Elevated glycosylated hemoglobin levels and its interactive effects on hypertension risk in non-diabetic population: a cross-sectional survey in China

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Abstract

Background Abnormal glucose metabolism have been suggested to be involved in the development of hypertension. The present study aimed to investigate the associations and potential interactions of hemoglobin A1c (HbA1c) with other factors on the risk of hypertension among Chinese non-diabetic adults. Methods As a cross-sectional survey, the current work provided questionnaire survey, anthropometric tests and biochemical measure for each of the eligible participants. The HbA1c levels were quantified and grouped by quartiles. The correlation between HbA1c and hypertension risk in non-diabetic were investigated by univariate and multivariate analyses. For evaluating the interactive effects, the parameters of Relative Excess Risk due to Interaction (RERI), Attributable Proportion due to Interaction (AP) and Synergy Index (SI) were calculated, respectively. Results In the current study, 1462 non-diabetic subjects were enrolled. Totally, the prevalence of hypertension was 22.4% (n=327) in the individuals without diabetes. When the HbA1c levels were grouped by quartiles, it was revealed that the prevalence of hypertension substantially elevated across groups (P for trend <0.001). In the multivariable logistic regression analyses, in comparison with the first quartile of HbA1c, the normalized OR for hypertension risk were 1.90 (95% CI:1.28-2.80) for the highest quartile. Besides, the ROC curve analysis indicated that the best threshold of HbA1c as the predictor for hypertension risk was 4.95 in non-diabetic subjects, with the AUC of 0.60 (0.58-0.63). Eventually, it was demonstrated from the interactive effect analysis that the HbA1c significantly interacted with abdominal obesity (RERI: 1.48, 95% CI: 0.38- 2.58; AP: 0.37, 95% CI: 0.14-0.60 and SI: 1.96, 95% CI: 1.06-3.62) and family history of hypertension (AP: 0.37, 95% CI: 0.05-0.70) on the risk of hypertension in non-diabetic participants. Conclusion The risk of hypertension was aggravated by the up-regulated HbA1c in an independent and synergistic manner with abdominal obesity and family history of hypertension in Chinese subjects without diabetes.

Background

As one of the most common cardiovascular diseases, hypertension has become a prominent social public health problem globally[1]. A national survey containing 451,755 participants from 31 provinces in China has estimated that nearly 244.5 million were suffered from hypertension[2]. What was worse, there was a low rate of awareness, treatment and control of hypertension[2,3]. Additionally, several meta-analysis have proved that hypertension was dramatically associated with the increased risk of a series of diseases such as Parkinson's disease, stroke, and even cancer[4-6]. It was considered that 54% of stroke and 47% of patients with ischemic diseases were attributable to hypertension worldwide[7]. Consequently, distinctly investigating the risk factors and effective predictors of hypertension were essential for alleviating the public health burden.

Often accompanied with abnormal glucose metabolism, hypertension was reported to be observed in more than 2/3 of patients suffered from type 2 diabetes[8]. Besides, numerous researches have suggested that the development of hypertension was consistent with hyperglycemia[8]. It was well-known that HbA1c can precisely reflect the glycemic control stability within nearly 8 to 12 weeks, which was a stable indicator of long-term glycemia[9]. Furthermore, HbA1c was the indicator of the defects of

pancreatic β-cell function as well as the degree of insulin resistance[9,10]. Increasing evidence have demonstrated that not only the patients with higher risk of developing diabetes, but also those with cardiovascular diseases, could be identified by HbA1c[11,12]. Higher HbA1c expression was also implied to be correlated to the increase of mortality even among the subjects without the diagnosis of diabetes[13]. A Nationwide Survey in Korean revealed that the up-regulated HbA1c levels in non-diabetic participants were dramatically related to the risk of developing chronic kidney disease[14]. Also, there was a positive relationship between HbA1c and coronary and peripheral atherosclerotic burden in subjects with normal fasting glucose[15].

Additionally, regarded as a multifactorial disease, hypertension was affected by a series of factors on its occurrence and development. Conclusively, the combined effect among factors may aggravate the risk of hypertension, for instance, there was a remarkable interaction between smoking and smoking and overweight on hypertension risk [16]. A case-control study based on Chinese population indicated that Body Mass Index (BMI) dramatically interacted to the family history of hypertension on the risk of hypertension, and 43.87% of which with both of them was attributable to the additive interaction [17]. However, based on the existing data, no previous work has explored the potentially interactive effect between HbA1c levels with other factors on the risk of hypertension.

Consequently, with the data of the cross-sectional survey, our work aimed to investigate the association and potentially interactive effects of HbA1c with other factors on the risk of hypertension.

Methods

Subjects

Study participants were recruited from a project termed as “creating a provincial demonstration area of chronic diseases management in community”, which was conducted in Longzihu, Bengbu, China in 2015 and mainly designed to identify the epidemiological characteristics of chronic non-communicable diseases among the local residents. Multistage random sampling was utilized to select qualified subjects. The exclusion criteria were listed as below: (1) unable to complete the survey independently; (2) with a diagnosis of neuropathy previously; (3) temporary residents. In the present study, for the purpose to analyze the data of non-diabetic, the members with diagnosed diabetes, FPG value ≥ 7.0 mmol/L or the treatment for hyperglycemia were also excluded [18]. Eventually, 1462 non-diabetic subjects were selected. All the participants were required to complete the whole survey in community clinics and signed informed consent. The study protocol was approved by the Ethics Committee of Bengbu medical college.

Data collection

The data of general characteristics and lifestyle information were collected by trained staffs based on a face to face questionnaire survey. The established questionnaire included the information about birth date, gender, smoking status, marital status ("currently married" or "currently not married"), education level

("middle school graduate or lower" or "high school graduate or above"), income ("≤ 2000 (yuan)" or "> 2000 (yuan)"), self-reported disease history, and family history of hypertension (yes or no).

The blood pressure, weight (accurate to 0.5 kg), and height (accurate to 0.5 cm) were obtained based on unified standardized measurement methods. Each subject was required to have a rest at least for 10 minutes in a quiet room prior to the triple measurements of blood pressure. The average results was calculated and adopted. Hypertension was defined as the members with Systolic Blood Pressure (SBP) greater or equal to 140 mmHg or Diastolic Blood Pressure (DBP) greater or equal to 90 mmHg, or under the therapy of hypertension medication[19]. The height and weight of each subject were measured with light indoor clothing and BMI was calculated as weight (kg)/height^2 (m^2). The participants with BMI ≥ 28 kg/m^2 were regarded as general obesity[20]. For the measurement of Waist Circumference (WC), the subjects were required to maintain the fasting state and an upright position. Abdominal obesity in males and females were diagnosed as WC ≥ 90 cm and 85 cm, respectively[21].

The venous blood samples were collected in the morning and all the subjects were required to perform overnight fasting for more than eight hours. Subsequently, HbA1c, FPG, and triglycerides (TG) were analyzed.

Statistical methods

Statistical analyses were performed using R software. Normally distributed data were expressed as mean ± Standard Deviations (SD), which were further compared based on *t*-test, while the non-normally distributed data were described as median (P_{25}, P_{75}) compared by Wilcoxon rank sum test. Additionally, percentages (%) were applied for the representation of categorical variables, which were subsequently analyzed by Chi- squared test. The levels of HbA1c could be divided into four groups by quartiles (Q1, Q2, Q3 and Q4). Univariate and multivariate logistic regression model were conducted with Odds Ratio (OR) and the corresponding 95% confidence interval (95% CI). In order to maximize the ability of HbA1c to predict the hypertension among non-diabetic subjects, the Receiver Operating Characteristics (ROC) curves analysis was adopted. Finally, three indicators reflecting interactive effects including RERI, SI and AP were analyzed [22, 23]. RERI = 0 or AP = 0 or SI = 1 was considered as no additive interaction. Two-sided *p* values were calculated and $p<0.05$ was considered as statistically significant.

Results

Among the 1462 enrolled participants, the mean age was 59.9±11.3 years old. Specifically, 692 males (40.5%) and 870 females (59.5%) were included, respectively. Overall, the prevalence of hypertension was 22.4% in the non-diabetic subjects, and male had a significantly higher rate of hypertension than female ($p = 0.004$). Compared with the subjects with normotension (59.5 ± 11.4), the ones with hypertension (61.4 ± 10.8) exhibited a higher mean age ($p = 0.008$). Additionally, there was a remarkable difference of the prevalence of family history of hypertension ($p = 0.042$) between the normotension and hypertension participants. Individuals with hypertension had a relatively higher smoking rate (32.1%) than

normotension (27.4%), without any statistical difference (p = 0.096). Meanwhile, no statistically significant differences of the educational level (p = 0.068), marital status (p = 0.226) and income (p = 0.806) were observed. As for the obesity indices, either BMI (p < 0.001) or WC (p < 0.001) were proven to be dramatically up-regulated in the hypertension subjects compared with the normotension ones. Similarly, FPG (p = 0.037), TG (p < 0.001) and HbA1c (p = 0.002) varied markedly between groups. The characteristics of the study population were detailed described in Table 1.

The results of HbA1c expressions and the risk of hypertension in non-diabetic subjects based on logistic regression analysis were listed in Table 2. The prevalence of hypertension predominantly elevated across the quartiles of HbA1c ($p_{\text{for trend}}$ < 0.001). In the untreated model, there was a remarkable up-regulation of the risk of hypertension across the quartiles of HbA1c, and the ORs (95% CI) were 1.00 (ref), 1.31 (0.90-1.92), 2.13 (1.48-3.06), and 2.57 (1.79-3.70), respectively. For the adjusted model, in contrast to the lowest quartiles of HbA1c values, the OR (95% CI) was 1.90 (1.28-2.80) for the highest quartiles of HbA1c values. In Fig. 1, the ROC curve analysis suggested that the best threshold of HbA1c for predicting the risk of hypertension was 4.95%, with the AUC of 0.60 (0.58-0.63).

As represented in Table 3, the participants were separated into 4 subgroups based on HbA1c and other factors. After normalizing for the confounders, the subjects with positive HbA1c and family history of hypertension simultaneously exhibited the highest OR (2.96, 95% CI: 1.90-4.62). It could be estimated from AP (0.37, 95% CI: 0.05-0.70) that there was an additive interaction between HbA1c and the family history of hypertension on the risk of hypertension, rather than the value of RERI (1.12, 95% CI: -0.17-2.40) and SI (2.31, 95% CI: 0.83-6.44). The participants with alternative positive hypertension or general obesity showed a dramatically aggravated risk of hypertension in comparison with those with no positive hypertension level and general obesity (OR: 2.37, 95% CI: 1.69-3.33 and OR: 1.79, 95% CI: 1.25-2.58, respectively). However, no noteworthy synergistic interaction was observed between HbA1c and general obesity (RERI: 1.12, 95% CI: -0.18-2.42; AP: 0.24, 95% CI: -0.01-0.49; and SI: 1.44, 95% CI: 0.91-2.27). As for the abdominal obesity, the HbA1c (+) and abdominal obesity (+) subjects exhibited a higher risk of developing hypertension than the reference group (OR: 4.02, 95% CI: 2.81-5.74). There was a conspicuous additive interaction between the above parameters on hypertension (RERI: 1.48, 95% CI: 0.38-2.58; AP: 0.37, 95% CI: 0.14-0.60 and SI: 1.96, 95% CI: 1.06-3.62, respectively). Similarly, the participants with the combination of positive HbA1c and TG were more tended to develop hypertension compared with the reference group (OR: 3.66, 95% CI: 2.59-5.17), and all the indicators suggested a significant interaction (RERI: 1.87 (95% CI: 0.77-2.97), AP: 0.51 (95% CI: 0.30-0.72) and SI: 3.38 (95% CI: 1.32-8.66)).

Discussion

This population-based survey demonstrated that the higher HbA1c levels dramatically aggravated the risk of hypertension in subjects without diabetes, which further emphasized the role of abnormal glucose metabolism in the pathogenesis of hypertension. Owing to the specific merits, HbA1c generally serves as an effective indicator in the management of diabetes, rather than FPG and postload plasma glucose. Firstly, HbA1c has less biological variability and higher stability [9]. Secondly, HbA1c could be less

affected by relevant factors such as acute infection, short-term lifestyle alterations and recent eating behavior[24]. Thirdly, FPG only reflects the immediate glycemia level at that time in a single measurement, in contrast, HbA1c could stably indicate the chronic glycemia levels which reflect the average glycemia levels within nearly 2-3 months. A cohort study consisting of 31,148 adults revealed that HbA1c was closely correlated to all -cause mortality and coronary heart disease in contrast to the fasting glucose [25]. Arbel et al [26] also investigated the relationship between the glucometabolic markers (including admission glucose, FPG and HbA1c) and the severity of coronary artery disease in non-diabetic patients, which indicated that only HbA1c was associated with the severity of coronary artery disease.

The relationship between glycemic control and hypertension can be explained by several possible mechanisms. Firstly, the function deficits of pancreatic beta cells as well as insulin resistance could be indicated by the expressions of HbA1c[9,10]. It was well recognized that insulin resistance was the common pathophysiological basis for the developments of type 2 diabetes and hypertension [27]. When the homeostasis model assessment of insulin resistance (HOMA-IR) was applied to estimate insulin resistance, it revealed that HOMA-IR dramatically up-regulated across the quartile levels of HbA1c in Korean males without diabetes[28]. Additionally, HbA1c was also reported to be one of the best indices in identifying insulin resistance in the obese non-diabetic individuals [29]. Secondly, numerous researches have implied that HbA1c may play a role in arterial stiffness via pro-inflammatory cell signaling and oxidative stress [30,31]. It was demonstrated in a cross-sectional survey containing 11,014 Chinese participants that brachial-ankle pulse wave velocity and central systolic blood pressure markedly elevated across the quartiles of HbA1c[32]. Thirdly, increased levels of HbAlc can contribute to the endothelial damage that further promoted the release of endothelin from endothelial cells, and inhibited the production of nitric oxide and prostacyclin, resulting in vasomotor dysfunction and further the blood pressure[24,33]. Moreover, it has been reported that there was a direct association between HbAlc and the activation of the renin-angiotensin - aldosterone-system, and a liner relationship between HbAlc and renin activity and direct renin concentration [34]. Also, it has been indicated in clinical researches that blood lipids could be positively regulated by the high level of HbAlc, which contributed to the increase of blood viscosity and further the incidence of cardiovascular diseases[24]. With the increase of HbA1c level, the number of cardiovascular risk factors clustering including fasting blood glucose, high total cholesterol, high triglyceride, high and low density lipoprotein cholesterol, and low high density lipoprotein cholesterol were also dramatically up-regulated [35].

To our knowledge, only a few studies have investigated the relationship between the HbA1c levels and risk of hypertension, however the conclusions were inconsistent. A cohort study in American with 9,603 participants demonstrated that the higher baseline HbA1c concentrations were predominantly associated with the incidence of hypertension independently of obesity indices and other factors in diabetes as well as in non-diabetic individuals[36]. Similarly, in a Women's Health Study, 19,858 American women initially without diabetes were followed up with a median of 11.6 years. The subjects were grouped based on HbA1c by clinical cutpoints quintiles, and the Hazard Ratios (HR) for the highest group of HbA1c in comparison with that of the lowest was statistically significant in both the unvariable analysis and

multivariable analysis[37]. However, when grouped HbA1c by quintiles, the above significant association eliminated after normalizing for BMI, which emphasized the crucial role of obesity in the correlation between glucose metabolism and hypertension. Furthermore, elevated HbA1c dramatically aggravated the risk of hypertension in an independent manner even after normalizing traditional risk factors in general middle-aged and elderly Chinese subjects [38]. Besides, the Framingham Heart Study also demonstrated that the high HbA1c expressions was associated with the prevalence of hypertension, only based on an unvariate analysis [39]. Yeung et al [40]`conducted a survey based on a Mendelian randomization design and identified related Single Nucleotide Polymorphisms (SNPs) that strongly correlated to HbA1c in an independent manner, suggesting that there may be a correlation between HbA1c and the risk of hypertension. However, in a Japanese cohort study with 5-year follow-up, 9,584 individuals were investigated, implying that the elevated expressions of HbA1c were not associated with the increased risk of developing hypertension in the multivariable analysis [41]. An increment in the HbA1c level was reported not to be independently involved in the future development of hypertension among Israel populations [42]. Kroke et al[43] revealed that there was a non-significant relationship between HbA1c and arterial hypertension in non-diabetic participants, nevertheless, arterial hypertension was defined as blood pressure ≥ 160/95 mmHg. The inconsistencies may be explained by the diversity of of HbA1c in age, gender and ethnicity.

The present study further demonstrated that HbAlc played a significantly interactive role in abdominal obesity rather than general obesity on the risk of hypertension. Several studies have suggested that abdominal fat distribution may be more strongly related to adverse outcomes such as cardiovascular disease than BMI. It is well acknowledged that obesity was a predominant risk factor of hypertension[44]. When evaluating the predicting performances of different obesity indices on hypertension, WC was superior to BMI based on the ROC curve analysis [45]. It was illustrated that obesity was dramatically associated with the elevated HbA1c levels in diabetes as well as in non-diabetic subjects. Obesity can lead to insulin resistance, resulting in the poor glycemic control [24]. In addition, adipocytokines secreted from the adipose tissue were also involved in the insulin resistance and the dysfunction of beta cells[46]. Furthermore, the occurrence of hypertension was the combinative consequence of genetic and environmental effects. Family history of hypertension was a simple and alternative genetic indicator. Moreover, a case-control study among Chinese individuals have also proven that family history of hypertension and BMI were positively interacted on hypertension[17]. Our results also illustrated that HbAlc had a remarkable interaction with family history of hypertension on the risk of hypertension.

However, there were several limitations in our work. Firstly, the causality of the results were failed to be inferred for it was a cross-sectional study. Secondly, the effects of different antihypertensive drugs varied on glucose metabolism, which were not investigated. Thirdly, the blood pressure was measured in a single survey, which may influenced by various external factors.

Conclusions

In conclusion, this study demonstrated the independent and interactive effect of HbA1c on the risk of hypertension risk in non-diabetic Chinese subjects, suggesting that abnormal glucose metabolism played an essential role in the pathogenesis of hypertension. Further cohort studies with large sample sizes are necessary to verify our results and the underlying mechanism need to be elucidated, which will eventually be beneficial to develop more effective prevention strategies on hypertension.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Bengbu Medical College. Written informed consent was obtained from all participants.

Consent to publish

Consent for publication was obtained in all participants.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors report no conflicts of interest.

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Tables

Table 1 Basic characteristic of the enrolled participants

Variables	Total (N=1462)	Normtension (N=1135)	Hypertension (N=327)	*P* value
Gender				0.004[1]
Male(n(%))	692(40.5)	437(38.5)	155(47.4)	
Female (n(%))	870(59.5)	698(61.5)	172(52.6)	
Mean age (SD)	59.9(11.3)	59.5(11.4)	61.4(10.8)	0.008[2]
Educational level				0.068[1]
Middle school graduate or lower (n(%))	467(31.9)	349(30.7)	118(36.1)	
High school graduate or higher(n(%))	995(68.1)	786(69.3)	209(63.9)	
Marital status				0.226[1]
Currently married (n(%))	1234(84.4)	951(83.8)	283(86.5)	
Currently not married (n(%))	228(15.6)	184(16.2)	44(13.5)	
Income(yuan)				0.806[1]
<=2000 (n(%))	805(55.1)	623(54.9)	182(55.7)	
>2000 (n(%))	657(44.9)	512(45.1)	145(44.3)	
Family history of hypertension(n(%))	266(18.2)	194(17.1)	72(22.0)	0.042[1]
Smoking(%)	416(28.5)	311(27.4)	105(32.1)	0.096[1]
BMI(kg/m^2) (M(P_{25},P_{75}))	24.3(22.1,26.5)	23.8(21.9,26.1)	25.5(23.6,27.7)	<0.001[3]
WC (cm) (M(P_{25},P_{75}))	85.0(80.0,91.0)	83.0(78.0,90.0)	90.0(83.0,96.0)	<0.001[3]
FPG (mmol/L) (M(P_{25},P_{75}))	4.9(4.5,5.4)	4.8(4.4,5.3)	4.9(4.5,5.5)	0.037[3]
TG (mmol/L) (M(P_{25},P_{75}))	1.4(0.9,1.9)	1.3(0.9,1.8)	1.6(1.1,2.3)	<0.001[3]
HbA1c(%) (M(P_{25},P_{75}))	5.0(4.4,5.6)	4.9(4.4,5.5)	5.1(4.6,5.8)	0.002[3]

Table 2 HbA1c levels and risk of hypertension in non-diabetic population by logistic regression analysis

	Quartiles of HbA1c				p for trend
	Q1(<4.4)	Q2(4.4-5.0)	Q3(5.0-5.6)	Q4(>5.6)	
Hypertension(%)	14.7	18.5	26.9	30.7	<0.001
Unadjusted model	1.00(ref)	1.31(0.90-1.92)	2.13(1.48-3.06)	2.57(1.79-3.70)	
Adjusted model [1]	1.00(ref)	1.16(0.78-1.74)	1.88(1.28-2.75)	1.90(1.28-2.80)	
Continuous (per 1 SD)[1]	1.23(1.08-1.40)				

[1]:adjusted for other variables;

Table 3 interactions analysis of HbA1c with other factors on risk of hypertension

Variables		OR[1](95%CI)	Measures of interaction[1]		
			RERI	AP	SI
HbA1c	Family history of hypertension				
-	-	1(ref)	1.12(-0.17-2.40)[2]	0.37(0.05-0.70)[3]	2.31(0.83-6.44)[2]
-	+	1.31(0.80-2.13)			
+	-	1.54(1.14-2.08)			
+	+	2.96(1.90-4.62)			
HbA1c	General obesity				
-	-	1(ref)	1.12(-0.18-2.42)[2]	0.24(-0.01-0.49)[2]	1.44(0.91-2.27)[2]
-	+	1.98(1.27-3.09)			
+	-	2.59(1.71-3.92)			
+	+	4.69(3.17-6.94)			
HbA1c	Abdominal obesity				
-	-	1(ref)	1.48(0.38-2.58)[3]	0.37(0.14-0.60)[3]	1.96(1.06-3.62)[3]
-	+	2.10(1.41-3.12)			
+	-	1.44(0.92-2.22)			
+	+	4.02(2.81-5.74)			
HbA1c	TG				
-	-	1(ref)	1.87(0.77-2.97)[3]	0.51(0.30-0.72)[3]	3.38(1.32-8.66)[3]
-	+	1.34(0.89-2.02)			
+	-	1.45(1.04-2.02)			
+	+	3.66(2.59-5.17)			

[1]:adjusted for other variables;

[2]:$p<0.05$;

[3]:$p>0.05$;

Figures

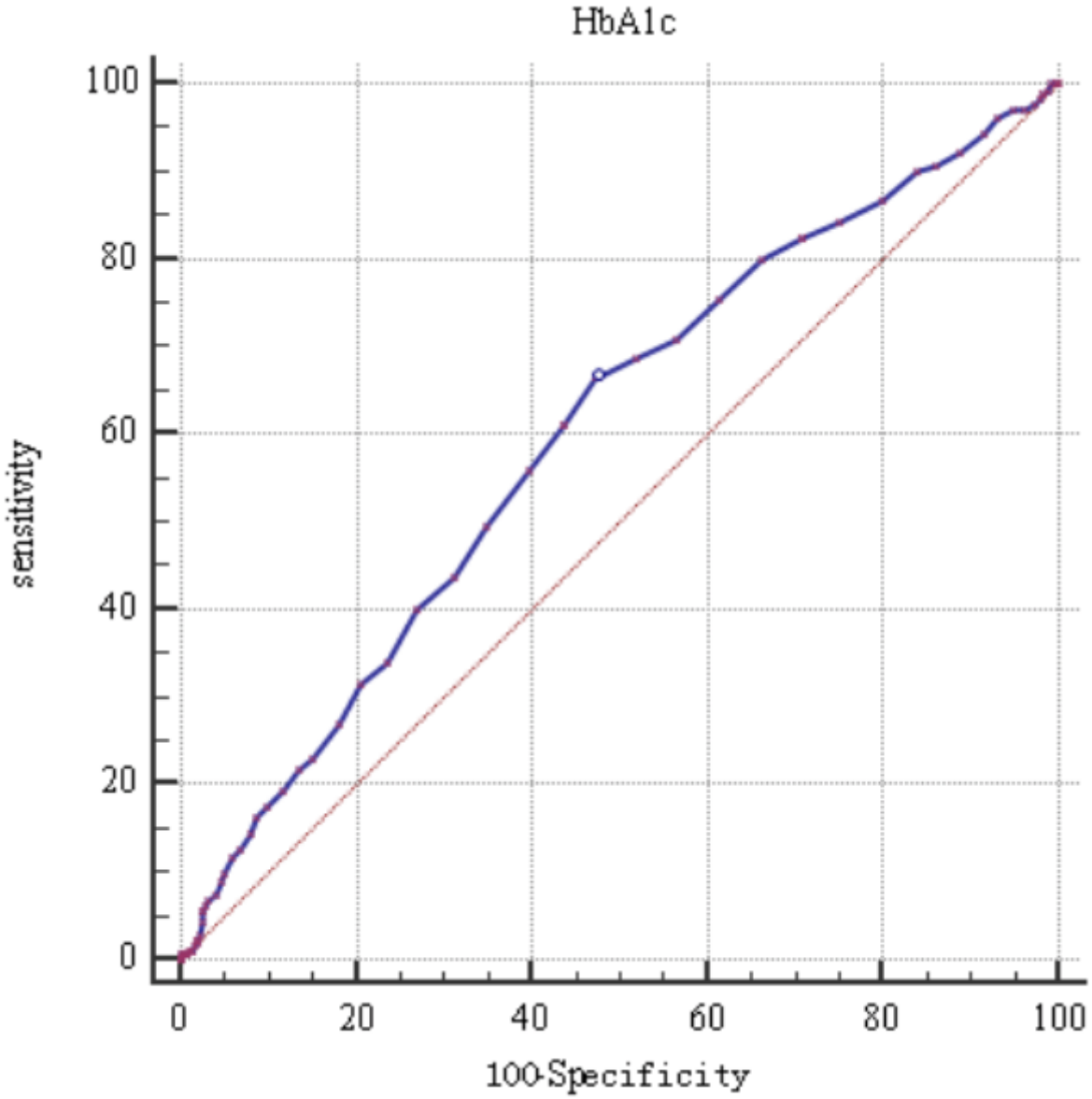

Figure 1

ROC curve analysis of HbA1c and hypertension risk in non-diabetic subjects