age 20–65 group in Beijing population were not significantly different from American and European populations (Table 1). It suggested that the published reference intervals on FRA

by manufacturers be not applicable for the local elder residents in Beijing. In this study, a novel reference interval on serum FRA level was established on basis of the healthy adults, which might be relatively suitable for adult Chinese in Beijing. Moreover, the novel reference intervals of FRA in each subgroup passed the validation according to the C28-A2 guideline from CLSI (data not shown).

Previous studies have also shown that the glucose intolerance increases with age (15). Therefore, the principles of managing type 2 diabetes mellitus in the elderly were not different from those in younger patients, and the higher FRA level detected did not represent worse diabetes control in elder population. Apart from genetic predisposition and environmental influence, the lifestyle, stress, and minor physical activity may also be of particular importance.

CONCLUSION

We observed 1,497 healthy Chinese in Beijing area and established the FRA reference intervals of the local population. The data obtained from this study demonstrated that there was no gender difference on FRA level, while which was higher in elder age groups. Although it is hypothesized that similar reference intervals for fructosamine are likely applicable to populations in other Chinese cities as well, other clinical laboratories should investigate the transferability of the expected values to local population and determine their own reference ranges if practical. In addition, further researches on FRA as a useful indicator on the screening, diagnosis, treatment, and prognosis for diabetes mellitus are highly required.

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ETHICAL APPROVAL

This study was approved by the Ethics Committee of Xiyuan Hospital, China Academy of Chinese Medical Sciences (REC number: 2015XL038-1).

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