The relationships between hemoglobin and diabetogenic factors in young Chinese adults

Yen-Shan Yang, Jiunn-Diann Lin, Chung-Ze Wu, Dee Pei, Yao-Jen Liang, Yen-Lin Chen

Original Article

The relationships between hemoglobin and diabetogenic factors in young Chinese adults

Yen-Shan Yang[1], Jiunn-Diann Lin[2], Chung-Ze Wu[2], Dee Pei[3], Yao-Jen Liang[4], Yen-Lin Chen[5]*

[1]Department of Medicine, School of Medicine, Fu Jen Catholic University, New Taipei City, Taiwan
[2]Division of Endocrinology, Department of Internal Medicine, Shuang Ho Hospital, Taipei Medical University; Division of Endocrinology and Metabolism, Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan
[3]Department of Internal Medicine, Cardinal Tien Hospital, School of Medicine, Fu Jen Catholic University, New Taipei City, Taiwan
[4]Department of Life Science, Graduate Institute of Applied Science and Engineering, College of Science and Engineering, Fu Jen Catholic University, Taipei, Taiwan
[5]Department of Pathology, Cardinal Tien Hospital, School of Medicine, Fu-Jen Catholic University, New Taipei City, Taiwan

Corresponding author:
Yen-Lin Chen
Department of Pathology (YL Chen),
Department of Internal Medicine (K Wang),
Cardinal Tien Hospital,
No.362, Zhongzheng Rd.,
Xindian Dist.,
New Taipei City 23137,
Taiwan (R.O.C.)
Phone: +886-2-22193391
Fax: +886-2-22193506
E-mail: anthonypatho@gmail.com (YL Chen)

ABSTRACT

Objective: Four diabetogenesis factors (DF) are recognized as the pathophysiology for diabetes; increased insulin resistance (IR); decreased glucose effectiveness (GE); first- and second-phase insulin secretion (FPIS and SPIS). The relationships between hemoglobin (Hb), IR and FPIS are well investigated. However, little is known about the associations between Hb and the other two DFs. Nowadays, the incidence of type 2 diabetes has increased dramatically in young adults in Taiwan. A group of young adults are enrolled for investigating relationships between Hb and the DFs.

Design: Cross-sectional

Setting: Health check-up centers and hospitals

Subjects: 21,112 and 20,687 healthy males and females (18-27 years old) were recruited.

Main outcome measures: The four DFs were measured by the equations published in our previous studies. Participants were divided into quartiles by Hb levels and ANOVA was used to compare the differences of DFs in these four groups. Then simple correlation was applied for evaluation the correlation between Hb and the DFs.

Results: In both genders, IR, FPIS and SPIS had negative trends from the lower to the higher Hb quartiles, but GE had a positive one. Simple correlation showed negative relationships between Hb and FPIS, SPIS and IR, similarly, it was positive for GE. Besides, GE is most closely related to Hb, followed by IR, SPIS and FPIS.

Conclusions: Our study showed that in young Chinese adults, all the DFs except GE were negatively correlated with Hb. Among these correlations, GE had the highest r value, followed by IR, SPIS and FPIS.

KEYWORDS: first phase insulin secretion; glucose effectiveness; insulin resistance; second phase insulin secretion;

INTRODUCTION

Due to the increasing prevalence of obesity in recent years, type 2 diabetes (T2D) has become an endemic disease in many countries [1, 2]. Owing to the various symptoms and accompanying complications, it influences not only individuals' health but also has serious impacts on the society in many different aspects. As a result, searching for modalities for early detection and treatments are important issues for health providers. However, many parts of the underlying pathophysiology of T2D still remain unclear.

Until now, it is generally agreed that there are four diabetogenesis factors (DF): increased insulin resistance (IR), diminished first- and second-phase insulin secretion (FPIS, SPIS, respectively) and glucose effectiveness (GE). IR refers to the diminished ability of cells to respond to the action of insulin in transporting glucose from plasma to glucose-utilizing tissues [3]. FPIS is the insulin secreted from the storage granules and after acute glucose loading within first 10 min. The following newly produced insulin is the SPIS [4, 5]. GE is the ability of glucose per se to promote its own disappearance from the plasma which

includes suppression of its production and stimulation of its uptake [6]. However, other than IR, the other three factors were much less investigated [4, 7-9]. This may be because the methods for measuring FPIS, SPIS and GE are both time-consuming and expensive.

In the past, researchers have found the level of Hb was positively correlated with the chance of having T2D [10]. The underlying mechanisms might be due to the evidences showing that IR was positively and FPIS was negatively related to the level of Hb [11-13]. Both associations could be explained by oxidative stress [14, 15]. However, little is known about the correlations between Hb, SPIS and GE. In the present study, we enrolled 41,799 non-diabetic subjects. By using the equations developed by our group, four DFs were measured simultaneously in one subject. Our purposes were: 1. Is Hb related to DFs individually? 2. If there is a significant relationship, which one is the closest? Thus, we can understand the roles of Hb in the pathogenesis of T2D more thoroughly.

SUBJECTS AND METHODS

The data of the study participants were collected from an MJ Health Screening Centers, which are private chain clinics around Taiwan. It provides its members regular health examination. The study protocol was approved by the institutional review board and the data obtained were used for research purposes only. 21,112 males and 20,687 females aged between 18 and 27 years old were randomly recruited and have undergone the health checks at the time of the study. All the participants gave informed consents and they were anonymous in the analysis. Participants with obesity (BMI≧25 kg/m^2), and/or taking any medications that are known to affect blood pressure, glucose and lipid levels were excluded. Subjects were divided into two groups: those with metabolic syndrome (MetS+), and those without (MetS-), according to the World Health Organization criteria [16].

On the day of the study, individual current medical history was obtained; thorough questionnaire and standard physical examinations were performed, including measurement of body weight, height, waist circumference, systolic blood pressure (SBP) and diastolic blood pressure (DBP). Body mass index (BMI) was calculated as the weight (kg) divided by the square of the subject's height (m^2). Each participant was instructed to have fasted for 10 hours before samples of blood were drawn from the antecubital vein for biochemical analysis. Plasma was separated from blood within 1 hour and stored at 30°C until the analysis for fasting plasma glucose (FPG) and lipid profiles. FPG was measured using a glucose oxidase method (YSI 203 glucose analyzer, Yellow Springs Instruments, Yellow Springs, USA). Total cholesterol and triglycerides (TG) were measured by the 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 concentration were analyzed through an enzymatic cholesterol assay after dextran sulfate precipitation.

The equation used to calculate IR, FPIS, SPIS, GE are listed below, which were taken from our study

groups. All units are in international units. To demonstrate the reliability of our equations, here is a short statement. When we performed these data, approximately 70% of the participants were used to build the equation while the data from the remaining 30% were used as external validation. Thus, the accuracy of the equations could be tested.

1. IR: In total, there were 327 subjects enrolled. The IR was measured by insulin suppression test. The r value between the measured and calculated GE was 0.581 ($p < 0.001$). It was published in 'Journal of Diabetes Investigation' in 2013.

   $IR = \log (1.439 + 0.018 \times sex - 0.003 \times age + 0.029 \times BMI - 0.001 \times SBP + 0.006 \times DBP + 0.049 \times TG - 0.046 \times HDLC - 0.0116 \times FPG) \times 10^{3.333}$ [17]

2. FPIS: In total, there were 186 subjects enrolled. The FPIS was measured by frequent sampled intravenous glucose tolerance tests. The r value between the measured and calculated GE was 0.671 ($p < 0.000$). It was published in 'International Journal of Endocrinology' in 2015.

   $FPIS = 10^{(1.477 - 0.119 \times FPG + 0.079 \times BMI - 0.523 \times HDLC)}$ [18]

3. SPIS: In total, there were 82 participants. The SPIS was measured by a modified low dose glucose infusion test. The r value between the measured and calculated GE was 0.65 ($p = 0.002$). It was published in 'Metabolic Syndrome and Related Disorders' in 2016.

   $SPIS = 10^{(-2.4 - 0.088 \times FPG + 0.072 \times BMI)}$ [19]

4. GE: In total, there were 227 participants. The GE was measured by frequent sampled intravenous glucose tolerance tests. The r value between the measured and calculated GE was 0.43 ($p = 0.001$). It was published in 'Metabolic Syndrome and Related Disorders' in 2016.

$GE = (29.196 - 0.103 \times age - 2.722 \times TG - 0.592 \times FPG) \times 10^{-3}$ [20]

Statistical analysis

All statistical analyses were performed using the SPSS software version 19.0 (IBM Inc., Armonk, New York). The data are expressed as mean ± standard deviation. All data were tested for normal distribution with the Kolmogorov–Smirnov test and for homogeneity of variances with the Levene's test. Data of FPIS, SPIS and TG were log transformed before analysis due to the fact that they were not normally distributed. The *t*–test was used to compare the differences between the MetS+ and MetS- groups of two genders separately. To evaluate the differences of the mean values of the four groups, from the highest to the lowest levels of Hb, One-way ANOVA was used, followed by Bonferroni test for post-hoc examination.

Simple correlation was applied to determine the association between concentrations of IR, FPIS, SPIS and GE with Hb. The slopes of those DFs with Hb of two genders were also obtained separately in linear regression analysis. Since the units and scales of the four lines were different, it was impossible to compare their relationships. As a result, for each DF, we took the highest value of the variable as 100% and the lowest as 0%. The other continuous value between the two extremes were then converted into percentage

correspondingly. Thus, though using the method, those variables originally belonging to different units and scales can be compared with each other in the two genders.

Among these four factors, in both genders, only GE showed a positive correlation when Hb is higher while the other three DFs are negatively related to Hb. As a consequence, a mirror-line (or reciprocal line) was plotted for GE in order to compare their relationships.

RESULTS

In total, 41,799 subjects were enrolled in the study, including 21,112 males and 20,687 females. In table 1, they were divided into MetS (-) and MetS (+) as aforementioned. In both genders, other than HDL-C, GE, Hb, all the other components were higher in MetS (+) group.

Table 2 depicts the demographic, biochemistries and DFs after the data of participants were stratified into quartiles according to their Hb levels. It can be noted that all the parameters had a negative trend from the lower to the higher Hb quartiles, while GE and HDL-C were positively related to Hb. Table 3 showed the results of simple correlation between Hb and four DFs. In both men and women, negative correlations can be noted between Hb and FPIS, SPIS and IR. And between Hb and GE, the relationship becomes positive.

The comparisons of the closeness between these parameters are shown in Fig 1 (panel A for female and B for male, respectively). GE had the highest r value, following by IR, SPIS and FPIS in both genders.

DISCUSSION

In the present study, our results showed that the orders of the relationship closeness in both genders from the highest to the lowest were GE, IR, SPIS and FPIS. In both genders, all the DFs except for GE were negatively related to Hb. To our knowledge, there have been very few studies focusing on the relationships between Hb and the four DFs, particularly in this age group. Our study is the first to analyze these relationships simultaneously in the same individual. We believe that the results could provide deeper understanding about the pathophysiology for T2D. To further understand our findings, we will discuss these relationships separately in the following paragraphs.

1. The relationship between Hb and IR:

In the present study, we have shown that there was a negative correlation between Hb and IR. Moreover, the r^2 was the second highest among the four DFs. This is unusual. Our findings are contradictory to other three studies. However, in the first study done by Moan et al. there were only 20 men. The second study done by Reaven *et al*. enrolled 150 subjects. By using insulin suppression study, the quantified IR. The r^2 was only around 0.176; in addition, the mean age of their cohort was between 49 and 43 years old for men and women respectively. Since we enrolled much younger subjects in our study (24.7 years old in average), sex

hormones may play important roles in the relationships. For example, for females, a study conducted by Sivaporn Sivasinprasasn *et al*. using ovariectomized rats as model also demonstrated a negative relationship between estrogen and obese-insulin resistance [22]. As for males, Chaoyang Li *et al*. found testosterone was significantly and negatively associated with the level of insulin resistance in men [23]. At the same time, testosterone has been suggested to stimulate the production of Hb [24]. Though the mechanisms are not clearly understood, the above studies might provide evidences to support our results.

2. The relationship between Hb and insulin secretion:

There have been very few studies focused on the relationships between Hb and insulin secretion. In the present study, our data suggests that subjects with higher Hb levels had lower insulin secretion, both first and second-phase. This finding is in line with the reports done by others. For example, Shimodaira et al. showed a similar finding, however, only in men (r = -0.197 for men and -0.082 for women) [11]. In the same time, Hanley *et al*. also demonstrated decreased β-cell function across the Hb quartiles [25]. Although the underlying molecular mechanisms still remain unclear. The fact that anemia could induce iron overload might cause oxidative impairment of mitochondria, which are abundant in β-cells. Thus, the pancreatic function might be damaged, leading to decrease of insulin secretion.

3. The relationship between GE and Hb:

GE has long been proved to be an important factor of diabetes [6]; however, there has been no study to examine its relationship with Hb. Our study is the first to demonstrate that there was a positive association between these two factors. To explain our finding, we hypothesized that obesity might play a key role to connect Hb and GE. By using oral glucose tolerance test, also, it is well-known that obesity is often associated with multiple metabolic syndromes including hypertriglyceridemia [27, 28]. What's more, free fatty acid could also promote glucogenesis in liver and reduce glucose oxidation [18-22]. On the other hand, erythropoietin, an important hormone for Hb production, is suggested to be involved in the regulation of obesity through a signaling pathway. The level of erythropoietin is elevated during hypoxia, which may be induced by obesity [29, 30]. From the above discussion, we can conclude that obesity is related to higher GE and also to higher Hb.

Although abundance of clinical studies have proved a relatively higher prevalence of anemia in diabetic patients [31], the relationships among those four DF and Hb should still be further discussed considering the complex physical and chemical interactions involved. In the present research, we believe the analysis provides important information related to the pathophysiology of diabetes. However, there were still several limitations. First, the study was cross-sectional, so the evidences are not as solid as a longitude one. Second, the method we used for measurement of the four factors might be less accurate or precise compared to traditional ones; however, the large number of the study cohort might be able to compensate

this defect. Third, the study was conducted on a homogenous ethnic group. Exercising our results to other ethnic should be done with caution.

CONCLUSION

In conclusion, our data showed that the order of the closeness in both genders from the highest to the lowest was GE, IR, SPIS, FPIS in young Chinese. In both genders aged between 18 and 27 years old, IR, FPIS and SPIS were negatively, while GE was positively correlated with Hb.

ACKNOWLEDGMENTS

All of the authors wish to thank the study assistants for their help in data preparation and collection.

Y-SY: primarily writing the manuscript

J-DL: revision of the manuscript

C-ZW: gave suggest how to write the manuscript

DP: analyzed the data

Y-JL: gave statistical suggestion

Y-LC: create the hypothesis of this manuscript

Conflict of interest: None

Funding resources: This study was funded by the grant from Cardinal Tien Hospital No. CTH105A-214

REFERENCES

1. Tseng C-H, Chong C-K, Heng L-T, Tseng C-P, Tai T. The incidence of type 2 diabetes mellitus in Taiwan. Diabetes research and clinical practice. 2000;50:S61-S4.

2. Lin C-C, Li C-I, Hsiao C-Y, Liu C-S, Yang S-Y, Lee C-C, et al. Time trend analysis of the prevalence and incidence of diagnosed type 2 diabetes among adults in Taiwan from 2000 to 2007: a population-based study. BMC Public Health. 2013;13(1):318.

3. Reaven GM. The insulin resistance syndrome: definition and dietary approaches to treatment. Annu Rev Nutr. 2005;25:391-406.

4. Polonsky KS, Sturis J, Bell GI. Non-insulin-dependent diabetes mellitus—a genetically programmed failure of the beta cell to compensate for insulin resistance. New England Journal of Medicine. 1996;334(12):777-83.

5. Caumo A, Luzi L. First-phase insulin secretion: does it exist in real life? Considerations on shape and function. American Journal of Physiology-Endocrinology And Metabolism. 2004;287(3):E371-E85.

6. Tonelli J, Kishore P, Lee D-E, Hawkins MJCOiCN, Care M. The regulation of glucose effectiveness:

how glucose modulates its own production. 2005;8(4):450-6.

7. Nakamura Y, Nishida T. Effect of hemoglobin concentration on the oxidation of linoleic acid. Journal of lipid research. 1971;12(2):149-54.

8. Neuman JC, Fenske RJ, Kimple ME. Dietary polyunsaturated fatty acids and their metabolites: Implications for diabetes pathophysiology, prevention, and treatment. Nutrition and healthy aging. 2017;4(2):127.

9. Zeyda M, Stulnig TM. Obesity, inflammation, and insulin resistance–a mini-review. Gerontology. 2009;55(4):379-86.

10. Facchini FS, Carantoni M, Jeppesen J, Reaven GM. Hematocrit and hemoglobin are independently related to insulin resistance and compensatory hyperinsulinemia in healthy, non-obese men and women. Metabolism-Clinical and Experimental. 1998;47(7):831-5.

11. Shimodaira M, Okaniwa S, Nakayama T. Investigation of the relationship between hemoglobin and serum iron levels and early-phase insulin secretion in non-diabetic subjects. Acta diabetologica. 2016;53(5):783-9.

12. Gyawali P, Richards RS, Nwose EU, Bwititi PT. Whole-blood viscosity and metabolic syndrome. Clinical Lipidology. 2012;7(6):709-19.

13. Baron AD, Clark MG. Role of blood flow in the regulation of muscle glucose uptake. Annual review of nutrition. 1997;17(1):487-99.

14. Yuan T, Fan W-B, Cong Y, Xu H-D, Li C-J, Meng J, et al. Linoleic acid induces red blood cells and hemoglobin damage via oxidative mechanism. International journal of clinical and experimental pathology. 2015;8(5):5044.

15. Ditzel J, editor. Changes in red cell oxygen release capacity in diabetes mellitus. Federation proceedings; 1979.

16. Alberti KGMM, Zimmet Pf. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. Diabetic medicine. 1998;15(7):539-53.

17. Wu CZ, Lin JD, Hsia TL, Hsu CH, Hsieh CH, Chang JB, et al. Accurate method to estimate insulin resistance from multiple regression models using data of metabolic syndrome and oral glucose tolerance test. Journal of diabetes investigation. 2014;5(3):290-6.

18. Lin J-d, Hsu C-H, Liang Y-J, Lian W-C, Hsieh C-H, Wu C-Z, et al. The estimation of first-phase insulin secretion by using components of the metabolic syndrome in a chinese population. International journal of endocrinology. 2015;2015.

19. Lin Y, Wu C, Lian W, Hsu C, Hsieh C, Pei D, et al. Measuring second phase of insulin secretion by components of metabolic syndrome. International Journal of Diabetes and Clinical Diagnosis. 2015;2:113-8.

20. Chen Y-L, Lee S-F, Pei C, Pei D, Lee C-H, He C-T, et al. Predicting Glucose Effectiveness in Chinese

Participants Using Routine Measurements. Metabolic syndrome and related disorders. 2016;14(8):386-90.

21. Moan A, Nordby G, Os I, Birkeland KI, Kjeldsen SE. Relationship between hemorrheologic factors and insulin sensitivity in healthy young men. Metabolism-Clinical and Experimental. 1994;43(4):423-7.

22. Sivasinprasasn S, Sa-nguanmoo P, Pratchayasakul W, Kumfu S, Chattipakorn SC, Chattipakorn N. Obese-insulin resistance accelerates and aggravates cardiometabolic disorders and cardiac mitochondrial dysfunction in estrogen-deprived female rats. Age. 2015;37(2):28.

23. Li C, Ford ES, Li B, Giles WH, Liu S. Association of testosterone and sex hormone-binding globulin with metabolic syndrome and insulin resistance in men. Diabetes care. 2010.

24. Bachman E, Travison TG, Basaria S, Davda MN, Guo W, Li M, et al. Testosterone induces erythrocytosis via increased erythropoietin and suppressed hepcidin: evidence for a new erythropoietin/hemoglobin set point. Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences. 2013;69(6):725-35.

25. Hanley AJ, Retnakaran R, Qi Y, Gerstein HC, Perkins B, Raboud J, et al. Association of hematological parameters with insulin resistance and β-cell dysfunction in nondiabetic subjects. The Journal of Clinical Endocrinology & Metabolism. 2009;94(10):3824-32.

26. Weiss R, Magge SN, Santoro N, Giannini C, Boston R, Holder T, et al. Glucose effectiveness in obese children: relation to degree of obesity and dysglycemia. Diabetes care. 2015:dc142183.

27. Feingold KR, Grunfeld C. Obesity and dyslipidemia. 2015.

28. Bays HE, Toth PP, Kris-Etherton PM, Abate N, Aronne LJ, Brown WV, et al. Obesity, adiposity, and dyslipidemia: a consensus statement from the National Lipid Association. Journal of clinical lipidology. 2013;7(4):304-83.

29. Ban J-J, Ruthenborg RJ, Cho KW, Kim J-w. Regulation of obesity and insulin resistance by hypoxia-inducible factors. Hypoxia. 2014;2:171.

30. Alnaeeli M, Raaka BM, Gavrilova O, Teng R, Chanturiya T, Noguchi CT. Erythropoietin signaling: a novel regulator of white adipose tissue inflammation during diet-induced obesity. Diabetes. 2014:DB_130883.

31. Sahay M, Kalra S, Badani R, Bantwal G, Bhoraskar A, Das A, et al. Diabetes and Anemia: International Diabetes Federation (IDF)–Southeast Asian Region (SEAR) position statement. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2017;11:S685-S95.

Table 1: Basic information and DFs between MetS(-) and MetS(+) in young adults

Demographic data and diabetes factors	MetS (-)	MetS (+)	p
Male			
n	19367	1745	
Age (year)	24.3 ± 2.5	24.6 ± 2.5	<0.001
Body mass index (kg/m^2)	22.9 ± 3.0	28.8 ± 4.5	<0.001
Waist circumference	77.3 ± 7.7	92.1 ± 10.5	<0.001
Systolic blood pressure (mmHg)	118.9 ± 12.3	132.8 ± 12.1	<0.001
Diastolic blood pressure (mmHg)	68.4 ± 8.7	76.9 ± 9.9	<0.001
Fasting plasma glucose (mg/dl)	93.6 ± 6.7	100.5 ± 10.8	<0.001
Triglyceride (mg/dl)	88.0 ± 43.3	173.7 ± 74.0	<0.001
HDL-C (mg/dl)	51.4 ± 11.4	39.5 ± 8.2	<0.001
Cholesterol (mg/dl)	175.2 ± 31.2	192.1 ± 35.9	<0.001
LDL-C (mg/dl)	106.2 ± 28.5	117.9 ± 32.3	<0.001
FPIS (μU/min)	125.3 ± 145.5	513.3 ± 589.558	<0.001
SPIS (pmol/mmol)	0.072 ± 0.060	0.203 ± 0.207	<0.001
IR (10^{-4} · min^{-1} · pmol^{-1} · L^{-1})	3.688 ± 0.021	3.735 ± 0.026	<0.001
GE (10^{-2} · dL · min^{-1} · kg^{-1})	0.021 ± 0.001	0.018 ± 0.002	<0.001
Hemoglobin (10^3/μ L)	15.3 ± 1.2	14.3 ± 1.4	<0.001
Female			
n	20177	510	
Age (year)	24.3 ± 2.4	24.2 ± 2.6	0.415
Body mass index (kg/m^2)	21.2 ± 2.6	29.1 ± 5.4	<0.001
Waist circumference	67.7 ± 6.0	84.9 ± 11.0	<0.001
Systolic blood pressure (mmHg)	107.2 ± 11.2	125.5 ± 13.9	<0.001
Diastolic blood pressure (mmHg)	63.0 ± 8.1	73.3 ± 10.5	<0.001
Fasting plasma glucose (mg/dl)	90.1 ± 7.0	100.3 ± 14.3	<0.001
Triglyceride (mg/dl)	69.8 ± 31.1	146.6 ± 67.4	<0.001
HDL-C (mg/dl)	61.4 ± 13.9	43.2 ± 7.8	<0.001
Cholesterol (mg/dl)	174.6 ± 30.1`	184.7 ± 34.4	<0.001
LDL-C (mg/dl)	99.3 ± 26.6	111.9 ± 30.3	<0.001
FPIS (μU/min)	73.5 ± 123.6	574.7 ± 800.4	<0.001
SPIS (pmol/mmol)	0.055 ± 0.046	0.231 ± 0.254	<0.001
IR (10^{-4} · min^{-1} · pmol^{-1} · L^{-1})	3.674 ± 0.019	3.735 ± 0.031	<0.001

GE (10^{-2} · dL · min^{-1} · kg^{-1})	0.022 ± 0.001	0.019 ± 0.002	<0.001
Hemoglobin (10^3/μ L)	14.2 ± 1.5	13.3 ± 1.2	<0.001

MetS (-) = Without metabolic syndrome; MetS (+) = with metabolic syndrome;

FPIS = first phase insulin secretion; SPIS = second phase insulin secretion; IR = insulin resistance; GE = glucose effectiveness; HDL-C, high-density lipoprotein cholesterol; LDL-C = Low-density lipoprotein cholesterol; Logγ-GT = Log γ-Glutamyl transpeptidase

Data are shown mean ± SD

Table 2: The relationships between Hb and basic information/DFs in young adults (yr18-27)

Demographic data and diabetes factors	Hemoglobin 1	Hemoglobin 2	Hemoglobin 3	Hemoglobin 4	Total	p
Male						
n	5336	5386	5183	5207	211 12	
Age (year)	24.7 ± 2.4[234]	24.2 ± 2.5[1]	24.2 ± 2.6[1]	24.3 ± 2.5[1]	24.3 ± 2.5[1]	< 0.001
Body mass index (kg/m^2)	24.5 ± 4.0[234]	23.1 ± 3.3[1]	23.0 ± 3.3[1]	23.0 ± 3.2[1]	23.4 ± 3.5	< 0.001
Waist circumference	81.3 ± 9.9[234]	77.7 ± 8.5[1]	77.4 ± 8.6[1]	77.7 ± 8.1[1]	78.5 ± 9.0	< 0.001
Systolic blood pressure (mmHg)	121.7 ± 13.1[234]	119.5 ± 12.8[1]	119.6 ± 12.5[1]	119.2 ±12.7[1]	120.0 ± 12.8	< 0.001
Diastolic blood pressure (mmHg)	70.5 ± 9.5[234]	68.7 ± 9.0[1]	68.7 ± 9.0[1]	68.5 ± 8.9[1]	69.1 ± 9.1	< 0.001
Fasting plasma glucose (mg/dl)	95.3 ± 8.4[234]	93.7 ± 7.4[1]	93.7 ± 6.9[1]	94.0 ± 6.7[1]	94.2 ± 7.4	< 0.001
Triglyceride (mg/dl)	135.6 ± 73.3[234]	83.8 ± 39.4[13]	79.3 ± 30.3[12]	80.9 ± 27.5[1]	95.1 ± 52.2	< 0.001
HDL-C (mg/dl)	47.4 ± 11.5[234]	51.2 ± 11.7[1]	51.6 ± 11.5[1]	51.5 ± 11.4[1]	50.4 ± 11.6	< 0.001
Cholesterol (mg/dl)	186.1 ± 34.4[234]	173.4 ± 30.9[1]	173.0 ± 30.5[1]	173.9 ± 29.8[1]	176.6 ± 31.9	< 0.001
LDL-C (mg/dl)	111.5 ± 30.8[234]	105.4 ± 28.2[1]	105.5 ± 28.4[1]	106.2 ± 28.1[1]	107.2 ± 29.0	< 0.001
FPIS (μU/min)	216.8 ± 313.6[234]	141.8 ± 214.4[1]	136.7 ± 224.2[1]	132.5 ± 193.7[1]	157.266 ± 243.7	< 0.001
SPIS (pmol/mmol)	0.103 ± 0.112[234]	0.077 ± 0.078[1]	0.076 ± 0.081[1]	0.076 ± 0.082[1]	0.083 ± 0.090	< 0.001
IR (10^{-4} · min^{-1} · $pmol^{-1}$ · L^{-1})	3.703 ± 0.029[234]	3.689 ± 0.023[1]	3.688 ± 0.023[1]	3.688 ± 0.022[1]	3.692 ± 0.025	< 0.001
GE (10^{-2} · dL · min^{-1} · kg^{-1})	0.019 ± 0.002[234]	0.021 ± 0.001[13]	0.021 ± 0.001[12]	0.021 ± 0.001[1]	0.021 ± 0.002	< 0.001
Hemoglobin (10^3/μ L)	13.5 ± 0.9[234]	15.0 ± 0.3[134]	15.8 ± 0.2[124]	16.7 ± 0.5[123]	15.3 ± 1.3	<

						0.001
White blood cell count (10^3/μ L)	6.5 ± 1.8[4]	6.4 ± 1.5[34]	6.6 ± 1.6[24]	6.8 ± 1.7[123]	6.6 ± 1.6	< 0.001
Platelet count (10^3/μL)	265.5 ± 58.4[234]	245.9 ± 49.8[14]	242.8 ± 49.4[1]	241.1 ± 49.3[12]	248.9 ± 52.8	< 0.001
r-GT	15.1 ± 14.1[234]	21.1 ± 18.1[134]	23.0 ± 20.4[124]	26.9 ± 27.4[123]	21.5 ± 20.9	< 0.001
Logγ-GT	1.099 ± 0.234[234]	1.245 ± 0.240[134]	1.283 ± 0.239[124]	1.331 ± 0.262[123]	1.238 ± 0.259	< 0.001
Uric acid (mg/dl)	6.0 ± 1.5[234]	6.9 ± 1.5[134]	7.1 ± 1.4[124]	7.2 ± 1.4[123123]	6.8 ± 1.5	< 0.001
Female						
n	4847	5256	5114	5470	20687	
Age (year)	24.6 ± 2.3[34]	24.4 ± 2.4[34]	24.0 ± 2.5[12]	24.0 ± 2.5[12]	24.3 ± 2.4	< 0.001
Body mass index (kg/m^2)	21.9 ± 3.4[34]	21.8 ± 3.3[34]	21.2 ± 2.6[124]	20.9 ± 2.2[123]	21.4 ± 2.9	< 0.001
Waist circumference	69.4 ± 7.6[34]	69.0 ± 7.4[34]	67.5 ± 6.0[12]	67.0 ± 5.5[12]	68.2 ± 6.7	< 0.001
Systolic blood pressure (mmHg)	108.7 ± 11.9[34]	108.4 ± 12.0[34]	106.8 ± 11.5[12]	106.7 ± 11.1[12]	107.6 ± 11.6	< 0.001
Diastolic blood pressure (mmHg)	64.0 ± 8.6[34]	63.7 ± 8.5[34]	62.8 ± 8.1[12]	62.5 ± 8.0[12]	63.2 ± 8.3	< 0.001
Fasting plasma glucose (mg/dl)	91.7 ± 8.3[123]	91.1 ± 7.9[134]	89.5 ± 6.6[12]	89.0 ± 6.4[12]	90.3 ± 7.4	< 0.001
Triglyceride (mg/dl)	88.6 ± 38.9[123]	82.0 ± 40.4[134]	62.3 ± 27.3[124]	55.8 ± 15.1[123]	71.7 ± 34.6	< 0.001
HDL-C (mg/dl)	58.7 ± 14.3[34]	59.3 ± 14.2[34]	62.3 ± 13.9[12]	63.0 ± 13.4[12]	60.9 ± 14.1	< 0.001
Cholesterol (mg/dl)	178.9 ± 30.9[34]	177.0 ± 31.0[34]	172.7 ± 30.0[12]	171.3 ± 28.5[12]	174.9 ± 30.2	< 0.001
LDL-C (mg/dl)	102.4 ± 27.4[34]	101.2 ± 27.8[34]	97.9 ± 26.5[12]	97.1 ± 25.2[12]	99.6 ± 26.8	< 0.001
FPIS (μU/min)	108.1 ± 253.9[34]	101.8 ± 242.0[34]	73.1 ± 136.1[12]	62.3 ± 79.0[12]	85.8 ± 191.3	< 0.001

SPIS (pmol/mmol)	0.067 ± 0.083[34]	0.065 ± 0.081[34]	0.056 ± 0.055[12]	0.051 ± 0.035[12]	0.060 ± 0.066	< 0.001
IR ($10^{-4} \cdot min^{-1} \cdot pmol^{-1} \cdot L^{-1}$)	3.681 ± 0.024[123]	3.679 ± 0.024[134]	3.673 ± 0.019[124]	3.670 ± 0.017[123]	3.676 ± 0.022	< 0.001
GE ($10^{-2} \cdot dL \cdot min^{-1} \cdot kg^{-1}$)	0.021 ± 0.001[123]	0.021 ± 0.001[134]	0.022 ± 0.001[124]	0.022 ± 0.001[123]	0.022 ± 0.001	< 0.001
Hemoglobin (10^3/μ L)	12.2 ± 0.9[123]	13.7 ± 0.3[134]	14.6 ± 0.3[124]	16.0 ± 0.6[123]	14.2 ± 1.5	< 0.001
White blood cell count (10^3/μ L)	5.9 ± 1.7[123]	6.1 ± 1.6[134]	6.3 ± 1.7[124]	6.7 ± 1.7[123]	6.3 ± 1.7	< 0.001
Platelet count (10^3/μL)	246.5 ± 65.0[123]	231.9 ± 53.8[134]	220.5 ± 53.1[124]	215.6 ± 50.1[123]	228.2 ± 56.8	< 0.001
γ-GT	16.7 ± 34.2[34]	19.0 ± 31.7[34]	25.8± 38.3[124]	33.8 ± 45.4[123]	24.1 ± 38.5	< 0.001
Log γ-GT	1.083 ± 0.270[234]	1.152 ± 0.275[124]	1.293 ± 0.278[134]	1.416 ± 0.276[123]	1.242 ± 0.304	< 0.001
Uric acid (mg/dl)	5.2 ± 1.4[234]	5.6 ± 1.5[124]	6.3 ± 1.6[134]	6.7 ± 1.5[123]	6.0 ± 1.6	< 0.001

MetS(-) = Without metabolic syndrome; MetS (+) = with metabolic syndrome;

FPIS = first phase insulin secretion; SPIS = second phase insulin secretion; IR = insulin resistance; GE = glucose effectiveness; HDL-C, high-density lipoprotein cholesterol; LDL-C = Low-density lipoprotein cholesterol; Log γ-GT = Log γ-Glutamyl transpeptidase

Data are shown mean ± SD

Table 3: The results of simple correlation between hemoglobin and four diabetes factors

Diabetes factors	men	women
First Phase Insulin Secretion	−0.133*	−0.089*
Second Phase Insulin Secretion	−0.115*	−0.088*
Insulin resistance	−0.245*	−0.185*
Glucose effectiveness	0.410*	0.367*

* *p* value < 0.001

Figure 1: The comparisons of the relationships between hemoglobin and four diabetes factors in men (panel A) and women (panel B). It could be noted that glucose effectiveness had the tightest relationship with hemoglobin followed by insulin resistance, second phase insulin secretion and first phase insulin secretion. All of these slopes are significantly different from each other.