

The correlation between the Glycated hemoglobin (HbA1c) in non-diabetics and cardiovascular risk factors

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Abstract: This study aimed to discuss the relativity between the glycated hemoglobin (HbA1c) in non-diabetics and cardiovascular risk factors and definite the significance of predicting the cardiovascular risk factors through cross-sectional research method. There were 2007 cases volunteers (including 650 cases of male, 1357 cases of female) from city community with complete information involved in the research of diabetes. The value of HbA1c 6.5% was set as the diagnose boundary of the diabetes. Differences were considered to be statistically significant at $P < 0.05$. Hypertension, dyslipidemi, being overweight or obesity, age (male was over 45 years old and female was over 55 years old.), HbA1c 6.0% and fasting blood glucose (FBG) 6.1mmol/L were regarded as cardiovascular risk factors. Then we analyzed the number of risk factors for individuals in different HbA1c groups. Meanwhile, patients were grouped into zero, one, two, three, four or more groups with reference to the number of risk factors they had in order to compare the values of risk factors in different groups through Logistic regression. The results showed that (1) For those people who had no less than three risk factors, the frequency of risk factors was on the rise with the increase of HbA1c levels. (2) The value of HbA1c in different groups of risk factors rose with the increasing number of risk factors. There was a significant difference ($P < 0.001$) between groups. (3) The Regression analysis showed that there was a stronger correlation between HbA1c levels and impaired glucose tolerance (IGT), fasting blood glucose (FBG) rather than age. So Non-diabetics whose HbA1c levels ranged from 6.0% to 6.5% were at high risk of cardiovascular risk factors. HbA1c levels, which can be a prediction index for cardiovascular risk factors dependent from other cardiovascular risk factors for non-diabetics, and it were highly relevant with impaired glucose tolerance (IGT) and impaired fasting blood glucose (FBG).

Keywords: HbA1c; Cardiovascular risk factors; Non-diabetics.

INTRODUCTION

Patients with diabetes mellitus suffer from an excess of cardiovascular mortality despite the improvement in treatment strategies obtained in the last decade (1). So, it is of great importance to understanding of vascular complications and related early mortality in diabetic patients. Previous observational studies have focused on the association of poor glycemic control, low grade inflammation and low HDL-cholesterol (HDL-c) with all-cause mortality and the majority have showed a positive linear relationship between HbA1c and all-cause mortality (2, 3). As a golden index in terms of judgment of the glycemic control in diabetes, HbA1c is mainly used to detect the blood sugar in diabetics and learn about the average blood sugar levels of the diabetic patients in recent 2-3 months (4). HbA1c is often used to guide diabetic therapy and is predictive of long-term diabetic complications (5). It is highly correlated with long-term morbidity associated with type 2 diabetes, including retinopathy and nephropathy. Compared with the pervasive fasting glucose and oral glucose tolerance tests, measurement of HbA1c is faster and could be measured at any time regardless of the duration of fasting (5). Therefore, international experts committee recommended that HbA1c $> 6.5\%$ is as the diagnostic criteria of diabetes.

People with the HbA1c level between 6.0%-6.5% are defined as the high risky crowd of diabetes and supposed to take effective measures to prevent from diabetes (6). Many researches in recent years have shown that the occurrence rates of the cardiovascular events do not reduce despite of the intensive control of the blood sugar of the diabetic patients. Studies had shown that the cardiovascular pathological change of the diabetics occurs in the early stage of the disease. And it grows worse with time proceeding (7). As a result, the intensive control of blood sugar is not able to change the lesions which had already occurred and converse the development of irreversible illness. Early detection and interface should be an efficient method to prevent and slow down the progress and evil of the lesion. This study aimed to discuss the relevance of HbA1c in diabetics with the risk factors of the cardiovascular disease owing to the reason that understanding the connection between cardio metabolic risk factors and HbA1c may help in the design of robust public health interventions that are targeted toward individuals in order to prevent further complications as a result of diabetes.

MATERIALS AND METHODS

Clinical data

General data

From December 2011 to February 2012 in ancient

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community of Shijingshan in Beijing, we selected 3380 normal volunteers for the research of diabetes.

Standards for selection: (1) age is more than 18 years old and no gender limitation. Besides, people should be a volunteer for the survey and sign the agreement and cooperate of their own accord. (2) non-pregnant; no clear history or diabetes; No taking hypoglycemic drugs. Standards for exclusion (1) people who have a clear history of diabetes, coronary heart disease, brain Hemorrhagic stroke; or people whose examination results are consistent with the diagnosis. (2) New diabetics found in the census. (3) Patients with chronic nephritis.

For the experiments about investigations with human subjects, we should state that the study was performed according to the international, national and institutional rules considering clinical studies and biodiversity rights. All the research followed guidelines of the Declaration of Helsinki and Tokyo for humans and was approved by the institutional human experimentation committee or equivalent, and that informed consent was obtained.

Cross-sectional study method

Measure of blood pressure

We adopted domron medical electronic blood pressure gauge (BP-203rvC) from Colin company in Japan for the measure of blood pressure. Smoking, drinking alcohol or coffee is forbidden 30 minutes before measurement. Participants should empty their bladder and have a 5minute rest before test. Place the cuff sensor on the brachial arterial pulse points, above the elbow horizontal grain. Then we measured three times repeatedly every two minutes and then take the average.

OGTT

Participants should keep a normal diet for 3 days before examination. Alcohol and overeating is forbidden. The amount of Carbohydrate in taken every day should be no less than 250g. Food is forbidden for no less than 10 hours from the last night before examination until the check day to ensure that the participants keep an empty stomach on the day of examination. After blood sampling, Participants should drink an amount of 250~300mL of warm water solution within 5 minutes, which contains glucose 83g. We measured at the time of 120 minutes from the time of the first sip of sugar water. The time error should be controlled within ten minutes. Any strenuous exercise or food should be avoided during test.

Examination of biochemical indexes

Conventional methods in the lab were used to determine total cholesterol (TC)(2), three acyl glycerin (TG) and high-density lipoprotein cholesterol (HDL-C)(8), low density lipoprotein cholesterol (LDL-C), fasting blood glucose (FBG) and the blood sugar (2 HPG) and HbA1c levels 2 hours after dinner(9).

Diagnostic criteria

High risky crowd of diabetes.

People whose HbA1c levels fall in the range of 6.0%-6.5% are defined to be at the high risk of diabetes.

Diabetes

According to the WHO diagnostic criteria in 1999, people with the FBG value more than 7.0mmol/L, or OGTT blood sugar levels more than 11.1mmol/L are defined as diabetics.

Cardiovascular risk factors

According to "China guide for prevention from hypertension", the number of vascular risk factors refers to one or several of the following factors, (1) High Blood Pressure (including high systolic pressure and/or high diastolic pressure). It refers to people whose blood pressure is more than 140/90mmHg (1mmHg=0.133 kPa). (2) Metabolic disorders of blood lipid (including high TC and/or low TC and/or high LDL and/or HDL); (3) Overweight (BMI 24~27.9kg/m²) or obesity (BMI≥28 kg/m²); (4) High uric disease: Uric (UA>420umol/L); (5) Male is over 45 years old, and female is over 55 years old;(6) Diabetes: FBG >7.0 mmol/L and/or 2 HPG 11.1 mmol/L. The risk factor should be zero when all the indexes above are normal.

STATISTICAL ANALYSIS

All data were assessed by SPSS 16.0 program. Comparison among all groups was performed by One-way ANOVA analysis of variance when the measurement data were expressed as mean ±s; When the measurement results were expressed as number (%), comparison among all groups was performed by a square test; The relevant risk factors of HbA1c was determined by regression analysis.

RESULTS

The basic characteristics of the investigated crowd.

The number of participates with complete information totals is 2828 cases, with 552 cases excluded from the total of 3380 cases because of their incomplete information. Of the 2828 cases, 377 cases were excluded due to a history of diabetes or the use of blood sugar-lowering drugs. There was also an exclusion of 447 cases diagnosed as new diabetics based on FBG or OGTTI. At last, a total of 2007 cases took part in the research including 650 cases of male and 1357 cases of female, with age 37~81(56.07±8.54) years old. Patients were divided into two groups on the basis of HbA1c level: HbA1c <6.0% (1509 cases); taking up 75.2 percent of the patients. In the group, there are 493 cases of male and 1016 cases of female. HbA1c >6.0% (498 cases), occupying 24.8% of the patients including 151 cases of male and 341 cases of female.

Table 1: Comparisons of cardiovascular risk factors among individuals of different HbA1c levels cases (%)

Index	Overweight	obesity	Age (male>45, female>55)	impaired fasting glucose	impaired glucose tolerance	LDL-C≥130mg/L	TG≥200mg/L	TG≥150mg/L	HDL-C<40mg/L	High blood pressure
HbA1c 5.0%	19(57.6)	3(9.1)	19(57.6)	2(6.1)	6(18.2)	13(39.4)	17(51.5)	13(39.4)	1(3.0)	10(30.3)
HbA1c5.0% 5.4%	193(44.7)	66(15.3)	214(49.5)	12(2.8)	59(13.7)	127(29.4)	183(42.4)	87(20.1)	42(9.7)	145(33.6)
HbA1c5.5% 5.9%	482(46.2)	231(22.1)	619(59.3)	70(6.7)	276(26.4)	477(45.7)	613(58.7)	298(28.5)	101(9.7)	412(39.5)
HbA1c6.0% 6.4%	183(45.9)	130(32.6)	282(70.7)	50(12.5)	171(42.9)	200(50.1)	243(60.9)	157(39.3)	56(14.0)	198(49.6)
HbA1c≥6.5%	46(46.5)	31(31.3)	68(68.7)	6(6.1)	47(47.5)	42(42.4)	59(59.6)	24(24.2)	9(9.1)	51(51.5)
Total	923(46.0)	461(23.0)	1202(59.9)	140(7.0)	559(27.9)	859(42.8)	1115(55.6)	579(28.8)	209(10.4)	816(40.7)
X ₂	37.036	43.186	42.020a	162.5		44.162	40.176	40.254	8.556	29.224
P	0.000	0.000	0.000	0.000		0.000	0.000	0.000	0.073	0.000
HbA1c≥6.0%	229(24.8)	161(34.92)	367(27.0)	56(40)	219(39)	242(28.2)	302(27.1)	181(31.3)	65(31.1)	249(30.5)
χ ²										
23.960	43.934	32.794	10.669	119			9.083	6.942	18.133	4.943
0.000	0.000	0.000	0.001	0.000			0.003	0.009	0.000	0.028

Table 2: Comparison of values in groups with different risk factors (x ± SD)

Index	None (n=91)	One risk factor (n=262)	Two risk factors (n=396)	Three risk factors (n=489)	Over four risk factors (n=769)	F	Total	P
Age/years old	47.71 ±4.473	50.93±7.003	53.41 ±7.23	56.40±8.099	59.98±8.162	56.07±8.539	117.756	0.000
BMI/(kg/m ²)	21.8019 ±1.46083	23.4654 ±2.7862	24.9988±3.02328	25.9947±3.59917	27.2628±2.96335	25.7638±3.43669	127.105	0.000
Average systolic pressuremm Hg	115.13±9.84367	119.57 ±11.0508	123.68±11.6443	129.27±13.90535	137.87±16.11737	129.55±15.78351	143.959	0.000
Average diastolic blood pressure mmHg	70.011 ±7.44796	70.9042 ±7.90231	73.2184±8.57533	75.2859±8.84034	77.2866±10.64418	74.8314±9.66446	33.914	0.000
TC (mmol/L)	4.5609 ±0.56431	5.1213 ±1.02831	5.3301±0.87552	5.4333±1.20532	5.5439±0.93958	5.375±1.02218	25.492	0.000
TG (mmol/L)	0.8095 ±0.26701	1.026 ±0.45267	1.3017±0.72736	1.57±1.11945	1.8364±1.09827	1.5137±1.00192	57.314	0.000
HDL-C (mmol/L)	1.7784 ±0.37138	1.6913 ±0.38025	1.5645±0.45244	1.4773±0.45253	1.368±0.36562	1.4942±0.42683	47.795	0.000
LDL-C (mmol/L)	2.5290 ±0.39737	3.0031 ±0.84692	3.2401±0.71214	3.3077±0.79907	3.4536±0.79723	3.2752±0.80409	39.800	0.000
FBG (mmol/L)	5.1553 ±0.31517	5.2887 ±0.41166	5.4048±0.39304	5.5311±0.44607	5.8303±0.51561	5.5722±0.50693	120.506	0.000
Blood Sugar two hours after 80g glucose/ (mmol/L)	5.6573 ±1.07664	6.0420 ±1.19028	6.4283±1.38349	6.8078±1.5713	7.6570±1.67341	6.9062±1.64858	94.554	0.000
HbA1c%	5.5044 ±0.2366	5.6084 ±0.31344	5.7146±0.42586	5.7845±0.35552	6.0542±0.4948	5.8384±0.45722	95.714	0.000

The distribution frequency of Cardiovascular risk factors under different levels of HbA1c

With the increasing levels of HbA1c, the occurrence rate of overweight, obesity, high blood LDL-C, high TG hematic disease also increased. Impaired fasting glucose and glucose tolerance to reduce hematic disease followed. The occur rate reached the maximum when the levels of HbA1c ranged from 6.0% to 6.4%, which was shown in table 1.

Comparison of value of the frequency groups of each risk factor

All the patients were divided into 0,1,2,3,4 or more groups with reference to the number of risk factors they

had. After comparing the values of risk factor of different groups, we found that the value of HbA1c in groups of different risk factor was consistent with the number of risk factor. What was more, there was a significant difference (P 0.001) between groups. Other risk factors were shown in table 2.

Frequency distribution of risk factors under different levels of HbA1c

Frequency of more than two risk factors increased with the rise of HbA1c levels when the HbA1c levels ranged from 6.0% to 6.4%, the frequency reached the peak, which was described in table 3.

Table 3: Comparison between HbA1c levels and the groups with different risk factors Cases (%)

Index	None	One risk factor	Two risk factors	Three risks factors	Over four risk factors	Total
HbA1 5.0%	1 (3.0)	6 (18.2)	11 (33.3)	8 (24.2)	7 (21.2)	33 (1.6)
HbA1c 5.0% 5.4%	51 (11.8)	96 (22.2)	106 (24.5)	102 (23.6)	77 (17.8)	432 (21.5)
HbA1c 5.5% 5.9%	39 (3.7)	157 (15.0)	246 (23.6)	296 (28.4)	306 (29.3)	1044 (52)
HbA1c 6.0% 6.4%	0 (0)	2 (0.5)	21 (5.3)	71 (17.8)	305 (76.4)	399 (19.9)
HbA1c ≥ 6.5%	0 (0)	1 (1.0)	12 (12.1)	12 (12.1)	74 (74.7)	99 (4.9)
Total	91 (4.5)	262 (13.1)	396 (19.7)	489 (24.4)	769 (38.3)	2007 (100)

Table 4: Logistic regression analysis of HbA1c and cardiovascular risk factors

Variable	Partial regression confident β	Standard error	Wald	P	OR	OR of 95% CI
FBG 6.1mmol/L			121.325	0	1	
Impaired fasting blood glucose (6.1mmol/L≤FBG 7.0mmol/L)	1.130	0.171	43.551	0	3.096	(2.213, 4.33)
Impaired glucose tolerance (7.8mmol/L≤PBG 11.1mmol/L)	0.582	0.145	16.031	0	1.79	(1.346, 2.38)
Disorder of blood glucose)	1.690	0.168	100.888	0	5.42	(3.897, 7.537)
BMI normal 24kg/m ²			17.208	0	1	
Overweight (BMI24 28kg/m ²)	0.269	0.140	3.669	0.055	1.309	(0.994, 1.724)
Obesity (BMI≥28kg/m ²)	0.641	0.157	16.750	0	1.897	(1.396, 2.579)
Hig TG	0.272	0.121	5.072	0.024	1.312	(1.036, 1.662)
Age 45			38.647	0	1	
Age 45 54 years old	0.863	0.336	6.593	0.01	2.37	(1.227, 4.581)
Age 55 64 years old	1.296	0.335	14.995	0	3.653	(1.896, 7.038)
Age 65 74years old	1.641	0.349	22.097	0	5.158	(2.603, 10.223)
Age≥75years old	1.268	0.463	7.503	0.006	3.553	(1.434, 8.801)
Constant	3.071	0.341	81.254	0	0.046	

The Logistic regression analysis of relevant risk factors of HbA1c

All patients were grouped in terms of age. Indexes of smoking, being overweight or obesity, metabolic disorder of sugar, high TG levels, high TC levels, high LDC-C, low HDL-C, levels of blood pressure were set as the independent variables. HbA1c levels were no less than 6% was set as dependent variables. (No=0, Yes=1). Then we used logistic regression model to discuss the possible impact factors with step-by-step method. Results showed that HbA1c was closely related with impaired fasting glucose and reduced sugar tolerance coexistence of both being overweight, or obesity, high TG levels, and age groups (table 4).

DISCUSSION

This research focused on people from community census in order to analyze the relationships between HbA1c of different levels and cardiovascular risk factors. Study showed that frequency of 2-3 and more than 4 risk factors had a high proportion of distribution not only in people whose HbA1c level was more than 6.0%, but also in people whose HbA1c ranged from 5.5%-5.9%. However, with the rise of the level of HbA1c, frequency of more

than two risk factors increased simultaneously. At the same time, the HbA1c level rose with the increasing number of risk factors which indicate that people whose HbA1c level was more than 6.0% in the group were at high risk of diabetes as well as of cardiovascular disease.

Values of other factors such as age, BMI, systolic pressure, diastolic pressure, TG TC, FBG LDL-C rose with the increasing number of risk factors. Value of protective factors HDL of cardiovascular declined with the increase of the number of risk factors. Therefore, we may come to a conclusion that for those people who had no less than two risk factors, the value of risk factors was on the rose with the increase of the number of risk factors Therefore, there was a higher risk of CVD (cardiovascular disease) for individuals with numbers of risk factors due to the enhance of the risk level of his or her risk factors, which was consistent with the research results of document. Logistic regression results showed that the HbA1c level had a tight link with impaired fasting blood glucose, reduced glucose tolerance or coexistence of the two, being overweight or obesity, high TG levels, and age groups. People who have a higher HbA1c level or who are at high risk of diabetes could be found through the detection of HbA1c in the crowd. People who have

cardiovascular risk factors are supposed to take measures such as a positive and efficient lifestyle or drugs to prevent or slow down the process of diabetes. Along with the cardiovascular disease relevant with diabetes and diabetes complications.

In view of the correlations of between HbA1c levels and cardiovascular disease or events, HbA1c may be an index for predictions of cardiovascular disease or events for non-diabetics. The relationship between HbA1c level and cardiovascular risk factors for non-diabetics should be taken seriously. Further research should be done to learn more about the situations of the disease for non-diabetics.

CONCLUSION

In this paper, we discussed the relativity between the glycated hemoglobin (HbA1c) and cardiovascular risk factors to definite the significance of predicting the cardiovascular risk factors through cross-sectional research method. Our results showed that clustering of cardio metabolic risk factors is positively associated with elevated HbA1c, which revealed that complex and interwoven actions of these three risk factors may be responsible for the atherosclerotic process. It also improved our understanding of the pathways linking poor glycemic control, low grade inflammation and low HDL-c could have implications for future intervention strategies aimed at reducing cardiovascular harm in diabetic patients.

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