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Original Research

Optimal Cutoff Value of 1-Hour Postload Glucose to Identify Insulin Resistance in Women with Polycystic Ovary Syndrome

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Abstract

Background: Despite the active researches recently conducted into the relationship between 1-h postload glucose (1-h PG) during standard oral glucose tolerance test and future risk of type 2 diabetes, research regarding the clinical capacity of 1-h PG to assess insulin resistance in those with polycystic ovary syndrome (PCOS) is still insufficient. The purpose of this study was to investigate the optimal 1-h PG cutoff value to identify insulin resistance in women with PCOS. **Methods**: One hundred fifty-three women aged 18 to 35 years who were diagnosed with PCOS were enrolled in this study. Insulin resistance was defined as having abnormal insulin sensitivity or hyperglycemia. Spearman's rank correlation coefficient and receiver operating characteristic (ROC) curve analyses were conducted to assess the relationship between 1-h PG and other parameters and to determine the optimal 1-h PG cutoff for identifying insulin resistance, respectively. **Results**: Significant correlations were observed between 1-h PG, 2-h PG and fasting glucose, and other fasting-state insulin sensitivity assessment indices, other than fasting insulin level. The optimal 1-h PG threshold value for identifying insulin resistance was 138.5 mg/dL. Categorization of patients based on the 1-h PG threshold showed significant differences for all laboratory variables related to insulin sensitivity/resistance, other than fasting insulin. **Conclusions**: Our results suggest that a 1-h PG value of $\geq$138.5 mg/dL may be a promising assessment index for identifying insulin resistance in women with PCOS.

Keywords: one-hour postload glucose; oral glucose tolerance test; insulin resistance; polycystic ovary syndrome; insulin sensitivity

1. Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age [1,2]. Insulin resistance and the resulting hyperinsulinemia play a crucial role in the pathogenesis of reproductive disorders such as PCOS [1–4]. Indeed, PCOS is a leading risk factor for prediabetes and type 2 diabetes mellitus (T2DM) in reproductive-aged women [5]; moreover, up to 35% of women with PCOS exhibit impaired glucose tolerance (IGT) and up to 10% meet the criteria for T2DM. Approximately 80% of women with PCOS and 95% of obese women with PCOS have insulin resistance [6]. Therefore, some authors suggest referring to PCOS as "syndrome XX", just as metabolic syndrome is alternatively termed "syndrome X" [5].

Insulin sensitivity reflects the opposite effect of insulin resistance [7]. However, there remains no universal testing modality for insulin resistance, and this lack of standardization makes the diagnosis of insulin resistance difficult [7]. While the hyperinsulinemic-euglycemic clamp is the gold standard method for assessing insulin sensitivity/resistance, it is difficult to apply in real-world clinical situations owing to its cost and various technical difficulties [7]. Fasting insulin concentration, homeostatic model assessment of insulin resistance (HOMA-IR), quantitative insulin sensitivity check index (QUICKI), and glucose-to-insulin ratio (GIR) are uncomplicated and inexpensive quantitative fasting-state (homeostatic) methods used to evaluate insulin sensitivity; therefore, these insulin sensitivity assessment indices (ISAIs) are currently the most common measures for evaluating insulin sensitivity and resistance [7].

The oral glucose tolerance test (OGTT) is another standard method used to evaluate insulin sensitivity/resistance because it assesses hyperinsulinemia and glucose tolerance. Hyperglycemia, which consists of prediabetes (increased risk of diabetes) and diabetes, can be assessed by measuring fasting glucose levels and postprandial or postload glucose levels after a glucose challenge [8]. A standard 2-h 75-g OGTT, rather than the measurement of fasting blood glucose levels alone, is recommended to screen for IGT and T2DM in women with PCOS [9,10].

While postprandial glucose concentrations peak 60 min after a meal in the normal population, they generally do not peak until approximately 2 hours after a meal in patients with diabetes [11]. Thus, the measurement of glucose levels 2 hours after the start of a meal is practical in general [8] and 1-h postload glucose (1-h PG) level during OGTT has been overlooked thus far compared to fasting and 2-h postload glucose (2-h PG) levels, except in specific clinical conditions such as gestational diabetes [12]. Recently, however,

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some authors have suggested that 1-h PG can identify insulin resistance in the presence of normal glucose tolerance and is superior to fasting and 2-h PG levels as a predictor of T2DM and its associated complications [13–20].

Despite active researches on the relationship between 1-h PG and future T2DM risk, research on the clinical capacity of 1-h PG to assess insulin resistance in patients with PCOS remains insufficient. The present study investigated the relationship between 1-h PG during the standard 75-g OGTT and a variety of parameters related to insulin sensitivity/resistance, including fasting glucose, 2-h PG, and other fasting ISAIs, and further identified the optimal threshold value of 1-h PG to predict insulin resistance (determined by ISAIs) in women with PCOS.

2. Materials and Methods

2.1 Subjects

This retrospective study recruited Korean women aged 18–35 years who first visited Inje University Haeundae Paik Hospital between January 2010 and December 2013 and were diagnosed with PCOS according to the Rotterdam diagnostic criteria [2]. Among these patients, this study enrolled only those who met the recently revised diagnostic criteria in the international consensus guidelines for PCOS [21]. The exclusion criteria were [22,23]: patients previously diagnosed with diabetes, thyroid disease or hyperprolactinemia, had undergone ovarian surgery, or taking medications known to affect the level of any sex hormone or gonadotropin in the previous 6 months of enrollment (oral contraceptives, ovulation induction agents, glucocorticoids, or anti-androgens), or anti-diabetic drugs, including insulin sensitizers. This study was approved by the Institutional Review Board (IRB) of Inje University Haeundae Paik Hospital, which waived the requirement for written consent for subjects in the present study.

2.2 Measurement of Anthropometric Parameters and Ultrasound Examinations

Clinical anthropometric parameters were evaluated in all patients when they first visited the outpatient department. Pelvic ultrasound examinations (vaginal or rectal) were conducted in the early follicular phase using a Voluson LOGIQ S7 (GE Ultrasound Korea, Ltd., Seongnam, Korea) equipped with a microconvex intracavitary probe with a frequency range of 3.6–9.0 MHz. All ultrasound examinations were conducted by the same reproductive endocrinologist based on the international consensus on ultrasound assessment of PCOS [24].

2.3 Biochemical Measurements and Determination of Hyperglycemia

Blood samples were collected from all study participants following an overnight fast according to the guidelines of the Declaration of Helsinki. The sera were separated by centrifugation and used to evaluate glucose and insulin levels. Glucose levels during fasting and 60 and 120 min after glucose ingestion during the 2-h OGTT were measured using L-Type GluI (Wako Pure Chemical Industries, Ltd., Osaka, Japan). Fasting insulin levels were evaluated using an Elecsys insulin assay (Roche Diagnostics Corp.). Both the intra- and inter-assay coefficients of variation for all tests were $<5\%$. In the present study, hyperglycemia, comprising prediabetes (high fasting glucose or IGT) and diabetes, were diagnosed based on American Diabetes Association (ADA) [8] as fasting glucose $\geq$100 mg/dL or 2-h PG $\geq$140 mg/dL.

2.4 Assessment of Insulin Sensitivity and Determination of Insulin Resistance

We assessed insulin sensitivity in patients with PCOS using four established fasting ISAIs: fasting insulin and three other indices derived from a combination of fasting insulin and glucose levels, as follows [22,23]: HOMA-IR was calculated as glucose value (mg/dL) $\times$ insulin value (μU/mL)/405; GIR was calculated by dividing the glucose value (mg/dL) by the insulin value (μU/mL); and QUICKI was calculated as 1/{log[insulin value (μU/mL)] + log[glucose value (mg/dL)]}.

Patients with PCOS showing abnormal levels for at least one of the established ISAI criteria in previous studies of Asian women were defined as having abnormal insulin sensitivity: fasting insulin $\geq$15 μIU/mL [25], HOMA-IR $\geq$2.64 [26], GIR $\leq$10.7, or QUICKI $\leq$0.34 [27].

In the present study, insulin resistance was determined as the presence of abnormal insulin sensitivity or hyperglycemia.

2.5 Statistical Analyses

Values are expressed as means $\pm$ standard deviation (SD). Correlation analysis was conducted to assess the relationships between 1-h PG and other parameters using Spearman's rank correlation coefficients and linear regression analysis, with partial correlations used to control for the effects of other covariates. Data from all study participants were used to identify the optimal 1-h PG cutoff value for identifying insulin resistance based on receiver operating characteristic (ROC) curve analysis. The confidence intervals (CIs) for the areas under the ROC curves with sensitivity and specificity were also evaluated. The optimal cutoff value of 1-h PG for identifying insulin resistance was defined as the threshold value at which the value of sensitivity plus specificity reached a maximum. ROC curve analysis was performed for insulin resistance as defined by the criteria applied in this study (described above). Unpaired *t*-tests were used to compare continuous parameters between the two groups, which were defined by the cutoff value for 1-h PG. All statistical analyses were conducted using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA), with $p < 0.05$ considered statistically significant.

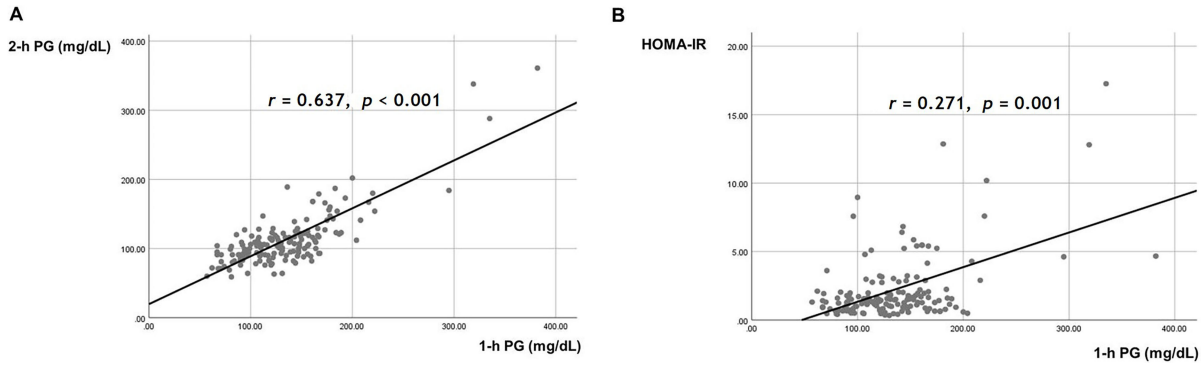

Fig. 1. Correlations of 1-h postload glucose concentration and other parameters related to glucose and insulin metabolism in women with polycystic ovary syndrome. (A) 2-h postload glucose level. (B) Homeostasis model assessment of insulin resistance.

Table 1. Baseline clinical characteristics of the study participants.

Characteristic	Participants (n = 153)
Age (years)	26.39 ± 5.18
Height (cm)	162.04 ± 5.32
Body weight (kg)	58.46 ± 14.44
Body mass index	22.23 ± 5.23
Waist to hip ratio	0.80 ± 0.07
Fasting glucose (mg/dL)	91.76 ± 13.42
Fasting insulin (μIU/mL)	9.24 ± 8.67

Values are mean ± standard deviation.

3. Results

This study included 153 patients. Table 1 shows the baseline anthropometric characteristics and laboratory parameters of the study participants.

To evaluate the ability of the 1-h PG test to identify patients with insulin resistance, we first performed a correlation analysis between 1-h PG levels and established ISAIs (Table 2). The 1-h PG level during the 75-g OGTT was significantly related to fasting glucose ($r = 0.302$, $p < 0.001$) and 2-h PG ($r = 0.637$, $p < 0.001$) level (Fig. 1A).

Significant correlations were observed between the 1-h PG and other ISAIs, despite the 1-h PG level was not significantly correlated with fasting insulin level ($r = 0.107$, $p = 0.189$). Fig. 1B shows the significant relationship between 1-h PG and HOMA-IR ($r = 0.271$, $p = 0.001$). These results did not change even after controlling for the effects of variables such as age, BMI, and waist to hip ratio (Table 2).

We conducted ROC curve analysis to determine the optimal 1-h PG cutoff value to identify insulin resistance. Based on the criteria for insulin resistance in the presence of abnormal insulin sensitivity or hyperglycemia in the present study, a total of 54 patients with PCOS showed insulin resistance. The ROC curve analysis revealed an optimal 1-h PG cutoff of 138.5 g/dL to reflect insulin resistance (Fig. 2), which was close to the existing 2-h PG reference value of 140 mg/dL for IGT [8].

Table 2. Correlations between 1-h postload glucose levels and other parameters related to glucose and insulin metabolism.

	r	p	r^a	p
Fasting glucose (mg/dL)	0.302	<0.001	0.637	<0.001
2-h PG (mg/dL)	0.637	<0.001	0.786	<0.001
Fasting insulin (μIU/mL)	0.107	0.189	0.152	0.080
HOMA-IR (fasting)	0.271	0.001	0.468	<0.001
GIR (fasting)	–0.210	0.009	–0.231	0.007
QUICKI (fasting)	–0.269	0.001	–0.354	<0.001

r, Spearman's rank correlation coefficient; and r^a, partial correlation coefficient adjusted by age, body mass index and waist to hip ratio.

2-h PG, 2-hour postload glucose; GIR, glucose-to-insulin ratio; HOMA-IR, homeostasis model assessment of insulin resistance; QUICKI, quantitative insulin sensitivity check index.

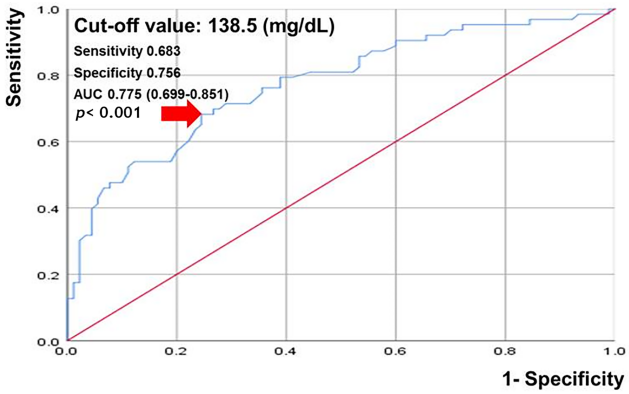

Fig. 2. Receiver operating characteristic curves were used to determine the optimal cutoff value of 1-h postload glucose on a 75-g oral glucose tolerance test in women with polycystic ovary syndrome.

All patients were divided into two groups according to the 1-h PG cutoff value: group 1 (1-h PG <138.5 mg/dL) and group 2 (1-h PG ≥138.5 mg/dL). Table 3 shows the significant differences in all laboratory parameters except fasting insulin levels between groups 1 and 2. While the mean

Table 3. Comparisons of clinical and biochemical parameters among patients with polycystic ovary syndrome and high or low 1-h postload glucose levels.

	Group 1 (n = 87)	Group 2 (n = 66)	*p*
Age	26.17 ± 5.04	26.67 ± 5.38	0.560
Height (cm)	161.93 ± 5.01	162.18 ± 5.74	0.771
Body weight (kg)	57.42 ± 14.24	59.82 ± 14.69	0.311
Body mass index (kg/m^2)	21.88 ± 5.25	22.70 ± 5.22	0.335
Waist-to-hip ratio	0.78 ± 0.06	0.81 ± 0.08	0.031
Fasting glucose (mg/dL)	88.67 ± 5.62	95.85 ± 18.70	0.003
1-h PG (mg/dL)	104.37 ± 20.74	174.80 ± 45.93	<0.001
2-h PG (mg/dL)	96.06 ± 17.64	135.33 ± 52.71	<0.001
Fasting insulin (μIU/mL)	8.45 ± 7.01	10.29 ± 10.43	0.220
HOMA-IR (fasting)	1.57 ± 1.36	3.07 ± 3.23	0.001
GIR (fasting)	18.49 ± 10.90	13.29 ± 8.35	0.002
QUICKI (fasting)	0.37 ± 0.04	0.35 ± 0.04	<0.001

Values are mean ± standard deviation.

Group 1 (1-h PG <138.5 mg/dL); and Group 2 (1-h PG ≥138.5 mg/dL).

1-h PG, 1-hour postload glucose; 2-h PG, 2-hour postload glucose; GIR, glucose to insulin ratio; HOMA-IR, homeostasis model assessment of insulin resistance; QUICKI, quantitative insulin sensitivity check index.

fasting insulin level of group 2 (10.29 ± 10.43 μIU/mL) was higher than that of group 1 (8.45 ± 7.01 μIU/mL), this difference was not statistically significant (p = 0.220). As shown in Table 3, the mean waist-to-hip ratio (WHR) of group 2 (0.81 ± 0.08) was significantly higher than that of group 1 (0.78 ± 0.06; p = 0.031). Neither body weight nor body mass index (BMI) differed between the two groups.

4. Discussion

Insulin resistance contributes to the pathophysiology of T2DM and is a cardinal characteristic of metabolic syndrome and many cardiovascular diseases [7]. Insulin resistance and compensatory hyperinsulinemia are critical components in the pathogenesis of PCOS [1,22] and are involved in the dysfunction of ovarian steroidogenesis in PCOS [1]. While it is difficult to explain the causes of insulin resistance in patients with PCOS, the complexity and polygenic nature of PCOS suggest that more than one mechanism may be involved. Although the most common cause of insulin resistance is obesity, obesity cannot thoroughly explain the relationship between PCOS and insulin resistance [1,6].

While the hyperinsulinemic-euglycemic clamp is considered the gold standard method to evaluating insulin sensitivity, clamp techniques and other methods requiring intravenous infusions and multiple blood samplings have no practical clinical application because of their costs, invasiveness, time-consuming nature, and dependence on experienced personnel [7,28]. Accordingly, we assessed insulin resistance in this retrospective study based on fasting insulin level, HOMA-IR, QUICKI, and GIR, all of which are uncomplicated and inexpensive quantitative fasting-state (homeostatic) methods for evaluating insulin sensitivity. In particular, QUICKI is a simple, accurate, and reproducible method use to accurately predict changes in insulin sensitivity after both therapeutic interventions and diabetes onset [7].

In the normal population, postprandial glucose concentrations are known to peak 60 min after the start of a meal, and return to preprandial levels within 2–3 hours [11,12]. Hulman *et al.* [29] reported that glucose curves varied greatly between classes, with peaks occurring after 32–61 min in clinically healthy participants. In contrast, in patients with diabetes, postprandial glucose levels generally peak approximately 2 h after the start of a meal and do not return to the control value for 4–6 hours [11,12]. Hence, 2-h PG is generally more practical than 1-h PG [8]. However, recent studies have suggested that 1-h PG following the standard OGTT may be more effective than fasting glucose or 2-h PG in identifying people at high risk for the future development of T2DM and its complications [14,16–18,20,30,31]. Abdul-Ghani *et al.* [14] conducted a study of 1551 non-diabetic subjects from the San Antonio Heart Study to assess the use of insulin secretion/insulin resistance indices to predict the risk of future T2DM over 7–8 years of follow-up, reporting a significant difference in the area under the ROC curve between 1-h PG, with a cutoff value of 155 mg/dL (0.84; 75% sensitivity and 79% specificity), and 2-h PG, with a cutoff value of 140 mg/dL (0.79; 92% sensitivity and 51% specificity). They also suggested in their other studies that a 1-h PG cutoff point of 155 mg/dL plus the Adult Treatment Panel III criteria for metabolic syndrome could be used to identify groups at high risk for future T2DM among currently nondiabetic subjects [15,16]. Bergman *et al.* [30] proposed that the measurement of 1-h PG might serve as a novel biomarker to detect dysglycemia

earlier than the currently recommended screening criteria for glucose disorders and could potentially replace the conventional 2-h PG following OGTT in a clinical setting.

Despite recent research advances on the effectiveness of 1-h PG in predicting T2DM and its associated complications, research on the clinical utility of 1-h PG to assess insulin resistance in patients with PCOS remains lacking. To our knowledge, this is the first study in women with PCOS to assess the optimal threshold of 1-h PG to identify insulin resistance; in the present study, however, the optimal cutoff point of 1-h PG for insulin resistance in PCOS patients was 138.5 mg/dL, which was close to the existing 2-h PG reference value of 140 mg/dL [9].

Insulin resistance is regarded as the single major determinant of 1h-PG [32]. Manco *et al*. [13] conducted a cross-sectional analysis in study participants with normal glucose tolerance from the Relationship between Insulin Sensitivity and Cardiovascular Risk study and suggested that the optimal 1-h PG if 8.95 mmol/L ($\fallingdotseq$ 161.26 mg/dL) on an OGTT to identify a subgroup of individuals with increased insulin resistance and β-cell dysfunction. Abdul-Ghani *et al*. [14] suggested that the optimal cutoff value for predicting future T2DM was 155 mg/dL. Our calculated optimal cutoff value of 1-h PG for predicting insulin resistance through the OGTT differed from those of previous well-validated studies [13,14]. The optimal 1-h PG threshold values in these two studies differed from ours. Although the discrepancy in cutoffs between these two studies and ours may be attributable to differences in factors, including subject race/ethnicity, sex, study design, blood samples (serum vs. plasma), and the criteria for determining insulin resistance, it may also suggest the need for a lower 1-h PG cutoff in patients with PCOS to predict insulin resistance. On the contrary, two studies to be mentioned below suggested 1-h PG cutoff values for identifying insulin resistance and predicting prediabetes which is similar to ours. Tricò *et al*. [33] reported that a 1h-PG concentration $\geq$7.4 mmol/L ($\fallingdotseq$ 133 mg/dL) during an OGTT is associated with a worse clinical and metabolic phenotype, and Marcovecchio *et al*. [34] suggested that a 1h-PG $\geq$132.5 mg/dL was able to identify those with impaired insulin sensitivity in overweight/obese Caucasian youth with normal glucose tolerance, and the suggested 1-h PG cutoff values of both studies were in agreement with ours.

In this study, WHR was the only anthropometric parameter that differed significantly between the two groups defined by the 1-h PG cutoff. Waist circumference is an important component of the diagnostic criteria for insulin resistance syndrome, as central adiposity is a cardinal characteristic of the syndrome [35] and WHR is a validated anthropometric indicator related to insulin resistance [36,37]. Given the significant relationship between obesity and insulin resistance, we expected that BMI would differ between the two groups in our study. Bianchi *et al*. [20], however, reported that patients with normal glucose tolerance with 1-h PG $>$155 mg/dL showed a significant difference in waist circumference but not in BMI compared with those with 1-h PG $\leq$155 mg/dL, which was strongly in agreement with our results. In another study, obesity did not affect the insulin response to oral glucose in PCOS-affected women with normal glucose tolerance [38].

Kulshreshtha *et al*. [38] reported amplified insulin response to glucose and that the difference between 1-h and 2-h post-glucose insulin decreased as glucose tolerance worsened in women with PCOS. Saxena *et al*. [3] noted that the 2-h postprandial insulin level was a good indicator of insulin resistance. In the present study, we only assessed the fasting insulin level and other ISAIs through a combination of fasting insulin and glucose levels; For accurate evaluation in this study, we should conduct an assessment of the postload insulin levels at 1 and 2 h following OGTT; however, an estimation of postprandial insulin levels is not in general included in the routine screening tests for those with PCOS, so we could not analyze the estimates of insulin sensitivity (e.g., Matsuda index) during the OGTT in this retrospective study, which leads to a major limitation of the present study. Furthermore, the sample size in this study was not large enough to conduct subgroup analysis according to the different specific PCOS phenotypes, which may be an additional drawback of our study.

5. Conclusions

In conclusion, the 1-h PG level during the standard 75-g OGTT was significantly correlated with other verified insulin sensitivity/resistance-related parameters. The 1-h PG value may be a promising alternative for the assessment of insulin sensitivity/resistance in women with PCOS, and the optimal calculated cutoff value reflecting insulin resistance was 138.5 mg/dL. Further large-scale prospective trials on predicting the future incidence of T2DM, with an additional analysis of postload/postprandial insulin levels, are needed to clarify these findings.

Author Contributions

These should be presented as follows. All authors—conceptualization; All authors—data curation; All authors—formal analysis; All authors—methodology; SC—project administration; SC—visualization; SC—writing–original draft; SL—writing–review & editing.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the guidelines of the Declaration of Helsinki. This study was approved by the Institutional Review Board (IRB) of Inje University Haeundae Paik Hospital (IRB No. 129792-2014-035), which waived the requirement for written consent for subjects in the present study.

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Conflict of Interest

The authors declare no conflict of interest.

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