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Research Article

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The Roles of Insulin Secretion, Insulin Resistance and Glucose Effectiveness in Developing Diabetes in Non-Obese Old Women

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Abstract

Background: *The impairment of glucose homeostasis are known to be attributed to the alterations of the four factors: first, second insulin secretion (FPIS, SPIS, respectively), glucose effectiveness (GE) and insulin resistance (IR).*

Objective: *Older women were enrolled to investigate the relationships of the four factors with T2DM.*

Designs: *A cross-sectional study.*

Settings: *MJ Health Screening Center in Taiwan*

Patients and Methods: *They were divided into normal glucose tolerance (NGT) and T2DM groups. Receiver operating characteristic (ROC) curve was performed and two models were built: Model 1: FPIS + GE and, Model 2: FPIS + GE + SPIS.*

Main Outcome Measures: *The area under ROC curve (AUC) was used to predict type 2 DM.*

Sample Size: *644 non-obese women.*

Results*: The AUC of SPIS was significantly higher than the diagonal line followed by GE and FPIS. Model 2 had the greatest AUC (0.968). An equation was built (-0.012-FPIS – 1003.9-GE – 119.4-SPIS + 20.7). It could predict the chance of having T2D with a sensitivity = 94.2% and specificity = 86.4%.*
Conclusions: SPIS is the most important contributor for T2DM in older women. The equation built from this model composed of FPIS, SPIS and GE could predict T2DM accurately.

Keywords: type 2 diabetes, first phase insulin secretion, second phase insulin secretion, insulin resistance, glucose effectiveness

Introduction

The roles of both insulin resistance (IR) and insulin secretion in triggering type 2 diabetes (T2DM) have been extensively studied, but mostly in Caucasians [1]. At the same time, after the diabetes is confirmed, these two factors are also important contributors to how well the blood glucose is controlled [2-4]. It should be noted that ethnic differences do exist in the pathophysiologies of T2DM. Thus, applying study results of Caucasians to Asians should always be exercised with cautious [2, 4].

Evidence has shown that first phase insulin secretion (FPIS) disappears even in the stage of prediabetes [5, 6]. Therefore, it is reasonable to postulate that, the maintenance of good glucose-control by only oral medications after diagnosis must be attributed to second phase insulin secretion (SPIS).Other than the aforementioned two factors, glucose effective (GE) is often overlooked by most of the researchers [7]. GE is the ability of glucose to reducing its own concentration in the circulation. In other words, there are two pathways for glucose to be cleared. One is insulin-dependent mechanism, which is the reciprocal of IR conceptually. The other one is non-insulin dependent, which is GE.

It should be noted that the methods used to quantify IR, PFIS, SPIS and GE are labor-intensive and expensive. For example, frequently sampled intravenous glucose tolerance test could give precise measurement of FPIS, insulin sensitivity and GE [8]. At the same time, hyperglycemic clamp is the 'gold standard' to quantify PFIS, SPIS and insulin sensitivity [9]. However, due to the complexity, these tests are unable to be used in a regular research center. To solve this problem, our group has published four equations to estimate

these factors by using only metabolic syndrome components and other simple demographic data [10-13].

Taiwan has already become an aging society since 2014 and approximately 11.4% of the population is over 65-year-old [14]. At the same time, diabetes is always on the 5th place of the top 10 causes of death [15]. Thus, how to early detect and prevent T2DM in the elderly is an important issue for health provider and the government. In the present cross-sectional study, we enrolled 644 old women and tried to elucidate the relative importance of FPIS, SPIS, GE and IR in developing T2DM.

Method

Study subjects: We randomly enrolled 644 females whose age was more than or equal to 65 years old from MJ Health Screening Center in Taiwan in 2011 and 2012. They received routine health examinations at the time of the study. MJ Health Screening Centers are private chain-clinics in Taiwan. They offer regular health examinations to their members. All study subjects were anonymous and written informed consents were obtained from all participants. All experiments were performed in compliance with the relevant laws. The study protocol was approved by the institutional review board of MJ Health Screening Center. Participants who were obese (BMI - 25 kg/m2) and on any medications known to affect blood pressure, glucose and lipids levels were all excluded. In the end, 644 qualified subjects were analyzed. They were further divided into normal glucose tolerance (NGT) and T2DM groups according to the criteria from American Diabetes Association [16].

On the day of the study, nursing staff obtained subjects' medical history, including medical information, thorough questionnaire, and complete physical examinations were performed. Waist circumference (WC) was measured horizontally at the level of the natural waist. BMI was estimated as the participant's body weight (kg) divided by the square of the subject's height (m). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by using mercury sphygmomanometers on the right arm of all subjects when they seated. After the subject had fasted for 8 hours, blood samples were collected from the antecubital vein for further analysis. Fasting plasma glucose (FPG) was quantified by using a glucose oxidase method (YSI 203 glucose analyzer, Yellow Springs Instruments, Yellow Springs, USA). Total cholesterol and triglycerides (TG) were quantified by using a dry, multilayer analytical slide method with the Fuji Dri-Chem 3000 analyzer (Fuji Photo Film, Tokyo, Japan). Serum high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) concentration were quantified by using an enzymatic cholesterol assay.

The equations used to calculate IR, FPIS, SPIS and GE are as following. It should be noted that all the units are in international unit. The journals they were published are coded after each equation.

$IR=\log^{10}$ (1.439+0.018-sex-0.003-age+0.029-BMI-0.001-SBP + 0.006-DBP + 0.049-TG-0.046-HDLC-0.0116-FPG) -103.^{333} [10].

$FPIS=10^{(1.477-0.119-FPG+0.079-BMI-0.523-HDLC)}$ [11].

$SPIS=10^{(-2.4-\ 0.088-FPG\ +\ 0.072-BMI)}$ [12].

GE=(29.196-0.103-age-2.722-TG-0.592-FPG) -10-3 [13].

Statistical analysis:

All statistical analyses were performed using SPSS 19.0 (IBM Inc., Armonk, New York). Data are presented as mean ± standard deviation. All data were tested for normal distribution with Kolmogorov–Smirnov test and for homogeneity of variances with Levene's test. Data were log transformed before analysis if data were not normally distributed. The t –test was used to evaluate the differences between the normal and diabetic groups. The receiver operating characteristic (ROC) curve was used to calculate the area under the curve (AUC). At the same time, binary logistic regression was used to calculate the predictability of the individual parameters for the diabetes, which would further be used to build the models and draw their AUC. During this procedures, we only selected the AUC with significance (higher than the diagonal line). Starting from the one with the smallest, and gradually add larger AUC onto the model. There were three models as following:

Model 1: FPIS + GE

Model 2: FPIS + GE + SPIS

The comparisons of whether the AUC of different factors and models were significantly different, MedCalc Software was used (1, 2015 Downloaded from 8 Broekstraat, Mariakerke, Belgium).

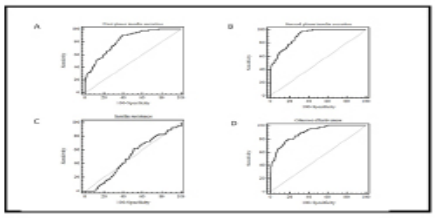
Results

Table 1

	NGT	Type 2 diabetes	
N	558	86	P value
Age (year) (mean, SD)	69.7 (14.5)	69.7 (5.0)	0.916
BMI (kg/m2) (mean, SD)	22.3 (1.8)	22.7 (1.5)	0.051
SBP (mmHg) (mean, SD)	133.4 (18.7)	133.8 (17.6)	0.013
DBP (mmHg) (mean, SD)	72.0 (10.9)	75.7 (10.7)	0.004
FPG (mmol/l) (mean, SD)	5.1 (0.3)	9.2 (2.3)	< 0.001
TG(mmol/l) (mean, SD)	1.3 (0.5)	1.7 (0.5)	<0.001
HDL-C (mmol/l) (mean, SD)	1.4 (0.4)	1.3 (0.3)	0.012
FPIS (μU/min) (mean, SD)	96.7 (54.3)	42.8 (26.8)	< 0.001
SPIS (pmol/ mmol) (mean, SD)	0.060 (0.017)	0.031 (0.013)	< 0.001
IR (10^{-4} · min^{-1} · $pmol^{-1}$ · L-1) (mean, SD)	3.67 (0.02)	3.67 (0.02)	0.546
GE (10^{-2} · dL · min^{-1} · kg-1) (mean, SD	0.016 (0.002)	0.012 (0.002)	<0.001

shows the demographic data of our study groups. It could be noted that other than the SBP, DBP, FPG and TG were higher and HDL-C; FPIS, GE and SPIS were lower in T2DM group than NGT group, which is not surprising. At the same time, no differences could be noted in age, BMI, and IR.

Figure 1



represents the ROC curves of the four factors and higher AUC represents for more precise prediction of the occurrence of the event. In our present study, the AUC of the four factors, from the highest to the lowest are SPIS, GE, FPIS and IR (0.906, 0.891, 0.819 and 0.502 respectively,

Table 2).

Models	Area under the ROC curve (95% CI)	P value
FPIS (mean, SE) (95% CI)	0.819 (0.022)	< 0.001
	0.819 (0.022)	
SPIS(mean, SE) (95% CI)	0.906 (0.014)	< 0.001
	(0.878-0.934)	
IR(mean, SE)(95% CI)	0.502 (0.031)	0.956
	(0.441-0.562)	
GE(mean, SE)(95% CI)	0.891(0.017)	< 0.001
	(0.857-0.925)	
Model 1 (mean, SE) (95% CI)	0.948 (0.011)	< 0.001
	(0.926-0.969)	
Model 2(mean, SE) (95% CI)	0.968 (0.008)	< 0.001
	(0.952-0.983)	

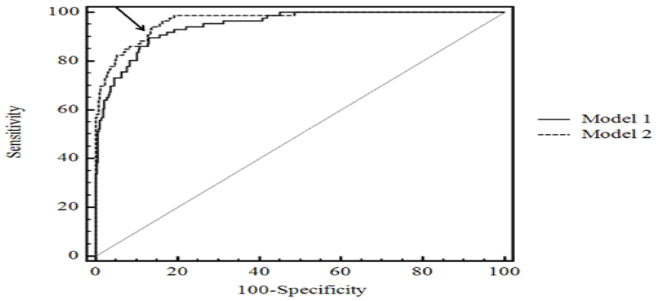
All these three AUC of the factors are higher than the diagonal line. It means that the predictability for T2DM is statistically significant.

To further improve the prediction accuracy, models were built (Table 2). We built the models by adding one more factor on to the original one in the order of their AUC, from the lowest to the highest (Table 2 and Figure 2). The AUC for model 2 was 0.968 (FPIS, GE and SPIS were added). Table 3 shows the comparisons of AUC of each factor and model. Based on this model, an equation was built (-0.012-FPIS – 1003.9-GE – 119.4-SPIS + 20.7). If the calculated value is equal or higher than zero (≥ 0), then the subject has higher chance to have T2DM (Figure 2, sensitivity = 94.2%, specificity = 86.4%).

Table 3

Pairwise comparison test between AUC of each models	*P value
FPIS vs. IR	< 0.001
SPIS vs. IR	< 0.001
GE vs. IR	< 0.001
Model 1 vs. SPIS	0.003
Model 2 vs. Model 1	0.002

Figure 2



Discussion

In the present study, we have demonstrated that among these four effectors, SPIS is the most critical one. Accordingly, the GE and FPIS are the 2nd and 3rd important. By building the models (composed by FPIS, GE and SPIS), the AUC of the ROC curve could further be increased to 0.968. This improves the prediction accuracy of the equation derived from the model to predict diabetes with a sensitivity of 94.2% and specificity of 86.4%. To our knowledge, this is the first study trying to expose the interactions between these four factors in older women.

It has been long debating that which one of the IR or insulin secretion begins earlier in the natural history of diabetes [17-19]. Numerous reports suggested that IR is the initiator of T2DM [1, 20, 21]. Evidence has shown that that genetic factor play a crucial role in the development of IR, and IR increases from approximately 20 years old and reaches to its plateau in the middle age [22-25]. To minimize the untoward effects derived from the compromised insulin sensitivity, insulin secretion begins to increase. After certain period, usually decades, the failure of beta cell happens and frank diabetes begins to be noted clinically. However, other skeptics have opposite opinions that beta-cell dysfunction played a more critical than the elevation of IR in the development of T2DM [26-28]. It is surprising to note that in the present study, the AUC of both SPIS and FPIS are both significantly higher than that of the IR. To closely examine the ROC curve of IR, it nearly overlaps the diagonal line. This reflects the fact the changes of IR between indi-

viduals has zero effects on the occurrence of diabetes. Our finding could not answer the question we raised in the beginning of this paragraph. However, our results still support that the IR does play a less important role than the insulin secretion in the older women. In other words, IR might increase gradually in younger age and reaches its plateau when one is older. Due to the complicated interactions between IR and insulin secretion, only a longitudinal study lasts for decades could answer this question.

Little is known about the roles of FPIS and SPIS on the presence of T2DM. Data from United Kingdom Prospective Diabetes Survey showed that 10 years before diabetes is clinically noted, the beta-cell function already began to drop [29]. However, in that study, homeostasis model assessment (HOMA) was used to quantify insulin secretion. This brings out an important issue that methods used to measure insulin secretion are crucial. Therefore, it should always be kept in mind when interpreting the results of a study. Although HOMA is easily to be used and suitable for larger cohort, it could only estimate the 'static' beta-cell function in the fasting state. The dynamic secretion of the insulin after a meal (or glucose) challenge in the physiological state could not be properly reflected. By using hyperglycemic clamp technique, Van Haeften et al. also showed that even the dynamic FPIS disappears when T2DM was first diagnosed [6]. Based on the clinical observation that blood glucose levels could be maintained years after its treatment with oral anti-diabetic drugs, it could strong support the existence and importance of SPIS. Nevertheless, this hypothesis has not been proved yet. The finding of the present study further confirmed the role of SPIS, particularly in the older women. In the future, how to stimulate or maintain the SPIS should be of the primary focus for diabetic treatment.

Evidences have shown that in subjects with NGT, both the insulin and non-insulin mediated glucose uptake are about 50% when the plasma glucose is 11.1 mmol/L. Here, the non-insulin mediated glucose uptake is synonymous of GE [30]. Interestingly, when the glucose tolerance begins to deteriorate, the role of GE increases rather than decreases. It contributes 67% of the glucose disappearance. If this is a fact, it would be very peculiar that little has been studied in this field. Till now, the most valuable information concerning GE is from the Insulin Resistance Atherosclerosis Study [31]. In that study, two important results could be noted. First, GE did not decrease at the end of the 5-year-followup. This could be interpreted that aging might cause little change of GE, if there is any. Second, when the FPG increased, insulin sensitivity, acute response after glucose loading (FPIS) and GE all decreased. However, the slope of insulin sensitivity reduced most seriously among these parameters, followed by FPIS and GE. Their findings are opposite to ours. In the present study, we showed that SPIS has the most significant impact on whether to have diabetes and then IR is the least important one. It would be difficult at present to clarify this controversy since there are only handful studies focusing on the comparison of these factors. Secondly, the complicated interaction between IR, insulin secretion and GE further aggravate this dilemma. However, the answer might be in the study of Møller et al [32]. By using oral glucose tolerance test, IR was estimated with homeostatic assessment of insulin resistance and Matsuda indices, whereas beta-cell response was measured by homeostatic model assessment of beta-cell function, insulinogenic indices and insulin secretion ratios [33, 34]. They found that the glucose intolerance in Japanese could be characterized by lower beta-cell function and better IR compared to Caucasians [32]. These findings are in line with our study results; i.e., IR plays a less important role than insulin secretion in Chinese. At the same time, Møller et al. also pointed out that these differences between Asians and Caucasians disappeared after BMI was adjusted. They concluded that BMI is the key determinants for the ethnic discrepancies. This explanation could also be used for the present study.

Although the roles of IR, FPIS, SPIS and GE in T2DM have been studied extensively in many researches, our study still provides important information. We have shown the relationships between these four factors in the same subjects. This has never been reported, particularly in older Chinese women. However, there are still limitations. First, compared to a longitudinal study, the present study is only cross-sectional and less persuasive. Secondly, the equations we used for estimation the four components are less accurate than those 'gold standard method' such as hyperglycemic clamp. However, study in this kind of scale could not use sophisticated tests since they are both labor- and budget-intensive. We believed that the large n number in this study might compensate the less accurate measurements. Finally, our data could only be applied to Chinese. Exercise should be taken when extrapolate the results to other ethnic groups.

In conclusion, in Chinese older women, SPIS has the most profound effect on whether to have diabetes, followed by GE, FPIS and IR. By building a model with these three components, the accuracy for predicting diabetes increases with a sensitivity 94.2% and specificity 86.4%.

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