Reference Values for Continuous Glucose Monitoring in Chinese Subjects

JIAN ZHOU, MD[1]
HONG LI, MD[2]
XINGWU RAN, MD[3]
WENYING YANG, MD, PHD[4]
QIANG LI, MD, PHD[5]
YONGDE PENG, MD, PHD[6]
YANBING LI, MD[7]
XIN GAO, MD[8]
XIAOJUN LUAN, MD[9]
WEIQING WANG, MD, PHD[10]
WEIPING JIA, MD, PHD[1]

OBJECTIVE — The widespread clinical application of continuous glucose monitoring (CGM) is limited by the lack of generally accepted reference values. This multicenter study aims to establish preliminary normal reference values for CGM parameters in a sample of healthy Chinese subjects.

RESEARCH DESIGN AND METHODS — A total of 434 healthy individuals with normal glucose regulation completed a 3-day period of glucose monitoring using a CGM system. The 24-h mean blood glucose (24-h MBG) and the percentage of time that subjects' blood glucose levels were ≥140 mg/dl (PT140) and ≤70 mg/dl (PT70) within 24 h were analyzed.

RESULTS — There was excellent compliance of finger stick blood glucose values with CGM measurements for subjects. Among the 434 subjects, the daily blood glucose varied from 76.9 ± 11.3 to 144.2 ± 23.2 mg/dl. The 24-h MBG, PT140, and PT70 were 104 ± 10 mg/dl, 4.1 ± 5.8%, and 2.4 ± 5.3%, respectively. As for these parameters, no significant differences were found between men and women. The 95th percentile values were adopted as the upper limits of CGM parameters, which revealed 119 mg/dl (6.6 mmol/l) for 24-h MBG, 17.1% for PT140, and 11.7% for PT70.

CONCLUSIONS — We recommend a 24-h MBG value <119 mg/dl, PT140 <17% (4 h), and PT70 <12% (3 h) as normal ranges for the Chinese population.

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Glucose monitoring is a key component in diabetes management. Monitoring results can be used clinically in determining the degree of glucose metabolic disturbance, evaluating therapeutic outcomes, and guiding the adjustment of treatment regimens (1). Compared with traditional monitoring methods, the recently developed continuous glucose monitoring (CGM) technique provides much more glycemic information, including magnitude, duration, and frequency of blood glucose levels, which is used to better understand the properties of shifting blood glucose levels throughout the day. Although some drawbacks exist, CGM is able to reveal hyperglycemia and asymptomatic hypoglycemia that are normally difficult to detect, so as to provide evidence for optimal treatment decisions (2–4). The extensive data obtained from CGM could further characterize the blood glucose profiles in patients with diabetes (5). With its capability of recording blood glucose fluctuations, CGM also represents a new tool for studying the influence of factors on glucose variations in real life (6). Thus, applications of CGM continue to expand in both clinical practice and research settings. However, few investigations of blood glucose profiles in the population without diabetes have been performed using CGM. Moreover, there remains a paucity of reference data reflecting the typical daily patterns and profiles of normal glycemia in the healthy population, negatively impacting the general application of the CGM technique and the rational interpretation of the data obtained. This multicenter study aims to generate preliminary normal reference values for CGM parameters using data collected over 3 consecutive days in a sample of healthy Chinese subjects.

RESEARCH DESIGN AND METHODS

— We enrolled Chinese subjects from 10 academic hospitals in China between October 2007 and July 2008. The inclusion criteria included the following: *1*) clinically stable condition with no previous medical history of diabetes, hypertension, dyslipidemia, coronary artery diseases, or cerebral stroke; *2*) fasting plasma glucose <100 mg/dl and 2-h plasma glucose (2-h PG) <140 mg/dl after a 75-g oral glucose tolerance test (OGTT), according to 2008 American Diabetes Association diabetes diagnostic criteria (7); *3*) normal BMI between 18.5 and 24.9 kg/m^2, according to 2004 World Health Organization obesity diagnostic criteria (8); *4*) triglycerides <150 mg/dl and HDL cholesterol ≥40 mg/dl, according to 2007 Chinese guidelines on pre-

From the [1]Department of Endocrinology and Metabolism, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai Diabetes Institute, Shanghai Clinical Center for Diabetes, Shanghai, China; the [2]Department of Endocrinology and Metabolism, Sir Run Run Shaw Hospital, College of Medicine, Zhejiang University, Hangzhou, China; the [3]Department of Endocrinology and Metabolism, West China Hospital, Sichuan University, Chengdu, China; the [4]Department of Endocrinology and Metabolism, China-Japan Friendship Hospital, Beijing, China; the [5]Department of Endocrinology and Metabolism, The Second Affiliated Hospital of Harbin Medical University, Harbin, China; the [6]Department of Endocrinology and Metabolism, Shanghai Jiao Tong University Affiliated First People's Hospital, Shanghai, China; the [7]Department of Endocrinology and Metabolism, The First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China; the [8]Department of Endocrinology and Metabolism, Fudan University Affiliated Zhongshan Hospital, Shanghai, China; the [9]Department of Endocrinology and Metabolism, The First People's Hospital of Foshan, Foshan, China; [10]Shanghai Clinical Center for Endocrine and Metabolic Diseases, Shanghai Institute of Endocrinology and Metabolism, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China.
Corresponding author: Weiping Jia, wpjia@sjtu.edu.cn.
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vention and treatment of dyslipidemia (9); and 5) systolic pressure <140 mmHg and diastolic pressure <90 mmHg (10). The exclusion criteria included the following: *1*) use of medications that may affect glucose metabolism, such as glucocorticoids, thyroid hormones, and thiazide diuretics, 1 month before the study and 2) hepatic or renal dysfunctions (>1.5-fold elevation of alanine aminotransferase, aspartate aminotransferase, or direct bilirubin or serum creatinine >115 μmol/l). This study was independently approved by the ethics committee of each participant hospital. All subjects gave and signed written informed consent before study initiation. No accompanied medications that adversely affect glucose tolerance were allowed during the trial.

CGM

CGM system. The CGM system (CGMS) sensor (Medtronic, Northridge, CA) was inserted into all subjects by the same specialized nurse at day 0 at ~8:00–9:00 A.M. in hospital. First CGMS calibration by finger stick blood glucose was performed after 1 h of initialization. If no abnormal CGMS situation was observed, the subjects were dismissed and continued with CGM at home for 3 consecutive days. Subjects were instructed to input at least four calibration readings per day. At day 3 at ~8:00–9:00 A.M., subjects came to the hospital and had the CGMS removed. Adopted from previous established criteria for optimal accuracy of the CGMS (11,12), the following criteria for optimal accuracy were adhered to: a correlation between the sensor and meter readings of at least 0.79 and a mean absolute difference of ≤28% (when the daily range [min–max] of meter values was ≥100 mg/dl) and a mean absolute difference of ≤8% (when the daily range [min–max] of meter values was <100 mg/dl).

CGM parameters. The 24-h mean blood glucose (24-h MBG) was calculated as mean blood glucose level from 288 readings measured by a CGMS over 24 h. Daytime and nighttime mean blood glucose levels were defined as blood glucose levels during the time intervals of 6:00 A.M. to 10:00 P.M. and 10:00 P.M. to 6:00 A.M., respectively. Postprandial blood glucose levels at 30, 60, 120, and 180 min and the area under the curve within 3 h after each meal were recorded and calculated. For each subject, the proportion of time spent on the blood glucose ranges of 70–140 (3.9–7.8 mmol/l), ≥ 140, and ≤70 mg/dl were determined from the CGM data. Percentage of time (PT) for blood glucose ≤70 mg/dl and ≥140 mg/dl within 24 h were recorded as PT70 and PT140, respectively (13,14). Other CGM parameters, including the area under the curve for blood glucose >100 mg/dl and the SD of blood glucose concentration within 24 h were also calculated (13,14). All of the above parameters were based on the mean values taken on days 1 and 2.

Mixed-meal method. All subjects received dietary instructions according to uniform criteria as the CGMS was implemented. The total calorie intake from the three daily meals was 30 kcal · kg^{-1} · day^{-1} during CGM, with 50% carbohydrates, 15% proteins, and 35% fats. The amount of drinking water was not restricted. The calorie distribution between breakfast, lunch, and dinner was 20, 40, and 40%, respectively. There was a disciplinary time of 6:30–7:30 A.M. for breakfast, 11:30 A.M. to 12:30 P.M. for lunch, and 6:00–7:00 P.M. for dinner. Each meal had to be consumed within 30 min. Subjects were required to follow the dietary instruction during the CGM.

Laboratory examinations

Plasma glucose was determined using the glucose oxidase method. Fully automatic biochemistry analyzer (Hitachi 7600-020; Hitachi, Tokyo, Japan) (enzymatic methods) was used to determine hepatic and renal function, triglycerides, and HDL, LDL, and total cholesterol. Surestep blood glucose meter (American Lifescan) was used to determine finger stick capillary blood glucose.

Statistical methods

CGM parameters were analyzed using CGMS software 3.0. Measurement data was presented as means ± SD. Statistical analyses were performed using SPSS software (version 13.0). The *t* test was used for comparison between two groups when data were normally distributed; otherwise, nonparametric analysis was applied. Pearson and Spearman analytical methods were employed for correlation analysis of two variables.

RESULTS

Subject characteristics

This study screened 588 subjects, among which 445 healthy subjects without related metabolic disorders were recruited for CGM. Eleven subjects were excluded for final analysis due to the CGMS signal interruption or not meeting the accuracy requirements. None of the subjects complained of discomfort, such as inflammation or allergy at the embedding sites. Data from the remaining 434 subjects (213 men and 221 women) were incorporated into the statistical analysis. The 434 subjects were 43 ± 14 years old (means ± SD), with a range in age from 20 to 69 years. Subject distribution among age-groups was similar: 23.5% were 20–29, 20.7% were 30–39, 19.8% were 40–49, 18.4% were 50–59, and 17.6% were 60–69 years old. The mean BMI was 21.8 ± 1.7 kg/m^2. Compared with women, men had higher BMI, blood pressure (both systolic and diastolic), triglyceride levels, and OGTT 30-min plasma glucose ($P < 0.05$) and lower levels of HDL cholesterol and OGTT 3-h plasma glucose ($P < 0.001$) (Table 1).

Correlation analysis of interstitial glucose values by CGM and corresponding capillary blood glucose

For 434 healthy subjects, a total of 379,308 CGM readings were obtained. The averages of 3,697 interstitial glucose values retrieved from the CGM and their corresponding finger stick capillary blood glucose were 103 ± 21 and 103 ± 17 mg/dl, respectively, with a mean absolute difference of 9.0 ± 8.4%. Pearson correlation analysis revealed a positive correlation between these two values ($r = 0.822$, $P < 0.001$).

Characteristics of glucose profiles in healthy subjects by CGM

A glucose profile using the 24-h mean data from 434 subjects is shown in Fig. 1. The 24-h MBG was 104 ± 10 mg/dl (5.77 ± 0.57 mmol/l), and the area under the curve for blood glucose >100 mg/dl was 9.7 ± 6.7 mg · dl^{-1} · day^{-1}. The nighttime MBG was lower than the daytime MBG by 9 ± 7% (98.6 ± 11.3 vs. 106.4 ± 11.3 mg/dl, $P < 0.001$). There were similar MBG levels for men and women (Table 1).

In 434 subjects, the daily blood glucose varied from a mean minimum of 76.9 ± 11.3 mg/dl to a mean maximum of 144.2 ± 23.2 mg/dl. The SD of blood glucose was 14.2 ± 5.8 mg/dl. There were no significant differences between men and women for these parameters (Table 1).

The postprandial blood glucose levels at 30, 60, 120, and 180 min after each meal, as well as postprandial area under the curve within 3 h, are listed in Table 2. Postprandial blood glucose level at 60

Table 1—*Characteristics of subjects by sex*

	Men	Women	*P*
n	213	221	NA
Age (years)	43 ± 14	42 ± 14	0.569
BMI (kg/m^2)	22.1 ± 1.7	21.5 ± 1.7	0.001*
Systolic blood pressure (mmHg)	117 ± 10	111 ± 13	<0.001*
Diastolic blood pressure (mmHg)	76 ± 6	71 ± 8	<0.001*
Total cholesterol (mg/dl)	174 ± 31	178 ± 35	0.171
Triglycerides (mg/dl)	93 ± 32	87 ± 32.8	0.038*
HDL cholesterol (mg/dl)	57 ± 14.3	64 ± 15.9	<0.001*
LDL cholesterol (mg/dl)	105 ± 29.0	104 ± 35.2	0.854
Fasting plasma glucose (mg/dl)	86.4 ± 7.7	86 ± 7.9	0.682
OGTT 30-min plasma glucose (mg/dl)	145 ± 29.3	134.1 ± 26.1	<0.001*
OGTT 1-h plasma glucose (mg/dl)	124 ± 38.5	118.1 ± 33.8	0.084
OGTT 2-h plasma glucose (mg/dl)	94 ± 21.1	98.1 ± 19.3	0.061
OGTT 3-h plasma glucose (mg/dl)	71 ± 15.8	74.4 ± 16.8	0.045*
MBG (mg/dl)			
24 h	104 ± 10.8	103.9 ± 9.9	0.854
Daytime	106 ± 11.5	106.6 ± 11.2	0.853
Nighttime	99 ± 11.9	98.3 ± 10.6	0.518
Percentage of time at glycemia (%)			
Blood glucose ≥140 mg/dl	4.2 ± 5.9	4.0 ± 5.7	0.612
70 < blood glucose < 140 mg/dl	93 ± 8	94 ± 7	0.550
Blood glucose ≤70 mg/dl	2.7 ± 6.1	2.1 ± 4.4	0.987
Area under the curve for blood glucose >100 mg/dl (mg · dl^{-1} · day^{-1})	10.1 ± 6.8	9.5 ± 6.5	0.471
SD of blood glucose (mg/dl)	14.2 ± 5.9	14.2 ± 5.8	0.928
Max blood glucose (mg/dl)	144.2 ± 23.8	144.2 ± 22.9	0.972
Min blood glucose (mg/dl)	77.2 ± 11.9	76.5 ± 11.0	0.754

Data are mean ± SD. *Significant difference between men and women ($P < 0.05$). NA, not applicable.

min was the highest among the four postprandial time points for all three meals. At the time points of 120 and 180 min, comparison between the meals revealed a significantly lower blood glucose level after breakfast than after lunch and dinner, respectively ($P < 0.05$). No significant differences were observed between blood glucose levels after lunch and after dinner.

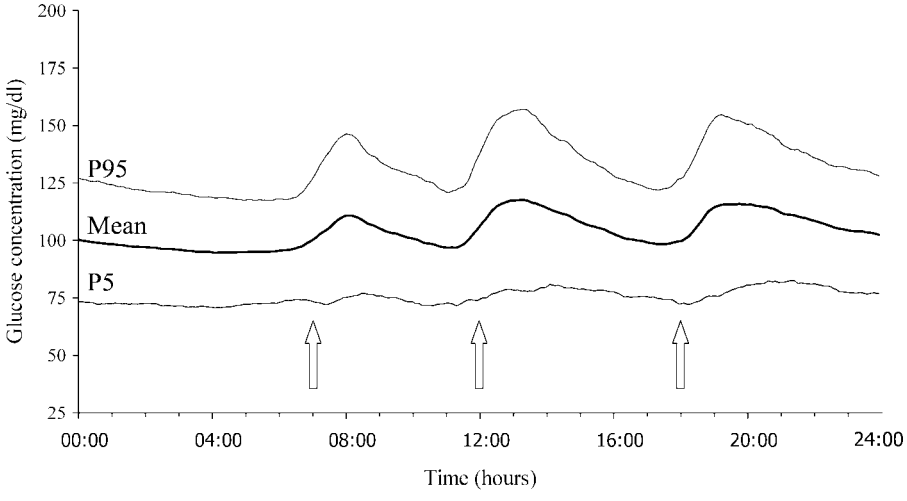

Figure 1—*Continuous glucose profiles representing mean data from 24 h of monitoring in 434 healthy subjects. The* center line *is the mean, the next two* outer lines *represent the 5th and 95th percentiles (P5 and P95, respectively). The arrows indicate the time for three meal intakes during a day.*

Fluctuation of blood glucose within 70–140 mg/dl accounted for 93 ± 8% of the total day for the 434 subjects. PT140 and PT70 were 4.1 ± 5.8% and 2.4 ± 5.3%, respectively. Approximately 60% of subjects ($n = 260$) experienced blood glucose ≥140 mg/dl, with a percentage of cumulative time duration of 6.8 ± 6.1%. Eight subjects (1.8%) experienced blood glucose ≥200 mg/dl, with the longest episode lasting 45 min. The cumulative time of blood glucose ≥200 mg/dl for these subjects was 37 ± 18 min. Blood glucose ≤70 mg/dl was detected in 176 (41%) subjects and blood glucose ≤50 mg/dl in 24 subjects (5.5%). The cumulative time duration for blood glucose ≤70 mg/dl accounted for 5.9 ± 7.0% of the day, and the cumulative time for blood glucose ≤50 mg/dl was 30 ± 26 min, lasting for 5–30 min each episode.

In all subjects, the distributions of 24-h MBG, PT140, and PT70 departed from normality. The coefficients of skewness for these parameters were −0.252, 1.785, and 3.673, respectively. The 95th percentiles of 24-h MBG, PT140, and PT70 were set as reference values, with the upper limit of 119 mg/dl (6.61 mmol/l) for 24-h MBG, 17.1% for PT140, and 11.7% for PT70 (Table 3).

CGM parameters in relation to sex and age

While both the 24-h MBG and PT140 showed a sex-independent weak positive correlation with age ($r = 0.243$, 0.277; $P < 0.001$; $r = 0.251$, 0.175; $P = 0.009$), the PT70 did not ($P > 0.05$). Analyses for different age-groups revealed an increased 24-h MBG level for men aged >40 years ($P < 0.01$) and for women aged >60 years ($P < 0.01$). PT140 increased in subjects aged >60 years for both sexes ($P < 0.01$). There was no significant difference for PT70 among the age-groups ($P > 0.05$). No significant difference between men and women was observed within any of the age-groups ($P > 0.05$) (Table 3).

Reproducibility of CGM evaluation

Reproducibility of CGM was evaluated in a subgroup of 20 subjects, of which two men and two women from each of the five age-groups (20–29, 30–39, 40–49, 50–59, and 60–69 years) were randomized. A 3-day CGM was repeated on these subjects 8–12 weeks after the initial measurements. The 20 subjects were aged 43 ± 16 years (range 22–68), with a BMI of 22.2 ± 1.8 kg/m^2. No significant differ-

Table 2—*Postprandial blood glucose characteristics after three meals in 434 healthy subjects*

	Breakfast	Lunch	Dinner
Postprandial blood glucose 30 min (mg/dl)	114.3 ± 15.6	117.2 ± 18.9	116.6 ± 17.8
Postprandial blood glucose 60 min (mg/dl)	121.1 ± 21.3	121.7 ± 20.9	123.1 ± 26.1
Postprandial blood glucose 120min (mg/dl)	104.8 ± 18.0	115.6 ± 22.3*	119.7 ± 21.2*
Postprandial blood glucose 180min (mg/dl)	97.6 ± 17.6	109.3 ± 17.3*	114.1 ± 18.1*
Postprandial area under the curve within 3 h ($mg \cdot dl^{-1} \cdot h^{-1}$)	327.3 ± 38.7	340.6 ± 47.4*	348.7 ± 51.5*

Data are means ± SD. For each parameter, *$P < 0.05$ vs. blood glucose level after breakfast.

ence was observed between the measurements taken at the two time periods for any of the parameters. The values obtained for the two measurements were 103.7 ± 10.8 mg/dl for 24-h MBG, 2.6 ± 3.8% for PT140, and 0.7 ± 1.1% for PT70 at the first session and, correspondingly, 106 ± 11.5 mg/dl, 3.8 ± 5.7%, and 1.3 ± 2.3%, respectively, at the second session ($P > 0.05$ for all three parameters).

CONCLUSIONS — The CGM technique, using interstitial fluid for glucose determination (15), provides continuous information on dynamic changes in a subject's blood glucose levels. The current study offers an opportunity to document the typical glycemic patterns in a large sample of continuously monitored healthy Chinese subjects, which provides a feasible and timely approach to obtaining reference values. Considering the distribution of certain parameters in people without diabetes as a starting point for the analysis, the study used means ± 2 SD or 95th percentile (for defining normality) to obtain a normal reference value. This proposal has been applied for determination of physiological parameters such as ambulatory blood pressure (16,17). Different from reference data derived from epidemiologic studies of large populations (18), the present study completed glucose measurement under routine living conditions, generating a more precise portrayal of typical daily glucose patterns of normal individuals.

The results of this study most likely reflect typical glycemic patterns for healthy subjects. The 24-h MBG of 434 subjects between ages 20 and 69 years was 104 mg/dl, a finding comparable with a recently reported 28-day CGM MBG (102 mg/dl) obtained from 32 healthy subjects using FreeStyle Navigator CGMS (19). Postprandial blood glucose level at 60 min was higher than 30, 120, and 180 min for all three meals. Generally, the glucose level after breakfast was lower than lunch or dinner, which might be closely related to the dietary structure and eating habits. In our study, more than half of the subjects experienced blood glucose ≥140 mg/dl, and 41% subjects experienced blood glucose ≤70 mg/dl. Similar glycemic excursions have also been reported by Mazze et al. (19) in subjects with normal glucose tolerance. The values for PT140 and PT70 obtained were 4 ± 4% and 3 ± 3%, respectively, while in our study they were correspondingly 4.1 ± 5.8% and 2.4 ± 5.3%, respectively. On average, healthy subjects had a daily blood glucose that fluctuated within the range of 70–140 mg/dl for 93% of the day in the present study.

CGM parameters provide general information on overall blood glucose levels and blood glucose stability. The 24-h MBG indicates glycemic control. Postprandial blood glucose levels, as well as percentage of time in hypoglycemia or hyperglycemia, provide the variability in glycemic characteristics (19). In the present study, the 95th percentile values for 24-h MBG, PT140, and PT70 were adopted as the upper normal limits, since all three parameters were non-normally distributed. The upper 95% confidence boundary for 24-h MBG was

Table 3—*Twenty-four-hour MBG and percentage of time at glycemia by sex and age*

	Men				Women				
	Aged 20–39 years	Aged 40–59 years	Aged 60–69 years	All	Aged 20–39 years	Aged 40–59 years	Aged 60–69 years	All	All subjects
n	93	80	40	213	99	86	36	221	434
MBG (mg/dl)	101.3 ± 10.8	105.3 ± 10.1	107.3 ± 10.4	104.4 ± 10.8	101.3 ± 9.2	103.9 ± 10.4	109.3 ± 9	103.7 ± 9.9	103.9 ± 10.3
P5	82.3	85.7	88.4	84.2	84.6	83.2	95.2	84.6	84.6
P10	85.7	89.3	95.4	88.2	86.4	89.6	97.2	90.2	89.1
P50	102.6	106.6	108	104.4	102.6	104.4	111.2	103.5	104.4
P90	116.1	117	119.5	117	111.6	117.9	121.0	117	117
P95	118.1	122.4	124.2	120.6	115.2	118.8	123.1	118.8	119.0
PT140 (%)	3.12 ± 4.96	4.24 ± 5.98	6.50 ± 7.08	4.17 ± 5.89	2.93 ± 4.47	3.80 ± 5.15	7.40 ± 8.05	4.0 ± 5.75	4.08 ± 5.76
P5	0	0	0	0	0	0	0	0	0
P10	0	0	0	0	0	0	0	0	0
P50	0.50	1.75	5.5	1.50	0.50	1.5	5.75	1.00	1.0
P90	9.30	13.0	17.0	12.8	9.0	11.4	21.3	12.5	12.5
P95	14.0	17.5	24.0	17.0	11.5	14.8	22.6	19.0	17.1
PT70 (%)	3.68 ± 7.25	1.60 ± 4.81	2.50 ± 4.95	2.68 ± 6.07	1.87 ± 3.59	2.40 ± 5.61	2.01 ± 3.42	2.10 ± 4.46	2.38 ± 5.31
P5	0	0	0	0	0	0	0	0	0
P10	0	0	0	0	0	0	0	0	0
P50	0	0	0	0	0	0	0	0	0
P90	9.3	3.95	10.9	9.0	6.0	7.2	9.10	7.00	8.0
P95	14.0	8.90	14.4	12.0	11.5	14.0	11.2	11.0	11.6

Data are means ± SD or percentile values.

~119 mg/dl (6.6 mmol/l), for PT140 was <17% (4 h), and for PT70 was <12% (3 h). Moreover, CGM measurements showed a favorable short-term reproducibility in one subgroup of healthy subjects. We found an excellent compliance of finger stick blood glucose with CGM measurements in this study. Establishment of the normal reference values may therefore provide important evidence for clinical determination of glucose metabolic disturbance and evaluation of diabetic therapeutic effects.

As indicated by evaluation of the relationship between CGM parameters with age and sex in this study, continuous blood glucose levels are independent of sex but increase with age. There was a significant increase in 24-h MBG in men aged >40 years and women aged >60 years. We also recommend a unified cutoff point for the normal reference values of the CGM parameters, similar to the normal glucose tolerance cutoff points recommended by the American Diabetes Association (7) or World Health Organization (20) without differentiating age or sex.

To our knowledge, this is the first multicenter study conducted that attempts to establish normal reference values for CGM parameters in a Chinese population. The operation consistency was well controlled by distributing uniform guidelines to each center and providing intensive subject education. The use of data from centers in different regions limits the potential for sample bias, which could be considered to enhance the validity of the results. However, it still has to be interpreted within the context of its limitations. This study does not cover age-groups other than ages 20–69 years. On the other hand, a cross-sectional study for determination of normal reference values requires a larger sample size and more geographic representations. Furthermore, the normal reference values of continuous blood glucose parameters established in this study need to be verified by future prospective follow-up studies.

There is an increasing demand for data that are able to capture both normal and abnormal blood glucose characteristics, due to the recent trend of reevaluation of blood glucose control in terms of diabetes complication–related factors such as blood glucose exposure, stability, and variability (21,22). CGM, by providing patterns of blood glucose fluctuations, meets this demand in clinical practice. The reported reference ranges for CGMS in a normal adult population can be used to aid diabetes management and to create a baseline for health monitoring. Future studies that explicitly define normal and abnormal CGMS parameter ranges in relation to resulting pathology would supplement this statistical definition and enable clinicians to better utilize CGM information to aid them in making therapeutic regimen adjustments.

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