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Original Article

The Relationships Between Hemoglobin and Diabetes Factors (Insulin Resistance, Glucose Effectiveness, First- and Second-Phase Insulin Secretion) in Old Chinese

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SUMMARY

Background: Diabetes is characterized by increased insulin resistance (IR) and decreased insulin secretion. The roles of glucose effectiveness (GE), first- and second-phase insulin secretion (FPIS, SPIS) are often overlooked. We denote these factors as diabetic factors (DF). Hemoglobin (Hb) has been shown to be related to IR and FPIS, but not to SPIS and GE. The aims of this study are to investigate the relationships between Hb and DFs and to compare which one has the tightest correlation with Hb in old Chinese.

Methods: We randomly enrolled 5109 men and 5851 women, whose age were over 65 years old. Subjects, who were obese or on medications, were excluded. Simple correlation was applied to evaluate the relationships between Hb and 4 DFs. To compare the relative tightness between each correlation lines, all the units of the DFs were transformed into percentage.

Results: All the biochemistry data were higher in subjects with metabolic syndrome (MetS) in both genders, except for GE and HDL. Similar trends were also noted when dividing subjects into quartiles of Hb. The results of simple correlation showed that all the DFs are significantly related to Hb except for FPIS in women. The association between Hb and GE is negative. After transforming the different units into percentage, the relationships with Hb, from the highest to lowest, were IR, SPIS, GE and FPIS in both genders.

Conclusion: Our data show that all DFs are almost related to Hb. IR has the tightest correlation with Hb in old Chinese.

1. Introduction

Insulin resistance (IR), impaired first- and second-phase insulin secretion (FPIS, SPIS) and glucose effectiveness (GE) are diabetic factors (DFs) compromising glucose homeostasis.[1] FPIS is referred to the acute insulin response within 10 min after an intravenous glucose bolus. Right afterwards, SPIS kicks in and lasts for about 2–3 h. Throughout the natural course of diabetes, as IR increases, insulin secretion increases proportionately to maintain normal glucose tolerance. By the time diabetes has developed, FPIS is virtually absent.[2] GE is another important initiator for impaired glucose tolerance or diabetes. In short, glucose eliminates itself through glucose utilization and decreased production under fasting and postprandial condition (~70%, ~30%, respectively). It should be noted that, when the role of IR has been explored in many studies,[2,3] the other three factors of equal importance are much less discussed.

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During the past decades, several studies reported that subjects with MetS have higher hemoglobin (Hb) levels.[4,5] The rationales behind this phenomenon might be the increased blood viscosity and inflammation.[6,7] Evidences show that Hb is related to IR and FPIS.[8,9] However, to our knowledge, there is no study focusing on neither the SPIS nor GE.

Type 2 diabetes is particularly prevalent in the elderly and, in the same time, aging does have effects on these 4 DFs.[10,11] Therefore, it would be important to investigate the relationships between Hb and these four factors and to compare which one has the tightest correlation with Hb in older Chinese.

2. Method

2.1. Study subjects

This study was approved by the Ethical Committee of the Cardinal Tien Hospital and the Ethical Committee of MJ Health Screening Centers. We randomly enrolled 5109 men and 5851 women, whose age were over 65 years old (included) from MJ Health Screening Center in Taiwan in 2011 and 2012. Participants who were obese (body mass index (BMI) $\geqq$27 kg/m^2) and taking blood pressure-, glucose- and lipid-lowering medications were all excluded. They were further divided into with and without MetS according to the World Health Organization criteria.[12] There were 768 with MetS and 4341 without MetS in men. For women, there were 794 with MetS and 5057 without MetS. In order to observe the effect of Hb, we divided study groups into quartiles according to Hb levels.

Waist circumference (WC), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured, when seated for 5 min, and blood samples were drawn by nursing staff. Plasma was separated from blood immediately and stored at −30 °C until analysis. Fasting plasma glucose (FPG) was assessed by a glucose oxidase method (YSI 203 glucose analyzer, Yellow Springs Instruments, Yellow Springs, USA). Triglycerides (TG) were measured 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) concentration was analyzed using an enzymatic cholesterol assay following dextran sulfate precipitation.

The equations used to calculate IR, FPIS, SPIS and GE are as following with international unit.

$$\text{IR: } (1.439 + 0.018 \times \text{sex} - 0.003 \times \text{age} + 0.029\ \text{BMI} - 0.001 \times \text{SBP} + 0.006\ \text{DBP} + 0.049 \times \text{TG} - 0.046 \times \text{HDL-C} - 0.0116 \times \text{FPG}) \times 10^{3.333}$$ [13]

$$\text{FPIS} = 10^{(1.477 - 0.119 \times \text{FPG} + 0.079 \times \text{BMI} - 0.523 \times \text{HDL})}$$ [14]

$$\text{SPIS} = 10^{(-2.4 - 0.088 \times \text{FPG} + 0.072 \times \text{BMI})}$$ [15]

$$\text{GE} = (29.196 - 0.103 \times \text{age} - 2.722 \times \text{TG} - 0.592 \times \text{FPG}) \times 10^{-3}$$ [16]

2.2. Statistical analysis

All statistical analyses were performed using SPSS 19.0 (IBM Inc., Armonk, New York). Data are presented as mean ± standard deviation (SD). 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 performed to evaluate the differences between normal and diabetic groups. To evaluate the differences of mean values of the four groups, from the highest to lowest levels of Hb, one-way analysis of variance was used. The ANOVA with Bonferroni post hoc analysis were applied

Table 1
Demographic data of the study participants with and without metabolic syndrome.

	MetS (−)	MetS (+)	P
Male			
n	4341	768	
Age (year)	65 ± 5.7	66 ± 6.0	<0.001
Hemoglobin (g/dl)	14.7 ± 1.2	15.0 ± 1.2	<0.001
FPIS (μU/min)	94.6 ± 46.5	143.7 ± 46.8	<0.001
SPIS (pmol/mmol)	0.060 ± 0.014	0.066 ± 0.013	<0.001
IR ($10^{-4}\cdot min^{-1}\cdot pmol^{-1}\cdot L^{-1}$)	3.669 ± 0.017	3.690 ± 0.017	<0.001
GE ($10^{-2}\cdot dL\cdot min^{-1}\cdot kg^{-1}$)	0.016 ± 0.002	0.013 ± 0.002	<0.001
Body mass index (kg/m^2)	22.5 ± 1.3	23.3 ± 1.2	<0.001
Waist circumference (cm)	80.9 ± 5.4	85.4 ± 5.9	<0.001
SBP (mmHg)	127.7 ± 19.2	141.7 ± 17.0	<0.001
DBP (mmHg)	74.8 ± 11.0	82.1 ± 11.1	<0.001
Fasting plasma glucose (mg/dl)	93.3 ± 5.1	95.0 ± 5.3	<0.001
Triglyceride (mg/dl)	102.5 ± 47.0	187.7 ± 71.7	<0.001
HDL (mg/dl)	53.2 ± 13.8	41.0 ± 8.1	<0.001
Female			
n	5057	794	
Age (year)	64 ± 4.8	67 ± 6.1	<0.001
Hemoglobin (g/dl)	13.2 ± 1.0	13.3 ± 1.1	0.051
FPIS (μU/min)	70.7 ± 36.1	123.8 ± 42.0	<0.001
SPIS (pmol/mmol)	0.060 ± 0.014	0.066 ± 0.013	<0.001
IR ($10^{-4}\cdot min^{-1}\cdot pmol^{-1}\cdot L^{-1}$)	3.669 ± 0.017	3.688 ± 0.016	<0.001
GE ($10^{-2}\cdot dL\cdot min^{-1}\cdot kg^{-1}$)	0.016 ± 0.002	0.013 ± 0.002	<0.001
Body mass index (kg/m^2)	22.5 ± 1.4	23.2 ± 1.2	<0.001
Waist circumference (cm)	74.0 ± 4.9	79.5 ± 5.8	<0.001
SBP (mmHg)	129.3 ± 19.9	144.4 ± 18.0	<0.001
DBP (mmHg)	73.2 ± 11.3	79.4 ± 11.0	<0.001
Fasting plasma glucose (mg/dl)	93.0 ± 5.0	94.2 ± 5.1	<0.001
Triglyceride (mg/dl)	107.5 ± 49.0	187.4 ± 67.4	<0.001
HDL (mg/dl)	62.9 ± 14.9	46.3 ± 10.0	<0.001

MetS (−) = without metabolic syndrome; MetS (+) = with metabolic syndrome; Data are shown as mean ± SD.
P = P value for T test.

Table 2
The anthropometric variables of subjects in different hemoglobin groups.

	Hb1	PH	Hb2	PH	Hb3	PH	Hb4	PH	Total	P
Male										
n	1278		1277		1277		1277		5109	
Age (year)	67 ± 6.3	2,3,4	66 ± 5.7	1,4	65 ± 5.3	1	65 ± 5.2	1,2	66 ± 5.7	<0.001
Hemoglobin (g/dl)	13.2 ± 0.8	2,3,4	14.5 ± 0.2	1,3,4	15.2 ± 0.2	1,2,4	16.2 ± 0.5	1,2,3	14.7 ± 1.2	<0.001
FPIS (μU/min)	99.0 ± 49.3	4	100.7 ± 49.5	4	102.0 ± 49.7		106.2 ± 50.2	1,2	102.0 ± 49.7	0.002
SPIS (pmol/mmol)	0.059 ± 0.013	2,3,4	0.060 ± 0.014	1,4	0.062 ± 0.014	1	0.063 ± 0.013	1,2	0.061 ± 0.014	<0.001
IR ($10^{-4}\cdot min^{-1}\cdot pmol^{-1}\cdot L^{-1}$)	3.666 ± 0.018	2,3,4	3.671 ± 0.018	1,3,4	3.673 ± 0.018	1,2,4	3.677 ± 0.018	1,2,3	3.672 ± 0.018	<0.001
GE ($10^{-2}\cdot dL\cdot min^{-1}\cdot kg^{-1}$)	0.0160 ± 0.0018	3,4	0.0158 ± 0.0020	4	0.0158 ± 0.0020	1	0.0156 ± 0.0002	1,2	0.0158 ± 0.0020	<0.001
Body mass index (kg/m^2)	22.4 ± 1.4	2,3,4	22.6 ± 1.4	1,4	22.7 ± 1.3	1	22.8 ± 1.3	1,2	22.7 ± 1.4	<0.001
Waist circumference (cm)	80.8 ± 5.8	3,4	81.1 ± 5.5	3,4	81.8 ± 5.7	1,2,4	82.8 ± 5.6	1,2,3	81.6 ± 5.7	<0.001
SBP (mmHg)	129.4 ± 20.3		129.2 ± 19.2		129.6 ± 19.0		131.1 ± 19.5		129.8 ± 19.5	0.062
DBP (mmHg)	73.8 ± 11.4	2,3,4	75.7 ± 11.2	1,4	76.3 ± 11.1	1,4	77.8 ± 11.2	1,2,3	75.9 ± 11.3	<0.001
FPG (mg/dl)	93.3 ± 5.4		93.7 ± 4.9		93.6 ± 5.2		93.6 ± 5.2		93.5 ± 5.2	0.232
Triglyceride (mg/dl)	104.1 ± 54.6	2,3,4	114.2 ± 60.9	1,4	117.6 ± 59.7	1,4	125.3 ± 61.8	1,2,3	115.3 ± 59.8	<0.001
Log Triglyceride	2.0 ± 0.2	2,3,4	2.0 ± 0.2	1,4	2.0 ± 0.2	1,4	2.1 ± 0.2	1,2,3	2.0 ± 0.2	<0.001
HDL (mg/dl)	51.3 ± 14.1		51.4 ± 13.5		51.7 ± 13.7		51.0 ± 14.0		51.4 ± 13.8	0.596
Female										
n	1463		1463		1463		1463		5852	
Age (year)	65 ± 5.6	2,3,4	64 ± 5.1	1	64 ± 4.8	1	64 ± 4.6	1	64 ± 5.1	<0.001
Hemoglobin (g/dl)	12.0 ± 0.5	2,3,4	13.0 ± 0.2	1,3,4	13.6 ± 0.2	1,2,4	14.4 ± 0.5	1,2,3	13.2 ± 1.0	<0.001
FPIS (μU/min)	80.3 ± 44.4	2,3	75.8 ± 40.3	1,4	75.5 ± 39.1	1,4	79.9 ± 40.6	2,3	77.9 ± 41.2	0.001
SPIS (pmol/mmol)	0.060 ± 0.014	3,4	0.061 ± 0.014	4	0.061 ± 0.014	1	0.062 ± 0.014	1,2	0.061 ± 0.014	<0.001
IR ($10^{-4}\cdot min^{-1}\cdot pmol^{-1}\cdot L^{-1}$)	3.668 ± 0.018	2,3,4	3.670 ± 0.017	1,3,4	3.672 ± 0.017	1,2,4	3.676 ± 0.018	1,2,3	3.672 ± 0.018	<0.001
GE ($10^{-2}\cdot dL\cdot min^{-1}\cdot kg^{-1}$)	0.0159 ± 0.0020	4	0.0160 ± 0.0019	4	0.0159 ± 0.0019	4	0.0156 ± 0.0020	1,2,3	0.0158 ± 0.0020	<0.001
Body mass index (kg/m^2)	22.5 ± 1.4	3,4	22.6 ± 1.4		22.7 ± 1.3	1	22.8 ± 1.4	1,2	22.6 ± 1.4	<0.001
Waist circumference (cm)	74.7 ± 5.7		74.7 ± 5.3	4	74.6 ± 5.2	4	75.2 ± 5.3	2,3	74.8 ± 5.4	0.010
SBP (mmHg)	130.6 ± 20.5	4	130.3 ± 19.8	4	130.9 ± 20.4	4	133.7 ± 20.3	1,2,3	131.4 ± 20.3	<0.001
DBP (mmHg)	72.3 ± 11.0	3,4	73.4 ± 10.9	4	74.1 ± 11.8	1,4	76.4 ± 11.7	1,2,3	74.1 ± 11.4	<0.001
FPG (mg/dl)	92.9 ± 5.3	3	93.0 ± 5.0		93.4 ± 4.9	1	93.3 ± 5.0		93.1 ± 5.0	0.010
Triglyceride (mg/dl)	114.3 ± 58.5	4	114.0 ± 55.7	4	117.3 ± 57.0	4	127.8 ± 62.1	1,2,3	118.3 ± 58.7	<0.001
Log Triglyceride	2.0 ± 0.2	4	2.0 ± 0.2	4	2.0 ± 0.2	4	2.1 ± 0.2	1,2,3	2.0 ± 0.2	<0.001
HDL (mg/dl)	59.4 ± 16.1	2,3	61.3 ± 15.2	1	61.5 ± 15.0	1	60.4 ± 15.3		60.7 ± 15.4	0.001

Data are shown as mean ± SD.
P = P value for T test.
PH = post hoc analysis (The number represents the P value < 0.05 when the group compared with each other).

for groups' comparison. Simple correlation was applied to evaluate the relationships between Hb and 4 DFs. Moreover, multivariant linear regression was performed to adjust other confounding factors, such as age, BMI, and definition factors of MetS. In the same time, slopes of the relationships between Hb and 4 DFs could also be obtained. We also transformed the different units of these four factors into percentage correspondingly to compare their slopes. Take log FPIS as an example, it could be clearly that the lowest level of the regression line was −0.7 and the highest was 3.67. We took the highest value of FPIS as 100% and the lowest was 0%. Among these four factors, only the GE had a negative correlation with Hb. In order to compare the slope of GE with other three factors, we plotted a mirror-line (or reciprocal) from the 4th quadrant to the 1st quadrant.

3. Results

Table 1 shows all the demographic data and parameters derived from our equations. Hb was significantly different between subjects with and without MetS in male ($p < 0.001$), but borderline significant in female ($p = 0.051$). It is not surprising that all traditionally known MetS related parameters (BMI, WC, SBP, DBP, FPG, and TG) were higher in subjects with MetS except HDL. In addition, 4 DFs were all significantly different between subjects with and without MetS in both genders. There were higher FPIS, SPIS, IR, but lower GE in subjects with MetS.

Furthermore, we divided the study participants into quartiles according to Hb level, from the lowest to highest, Hb1 to Hb4. The post hoc analysis was also preformed (Table 2). There are trends showing that higher Hb level has higher FPIS, SPIS, IR, BMI, WC, DBP, TG, but lower GE in both genders. The positive trends for SBP and FPG and negative trend for HDL were only found in women. However, the FPIS seems to be less prominent correlation between different Hb levels in men. This can be seen in the post hoc analysis that FPIS was significantly different only between Hb1 and Hb4 group in men. Similarly, the GE seems to be less prominent correlation between different Hb levels in women. This can also be seen in the post hoc analysis that GE was significantly different only between Hb1 and Hb4 group in women.

Table 3 shows the simple relationships between Hb and 4 DFs with univariant (r and p values) and multivariant (β and p values) regression model. Indeed, SPIS and IR were significantly related to Hb (r values of SPIS were 0.115 and 0.065 for male and female; r values of IR were 0.231 and 0.160 for male and female). However, it should be noted that Hb and GE was negatively correlated (r values were −0.081 and −0.043 for male and female). Positive correlation between FPIS and Hb was just shown in men (r value was 0.049).

Table 3
Results of simple correlation of the four different insulin parameters.

	Uni-variant		Multi-variant	
	r	p	β	p
Male				
First Phase Insulin Secretion	0.049	<0.001	−0.027	0.569
Second Phase Insulin Secretion	0.115	<0.001	0.023	<0.001
Insulin resistance	0.231	<0.001	0.194	<0.001
Glucose effectiveness	−0.081	<0.001	−0.019	<0.001
Female				
First Phase Insulin Secretion	−0.009	0.491	−0.062	0.172
Second Phase Insulin Secretion	0.065	<0.001	0.055	<0.001
Insulin resistance	0.160	<0.001	0.162	<0.001
Glucose effectiveness	−0.043	0.001	−0.079	<0.001

Multi-variant model was adjusted for age, BMI, definition factors of MetS.

When they were adjusted by other baseline factors in multivariant regression model, the FPIS was not correlated with Hb, as was the case in women.

Fig. 1 shows that the tightness of the relationships with Hb and IR, SPIS, GE and FPIS (from the tightest to lowest) for both genders. However, the relationship between Hb and FPIS in women did not reach clinical significance (Fig. 1A).

Fig. 2 compares the slopes of 4 DFs after transforming different units into percentage. GE is the only one needed to be reciprocally plotted because it was negatively correlated to Hb. The change of IR was the most obvious among 4 DFs in both gender. The SPIS is the second obvious change even when compared with reciprocal GE ($P = 0.003$). The FPIS was not correlated in women and also showed least correlation with Hb in men.

4. Discussion

In the present study, we confirmed that Hb level is positively related to IR, FPIS, and SPIS and negatively to GE in both genders. Among these four factors in men, IR has the highest r value and followed by SPIS, GE and FPIS. We demonstrated that IR is most tightly related to Hb.

Leonardo et al. were the first to broach the idea that elevated level of hematocrit and blood viscosity are associated with IR and are independent predictors of type 2 diabetes.[17] Facchini et al. described the correlation coefficients (r) between Hb and IR ranges from 0.38 to 0.43 in 150 normal, healthy subjects.[8] This relationship could be hypothesized by the increased blood viscosity causing inadequate delivery of insulin to multiple tissues.[18] However, r value between Hb and IR is lower (0.160) in our study. This could be explained by several studies design. First, the volunteers were all older than 65 years old. Second, the BMI is less than Caucasian (24.4, 25.0 for men and women, respectively). Third, ethnic difference might also play a role.

Facchini et al. presented that Hb is independently related to IR and compensatory hyperinsulinemia, which supports our finding.[8] However, Shimodaira et al. suggested the opposite results.[9] By using insulinogenic index to estimate early insulin secretion from oral glucose tolerance, they had shown that the r values were −0.197 and −0.082 for male and female. Decreased insulin secretion should be caused by the oxidative stress.[19] As far as we know, oxidative stress and inflammation are closely related processes. However, Festa et al. believe differently that the inflammation causes worsen IR rather than decreased insulin secretion.[20] The discrepancy of these findings could be explained by the different ages or methods used.

In addition, there is a negative association between Hb and GE. To our knowledge, our study is the first report focusing on this area. We hypothesized that both inflammation and viscosity might explain our finding. First, GE is negatively related to chronic inflammation. By using lipopolysaccharide stimulation, Furgeson et al. successfully showed a decrease of GE.[21] Second, evidences suggest that chronic inflammation is related to higher Hb level through increased viscosity.[22] Thus, indirectly, these indirect relationships fulfill the puzzle of our results.

There are still limitations in the present study. First, this is only a cross-sectional study. Compared to the longitudinal one, it provides less solid evidence. Second, the methods we used should be less accurate than the other sophisticated tests such as intravenous glucose tolerance test or clamp. However, the large number of the cohort study might correct this drawback. Third, this study is done in homogenous ethnic group. Cautious must be exercised when extrapolate our findings to other ethnic groups. Finally, the

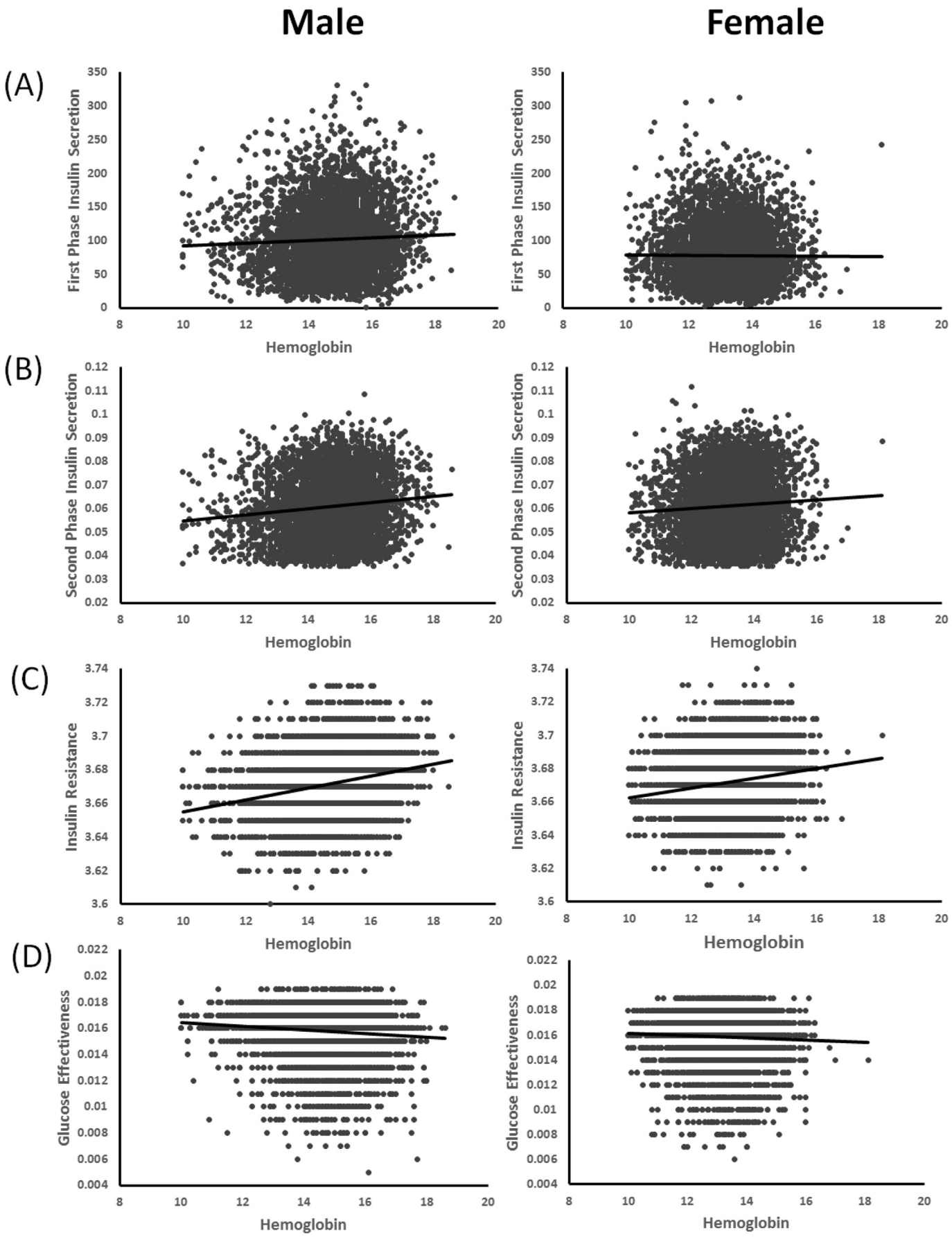

Fig. 1. Relationships between Hb and all other four diabetic factors for male and female.

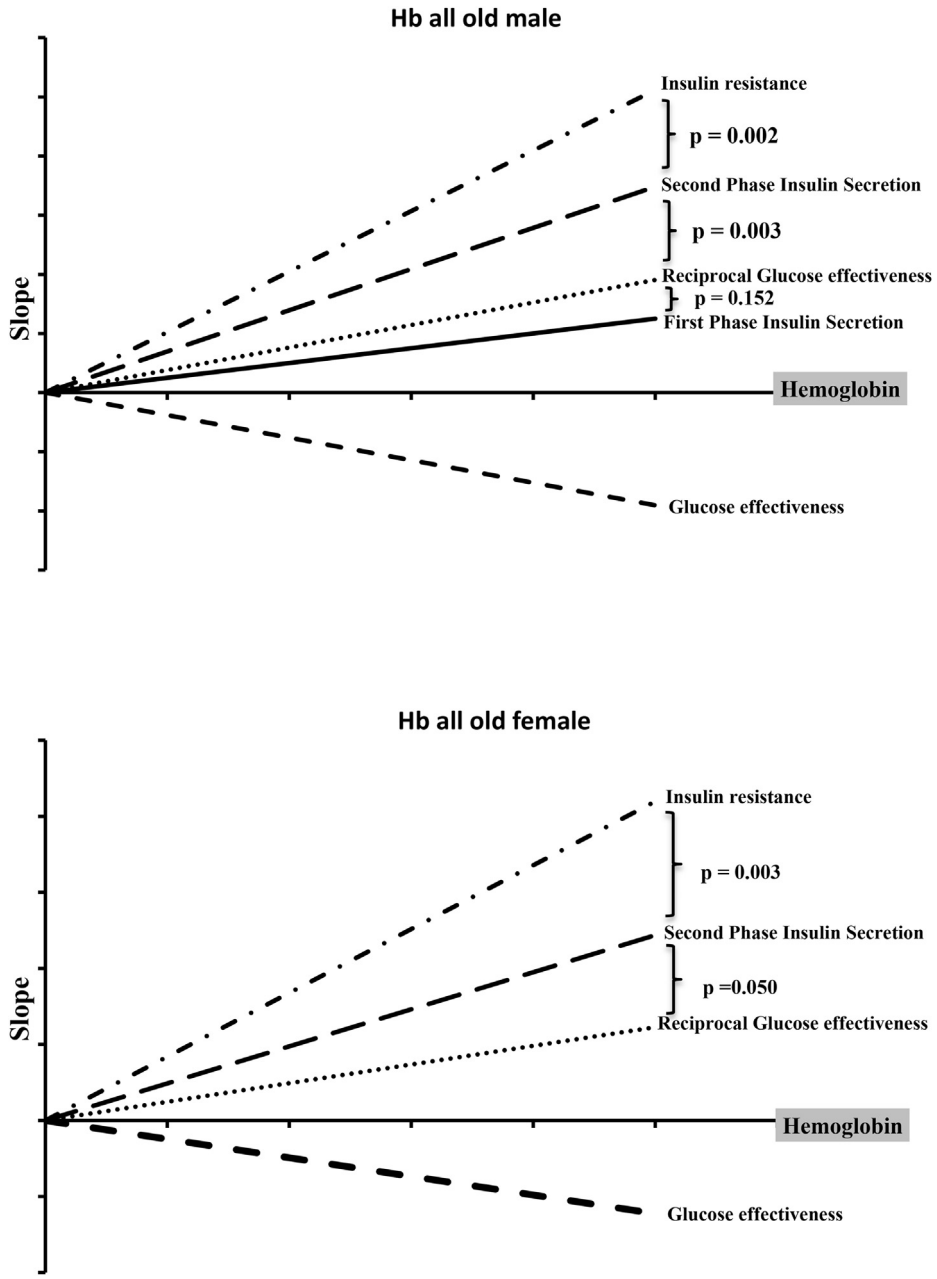

Fig. 2. Comparison of the different insulin parameter according to the increased hemoglobin.

controversial relationships between Hb and insulin secretion is still not solved. Further basic or clinical studies are needed to support our findings.

In conclusion, our data show that all DFs are related to Hb except for FPIS in women. The tightness of these relationships, from the highest to lowest, is IR, SPIS, GE and FPIS in old Chinese.

Conflicts of interest

None declared.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ijge.2018.05.007.

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