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The Relationship between Age, BMI, Insulin Resistance and B Cell Function in Chinese Population

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Abstract: ***Introduction*: Almost all related studies investigating the relative effects of insulin resistance and β cell function on fasting blood glucose in the past have faced two major disability factors: age and body mass index (BMI). The application of Homeostasis Model Assessment (HOMA) equation in daily routine faces more and more frequent to both aging and obesity problem. The current study, we want to shed light on the two main factors associated with HOMA equation. *Methods*: A total of 866 subjects were eligible for further analysis. Homeostasis Model Assessment-Insulin Resistance index (HOMA-IR) and Homeostasis Model Assessment β-cell function index (HOMA-β) were also calculated. *Results*: HOMA-IR was correlated only with BMI but not age. HOMA-β significantly correlated with both BMI and age. HOMA-IR was independently correlated with SBP, DBP, and TG only, other factors were washout after adjustment by either BMI only or both BMI and age. Only TG was independently correlated with HOMA-β after both BMI and age adjustment. *Conclusion*: Both insulin resistance and β-cell function were independently related to the body mass index. However, age seems related to insulin resistance but nor β-cell secretion. Larger sale analysis may be needed for further exploration of the underlying mechanism.***

Keywords: HOMA, insulin resistance, β cell function, Age, BMI

1. Introduction

Since 1980, the prevalence of type 2 diabetes (T2D) in the world population has doubled [1]. Taiwan faces a similar situation, and a recent report found a 70% increase in the total diabetic population from 2000 to 2009 [2]. Obesity is one of the key risk factors that explain these high prevalence [3]. However, the better health system that can extend lifespan could be another factor. Aging is a strong risk factor for many metabolic disorders, including cardiovascular disease and T2D [4]. Historically, T2D has been considered an age-related disease. Decreased insulin action in peripheral tissues and impaired homeostatic insulin secretion can impair glucose tolerance even in healthy elderly [5-6].

As we all know, T2D is a metabolic disorder due to insulin resistance and impaired insulin secretion. Homeostasis Model Assessment (HOMA) is one of the most widely used equations to assess insulin status. Insulin resistance and secretion are calculated by different equations, insulin resistance is called HOMA-IR, and insulin secretion is called HOMA-β. In fact, one of the main indicators of T2D is elevated fasting blood glucose (FPG) levels [7]. Almost all related studies investigating the relative effects of HOMA on FPG in the past have faced two major disability factors: age and body mass index (BMI) [8-11]. The application of HOMA equation in daily routine faces more and more frequent to both aging and obesity problem. The current study, we want to shed light on the two main factors associated with HOMA equation.

2. Materials and Methods

Study Population

We enrolled subjects from cardinal Tien hospital from 2015~2016. Data from the participants were collected anonymously, and informed consents were obtained before health checkup. The study protocol was approved by the Institutional Review Board and the data were provided for research purposes only. We randomly selected 1, 261 subjects at first. All subjects were newly diagnosed without past history of T2D. Subjects were taking medications known to affect FPG were all excluded. Finally, a total of 866 subjects were eligible for further analysis.

Anthropometric Measurements and General Data

A standard protocol of the checkup was followed in the

hospital. The senior nursing staff in the clinic used a questionnaire to obtain the subject's medical history, including any current medications. Then, complete physical examinations were performed. Waist circumference (WC) was measured horizontally at the level of the natural waist, which was identified as the level at the hollow molding of the trunk when the trunk was laterally concave. BMI was calculated as the subject's body weight (kg) divided by the square of the subject's height (m). Both systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by the nursing staff using a standard mercury sphygmomanometer fitted on the right arm of each subject when seated. Laboratory measurements after the subject fasted for 10 hours, blood samples were drawn from the antecubital vein for biochemical analysis. Plasma was separated from blood within 1 hour and stored at-30℃ and analyzed for FPG and lipid profiles. The FPG was detected using a glucose oxidase method (YSI 203 glucose analyzer, Scientific Division, Yellow Springs Instruments, Yellow Springs, OH). Insulin was measured by using automated analyzer. Total cholesterol and triglycerides (TG) were measured using the dry, multilayer analytical slide method in the Fuji Dri-Chem 3000 analyzer (Fuji Photo Film, Minato-Ku, Tokyo, Japan). Serum high-density lipoprotein (HDL) and low-density lipoprotein (LDL) concentration were analyzed using an enzymatic cholesterol assay following dextran sulfate precipitation. Homeostasis Model Assessment-Insulin Resistance index (HOMA-IR) and Homeostasis Model Assessment β-cell function index (HOMA-β) were also calculated.

Statistical Analysis

The data in this study are presented as mean ± standard deviation. Correlations between factors were evaluated by Pearson correlation. In order to evaluate the independent factors, multiple logistic regression was applied. A p-value (two-sided) < 0.05 was considered to be significant. All statistical analyses were performed by using SPSS 23.0 software (SPSS Inc., Chicago, IL).

3. Results

Demographic data of study subjects with normal glucose, impaired glucose tolerance and T2D were shown in the table 1. Generally, factors with HOMA, body weight (BMI and WC), lipidemia (HDL, LDL, TG) and blood pressure were worse in T2D patients than normal control. HOMA-IR was correlated with all parameters without age. Similarly, HOMA-β significantly correlated with all parameters without LDL (table 2). In this table we can see that BMI was correlated with both HOMA-IR and HOMA-β. The age was only associated with HOMA-β. We further analysis the associated factors by adjusting BMI and age. HOMA-IR was independently correlated with SBP, DBP, and TG only, other factors were washout after adjustment by either BMI only or both BMI and age. This result can be consistent with the simple correlation result that HOMA-IR was not correlated with aging. However, only TG was independently correlated with HOMA-β after both BMI and age adjustment.

4. Discussion

In our study, we found insulin resistance and β-cell function were both related to the glucose level and BMI. However, the age was related to β-cell function but nor insulin resistance. Moreover, insulin resistance and β-cell function were independently related to TG level. Insulin resistance correlated one more factor, the blood pressure. The results let us to know the clear relationships between age, BMI, insulin resistance and β-cell function.

Obesity is not always associated with insulin resistance. However, most people with insulin resistance are obese or overweight [12]. Therefore, obesity is a fundamental risk factor for insulin resistance. Possible causes of obesity, dysfunction of lipid organs, and metabolic disorders due to altered fat metabolism by imbalance in ROS production, antioxidant protection and chronic fat-free inflammation [13-14]. Tissue is also an important regulator of insulin sensitivity [15-16]. Excessive ROS can exacerbate inflammation and directly affect insulin signaling in the system's complex nutrients and nutrient networks, insulin-targeted tissues [15-16].

Adipose tissue is an important metabolic organ that stores excess nutrients in TG form, releases fatty acids on an empty stomach, and acts as an energy source for peripheral tissues in a constitutive state. Obesity can induce insulin resistance, during which immune cells permeate primarily white adipose tissue, liver and other metabolic organs and are released into the circulatory system. Cytokine levels in obesity are not very high and the most studied obesity inflammatory factors are TNFα, interleukin 6, interleukin 17 and CCL-2 [17-18].

Adipose tissue macrophages play important roles in obesity-related inflammation and insulin resistance. Macrophages increase in adipose tissue during aging [19]. Aging is a process in which the body gradually loses its physical integrity, impairing long-term function and leading to death. Aging is always associated with metabolic dysfunction, including obesity and insulin resistance. Recent studies have shown that aging-related insulin resistance is associated with immune-senescence and inflammatory-aging [20-22].

Chronic mild inflammation under hyperlipidemia is known to play an important role in the development of lipotoxicity and pancreatic cell abnormalities [22-23]. Obesity and diet improved the expression of androsine in adipose tissue, the proposed T2D contributor [24]. Basal hyperinsulinemia is primarily due to a moderate contribution of increased insulin secretion and decreased insulin scavenging rates related to body weight. Postprandial hyperinsulinemia in overweight is primarily due to secretion, whereas postprandial hyperinsulinemia in obese subjects is primarily due to a reduced cleaning rate. Therefore, postprandial insulin secretion cannot completely solve the problem of weight-dependent insulin resistance in non-diabetic obese patients [25].

Hypersensitivity to glucose and damaged cellular properties act as a dysfunction phenotype shared between aged and diabetic mouse β cells. Increases the expression of Nmnat2 (cytoplasmic NAD synthase), which induces a hyperactive glycolysis response are the common features of aging and diabetic β-cells [26]. In the rodent model, aging has been shown to increase insulin secretion [27], which is epigenetic activation of β-cell function [28], decreased KATP channel conductivity [29], and p16-mediated cellular senescence [30]. Beta cells have been shown to enter the refractory period post-replication, and the period of the refractory period increases with age and can last up to several months in older rodents which indicate that aging can lead to changes that inhibit β-cell proliferation [31].

There are several limitations in the current study need to be addressed: First, this is a cross sectional observation study. No longitudinal follow-up was applied for the cause-relationship clarify. In addition, the study population was not large enough for a national wide representative population study. However, the total of 866 subjects in the current study can still provide some informative conclusion. At last, no gender specific analysis was done and the only Han Chinese were included in the current study. However, the aging and obesity may be similar in both gender and we thought this study could still provide some informative results.

In conclusion, both insulin resistance and β-cell function were independently related to the BMI. However, age seems related to insulin resistance but nor β-cell secretion. Larger sale analysis may be needed for further exploration of the underlying mechanism.

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Table 1: Demographic data of the studying subjects in the current study

	Normal			IGT			T2D			P value
n	619			191			56			---
Gender (Male/Female)	381/238			150/41			41/15			< 0.001
Age (year)	53.3	±	0.4	57.2	±	0.6	58.8	±	1.4	< 0.001
HOMA-IR	1.4	±	0.0	2.9	±	0.2	3.8	±	0.4	< 0.001
HOMA-β (%)	89.7	±	2.5	86.9	±	5.6	36.4	±	4.6	< 0.001
Fasting plasma glucose (mg/dl)	89.1	±	0.2	107.9	±	0.5	167.6	±	5.6	< 0.001
Body mass index (Kg/m2)	24.2	±	0.1	26.1	±	0.3	26.4	±	0.5	< 0.001
Waist circumference (cm)	86.8	±	0.4	91.6	±	0.6	92.5	±	1.1	< 0.001
Systolic blood pressure (mmHg)	141.7	±	0.8	151.1	±	1.6	157.5	±	3.2	< 0.001
Diastolic blood pressure (mmHg)	71.8	±	0.4	75.2	±	0.9	78.1	±	1.4	< 0.001
High density lipoprotein (mg/dl)	47.1	±	0.5	44.2	±	0.6	41.0	±	1.4	< 0.001
Low density lipoprotein (mg/dl)	119.6	±	1.3	128.0	±	2.5	115.4	±	3.9	< 0.001
Triglyceride (mg/dl)	122.5	±	2.9	137.3	±	5.2	163.1	±	12.5	< 0.001

IGT, impaired glucose tolerance; T2D, type 2 diabetes; HOMA, homeostasis model assessment; HOMA-IR, HOMA for insulin resistance; HOMA-β, HOMA for insulin secretion.

Table 2: Simple correlation between different parameters, insulin resistance and β cell function

	HOMA-IR		HOMA-β	
	β	p value	β	p value

Fasting plasma glucose	0.388	0.000	-0.206	0.000
Age	-0.033	0.337	-0.190	0.000
Body mass index	0.408	0.000	0.302	0.000
Waist circumference	0.377	0.000	0.267	0.000
Systolic blood pressure	0.181	0.000	0.066	0.054
Diastolic blood pressure	0.185	0.000	0.080	0.019
High density lipoprotein	-0.191	0.000	-0.149	0.000
Low density lipoprotein	0.067	0.050	0.066	0.053
Triglyceride	0.198	0.000	0.157	0.000

HOMA, homeostasis model assessment; HOMA-IR, HOMA for insulin resistance; HOMA-β, HOMA for insulin secretion.

Table 3: Multivariant analysis of insulin resistance by adjusting age and body mass index

	Model 1		Model 2	
	β	p value	β	p value
Systolic blood pressure	0.008	0.004	0.010	0.002
Diastolic blood pressure	0.013	0.018	0.013	0.014
High density lipoprotein	-0.010	0.071	-0.010	0.074
Low density lipoprotein	0.001	0.592	0.001	0.616
Triglyceride	0.003	0.001	0.003	0.001
Model 1: with body mass index adjust Model 2: with body mass index and age adjust				

Table 4: Multivariant analysis of β cell function by adjusting age and body mass index

	Model 1		Model 2		Model 3	
	β	p value	β	p value	β	p value
Systolic blood pressure	-0.156	0.142	0.307	0.003	-0.031	0.770
Diastolic blood pressure	-0.129	0.502	0.446	0.019	-0.064	0.734
High density lipoprotein	-0.323	0.114	-0.869	0.000	-0.304	0.129
Low density lipoprotein	0.058	0.394	0.126	0.067	0.048	0.470
Triglyceride	0.081	0.007	0.129	0.000	0.068	0.020
Model 1: with body mass index adjust Model 2: with age adjust Model 3: with body mass index and age adjust						