Iranian J Publ Health, Vol. 43, No.4, Apr 2014, pp.432-440

Original Article

Predictive Power for Type 2 Diabetes Mellitus using Dynamic Change of Metabolic Syndrome, Dynamic Change of Fasting Plasma Glucose, Metabolic Syndrome and Fasting Plasma Glucose

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(Received 10 Nov 2013; accepted 15 Feb 2014)

Abstract

Background: The aim was to compare the predictive power for Type 2 Diabetes mellitus (T2DM) using dynamic change (Difference) of metabolic syndrome (MS), Difference of fasting plasma glucose (FPG), baseline MS and FPG in cohort study.

Methods: Overall, 3461 subjects were recruited from Prevention of Multiple Metabolic disorders and MS in Jiangsu of China Study with 3.8 years follow-up. Cox proportional-hazards regression and receiver operating characteristic were used to evaluate the predictive power for T2DM using Difference MS, Difference of FPG, baseline MS and FPG.

Results: Adjusted relative risk ($_{a}$RR 5.24, 95% CI 4.28-6.42) of Difference of FPG to T2DM was highest than other. Difference of FPG owns the largest AUC (0.89, P<0.05), the highest sensitivity (96.25%) and specificity (80.49%) demonstrating that Difference of FPG can provide strongest predictive information to T2DM, Difference of MS comes second. Between FPG related tools, sensitivity of Difference of FPG almost was twice than baseline FPG(96.25% vs. 54.38%) suggesting that using baseline FPG would missed found 46% T2DM patients. Among MS related indicators, sensitivity of Difference of MS almost was twice than baseline MS (sensitivity 66.25% vs. 39.38%) suggesting that using baseline would missed found 61% T2DM patients.

Conclusion: Dynamic change of FPG had the highest predictive power for T2DM in Chinese than Dynamic Change of MS, baseline MS and FPG.

Keywords: Type 2 diabetes (T2DM), Metabolic syndrome (MS), Cohort study, Dynamic change

Introduction

T2DM is a chronic metabolic disorder caused by an absolute or relative deficiency of the pancreatic hormone insulin. The principal function of insulin is to control the absorption of glucose from the circulation into body cells and its utilization as energy fuel. The diagnosis of T2DM is based on biochemical data: abnormal elevation of fasting plasma glucose and uncontrolled further elevation after a meal (abnormal glucose tolerance) (1). Metabolic syndrome (MS) is a major public health chal-

lenge worldwide. It is first described in 1988 by Reaven and is consisted of obesity (especially abdominal obesity), insulin resistance, impaired glucose metabolism, dyslipidemia of high triglycerides (TG), low level of high density lipoprotein cholesterol (HDL-C) and elevated blood pressure (BP) (2, 3). Clinically, the disease is determined when people presented more than 3 of the 5 traits (4, 5).

In the previous studies, the relationship between MS and T2DM has already been well established and described in many different populations (6-9). People with MS usually are at high risks of cardiovascular disease, type 2 diabetes and insulin resistant (2, 3, 10). Moreover, it is widely accepted that the early interventions on MS can delay or prevent the formation of T2DM. Clinical treatments of MS mainly focus on lifestyle interventions (such as improving diet quality and increasing physical activity) or take targeted therapies (such as lowering blood pressure, lowering cholesterol or modest weight-loss). Accordingly, dynamic changes of MS components could be observed in the subjects in cohort studies because of lifestyle interventions or treatments. However, the impacts of the dynamic changes of MS on the incidence of T2DM are poorly understood. In the previous studies, the relationships between MS and T2DM just carried out once follow-up (6-8), and investigated the association between incidence of follow-up T2DM and baseline MS (7-9).

Impaired fasting glucose (FPG) (i.e. fasting plasma glucose between 5.6 and 6.9 mmol/L; 100–125 mg/dL) is considered to be a prediabetic state. Indeed, 9–37% of patients with FPG develop T2DM in a period of 2.5–11.5 years (11-15). Simultaneously, fasting plasma glucose (FPG) is not only one of five MS components, but also is a composition of diabetes diagnosis. But, to our knowledge, there is few report in Asian population about dynamic change of MS, dynamic change of FPG on predicting T2DM.In the present study, we evaluated dynamic change of MS, dynamic change of FPG and MS as predicting T2DM in Prevention of Multiple Metabolic disorders and MS in Jiangsu of China (PMMJS).

Materials and Methods

Study cohort

PMMJS is a cohort study which aim to estimate the MS prevalence and to evaluate the incidence of CVD and T2DM in Jiangsu province at the baseline investigation, and to evaluate the incidence of CVD and T2DM during the follow-up survey. The information and methods of the program were described in detail in the previous publications (16, 17).

All participants were informed of the objectives and the procedures of the study. Further, they were also informed of their rights to withdraw at any stage or to prohibit their data from being used analyses. The investigation was only initiated after receiving written consent from the participants. This research was licensed by the ethical committee of Jiangsu Provincial Center for Disease Prevention and Control, China.

Multi-stage sampling method was used in the present study. In stage one, according to the economic condition of different regions in Jiangsu province, three districts of 13 urban districts and nine counties of 52 counties were randomly selected.

In the second stage, one community (similar as a street district or a residential committee) from each city and one rural township from each county were randomly sampled, separately.

In the final stage, households were randomly chosen from the selected communities and townships, followed by random selection of one participant from each household without replacement. Simple random sampling method was used at each stage. The local public health administrative institutes possess the address and telephone number of all participants in order to track their health status in follow-up.

Individuals who suffered from the cancer, severe disability, and severe psychiatric disturbance were excluded. Overall, 8685 participants, aged from 35 to 74 years old were randomly selected from 12 primary units, stratified by sex and age (10 years per group).

Measurement

The plasma and serum samples were collected from each participant and stored at -80°C until laboratory testing. Automatically recording instrument was used to measure height and weight. Three sitting blood pressure measurements with an interval of 30 seconds were taken by trained observers with a standard mercury sphygmomanometer according to a standard protocol, after the subjects had been resting for 5 min. Waist circumference (WC) was measured by the same physician at the umbilical level with the subjects standing and breathing normally during the physical examination.

Lipid biomarkers and fasting plasma glucose (FPG) were analyzed in the center laboratory, which is certified by Jiangsu Provincial Center for Disease Prevention and Control, China. TG (18), HDL-C (19) and FPG were detected in the examinees after fasted overnight with Hitachi 7020 analyzer. Low-density lipoprotein cholesterol (LDL-C) (20) was determined by a homogenous direct method. Quality control data were generated from a fresh sample and the coefficients of variation (CV) for FPG,TG,HDLC measurements was 1.92%,2.67% and1.63% separately .

Follow-up survey

Among 5888 subjects whose follow-time meets 2 years, 4582 participants (77.82%) received the first follow-up investigation and measurements between January 2002 and August 2003.The investigated contents and the measurement methods used in the follow-up survey were as same as those used in the baseline survey. In addition, the data on BP and the information on incidence of T2DM were collected at the first follow-up. Among 4582 subjects who received first follow-up investigation and whose follow-time meets 5 years, 3847 participants (83.96%) received the second follow-up investigation between March 2006 and November 2007. In this investigation, we mainly collected the information about the incidence of T2DM, which happened in five years. Those who did not attend twice follow-ups examination were similar to those who attended twice follow-ups in terms of age, sex, smoking, alcohol, family history of hypertension and metabolic variables. After excluding subjects who were found to have T2DM at the baseline or at the first follow-up (n=332), missing data (n=133), CVD (n=32), and BMI<18.5kg/m2 (n=22), 3461 participants (1406 males and 2055 females) were included in this study, the median duration of follow-up was 3.8 years from the first follow-up to the second follow-up.

Definition of MS

MS was diagnosed in the presence of any three of the followings according to ATPIII (AHA/NHLBI amended in 2005) (21): (1) WC ≥90cm in men and ≥80cm in women; (2) TG ≥ 1.7mmol/l; (3) HDLC <1.0mmol/l in men and <1.3mmol/l in women; (4) BP ≥130/85 mmHg; (5) FPG ≥5.6 mmol/l.

Definition of Dynamic Change of MS

Dynamic Change of MS has two analysis modes:

1.Difference of MS diagnosis was calculated as the following: All participants could be divided into four groups: baseline MS-/first follow-up MS-, baseline MS-/first follow-up MS+, baseline MS+/first follow-up MS- and baseline MS+/first follow-up MS+ group. Subjects of these four groups were assigned to 0,1,-1, 2.

2. Difference of MS component number was defined as the difference of the number of the compositions consistent with MS between the first follow-up and baseline. Difference >0 meant that MS compositions increased from baseline to the first follow-up, while Difference <0 meant that MS compositions decreased from baseline to the first follow-up.

Definition of Dynamic Change of FPG diagnosis (Difference of FPG diagnosis)

Difference of FPG diagnosis was calculated as the following: FPG diagnosis was defined level≥5.6mmol/l. All participants could be divided into four groups: baseline FPG-/first follow-up FPG-, baseline FPG-/first follow-up FPG+, baseline FPG +/first follow-up FPG- and baseline

FPG+/first follow-up FPG+ group. Subjects of these four groups were assigned to 0,1,-1, 2.

Validation of T2DM

Diabetes was defined based on self-reported, and/or a previous diagnosis in the medical records, and/or FPG level ≥7 mmol/l, and/or plasma glucose level ≥11.1 mmol/l when fasting status was uncertain, and/or self-reported use of anti-diabetic drugs (oral agents or insulin). In the present study, FPG was diagnosed in more than 95% of participants and thus most diagnoses were based on the criteria of fasting glucose. The physician defined the T2DM according to the American Diabetes Association criteria (22).

Definition of risk factors

Family history of diseases was characterized as the presence of parents with histories of CVD, T2DM, hypertension, obesity or dyslipidemia (16, 17). Participants who used more than 100 cigarettes were considered as smokers, while those consumed less than 100 considered were considered as non-smokers. The drinking definition was defined as a threshold of drinking more than 12 times per year with more than 50 g (every drink-contained alcohol) each time.

Statistical analysis

Statistical analyses were performed with the SPSS 13.0 statistical software system. Continuous variables were tested using the t-test and nonparametric test. Frequencies of categorical variables were tested using the chi-square test. The incidence of the disease was standardized with the fifth national population census constitutes (23). Cox Proportional-Hazards Regression, sensitivity analysis and area under ROC curve (AUC) were used to evaluate the predictive power(RR) for T2DM by using dynamic change of MS, dynamic change of FPG, MS at baseline and FPG at baseline, including the difference test of AUC (24).Potential confounding factors included age, sex, smoking, alcohol status, and family history of diseases. All reported *P* values were two-tailed, and those less than 0.05 were considered statistically significant.

Results

General data

Overall, 3461 subjects (1406 males and 2055 females) were included in the present study. The median of follow-up time was 3.8 years from the first follow-up to the second follow-up. All participants could be divided into four groups: baseline MS-/first follow-up MS- group (2098, 1007 males 1091 females), baseline MS-/first follow-up MS+ (547,168 males 379 females), baseline MS+/first follow-up MS-(313, 85 males 228 females) and baseline MS+/first follow-up MS+(503,145 males 358 females), respectively. The average ages of four groups were 49.7±9.9,49.0±9.4, 51.4±10.4 and 52.6±10.3 years. The significant differences of FPG, HDL-C, WC, TG, SBP, DBP, smoking rate and drinking rate were determined among four groups ($P<0.05$).

T2DM was diagnosed in 160 of 3461 subjects during the second follow-up. There were significant statistical differences of clinical characteristics between the new diagnosed T2DM patients (160) and those without T2DM (3461) ($P<0.05$), except for age, SBP, DBP, smoking rate and drinking rate (Table 1).

Relationships among dynamic change of MS, MS, dynamic change of FPG, FPG and T2DM

As Table 2 shows, in Cox regression hazard model, $_{a}$RR to T2DM in Difference of MS diagnosis groups is 2.040 (95%CI 1.71-2.42), increased one in Difference of MS component number, $_{a}$RR is 1.37(95%CI 1.22-1.54).

After adjustment for the confounding factors, the result also indicated $_{a}$RRs to T2DM of Difference of FPG diagnosis and FPG diagnosis at baseline was 5.24(95%CI 4.28-6.42) and 5.13(95%CI 3.72-7.08), respectively. The associated strength was higher obviously than dynamic change of MS.

Table1: Clinical and Biochemical Characteristics of the Subjects of non-T2DM and T2DM at follow-up

Characteristic	T2DM		non-T2DM		*P**
n(male)	160	(60)	3301	(1346)	
AGE (year) **	55.27	(8.90)	56.19	(10.01)	>0.05
Difference of ms	0.84	(1.25)	0.22	(1.28)	<0.01
Difference in wc(cm)**	4.62	(8.16)	3.10	(7.35)	<0.05
Difference in tg(mmol/L)*	0.40	(2.45)	-0.06	(1.22)	<0.05
Difference in hdlc(mmol/L)**	-0.24	(0.52)	0.03	(0.42)	<0.01
Difference in glu(mmol/L)**	2.87	(2.85)	-0.19	(0.91)	<0.01
Difference in sbp(mmHg)**	6.65	(23.97)	5.20	(19.91)	>0.05
Difference in dbp(mmHg)**	0.54	(11.45)	0.56	(12.00)	>0.05
Smoking rate （n,%）	29	(18.13%)	852	(25.81%)	>0.05
Drinking rate （n,%）	30	(18.75%)	700	(21.21%)	>0.05
Family history of T2DM （n,%）	16	(10.00%)	164	(4.97%)	<0.01

** Means (SD) showed the data of normal distribution.*Median (range) indicated the data of abnormal distribution

Table 2: Adjusted RR for T2DM and the control of dynamic change in MS , dynamic change in FPG and MS

	RR (95% CI) in Model 1				RR (95% CI) in Model 2			
	P	aRR	95.0% CI		*P*	aRR	95.0% CI	
Difference of MS diagnosis	0.000	2.12	1.80	-2.51	0.000	2.04	1.72	-2.42
Difference of MS component number	0.000	1.42	1.27	-1.60	0.000	1.38	1.22	-1.54
MS at baseline	0.000	2.18	1.59	-3.00	0.000	2.02	1.46	-2.80
Difference of FPG	0.000	5.42	4.43	-6.62	0.000	5.24	4.28	-6.42
FPG at baseline	0.000	5.45	3.97	-7.50	0.000	5.13	3.72	-7.08

* model 1 is a single variable Cox Proportional-Hazards Regression; Model 2 is multiple variables adjusted Cox Proportional-Hazards Regression which was adjusted by sex, age, smoking, drinking and relevant family history at baseline.

ROC curve of prediction of T2DM by using dynamic change of MS, MS, dynamic change of FPG

In Table 3, at prediction of T2DM, the area under the ROC curve (AUC) of Difference of FPG diagnosis was largest among other AUC (AUC 0.89, *P*<0.05),AUC of Difference of MS diagnosis (AUC 0.69, *P*<0.05) comes second.AUC of Difference of FPG diagnosis was 1.33 times than one of FPG diagnosis at baseline. As table 3 showed, sensitivity of Difference of FPG diagnosis predicting T2DM is highest than other (96.25%), and specificity of predicting to T2DM is highest (80.49%). The sensitivity value of Difference of FPG diagnosis almost was twice than that of FPG diagnosis at baseline (96.25 vs 54.38%), but they had similar specificity (80.49% vs79.73%), suggesting that using FPG diagnosis at baseline would missed found 46% of patients with T2DM. In three indicators related to MS, AUC of Difference of MS diagnosis (AUC 0.69, *P*<0.05) was larger than other two indicators. The sensitivity value of Difference of MS diagnosis almost was twice than that of MS at baseline (sensitivity 66.25% vs 39.38%), but they had similar specificity (71.40% vs77.19%), suggesting that using MS at baseline would missed found 61% of patients with T2DM. Figure 1 shows a plot of five ROC curves, representing the prediction of T2DM by using Difference of MS diagnosis, Difference of MS component number, MS at baseline, Difference of FPG diagnosis, FPG diagnosis at baseline. The Difference of FPG diagnosis performed best in sample, Difference of MS diagnosis second.

Table 3: Predictive power for T2DM by using dynamic change in MS , dynamic change in FPG and MS

Variables	AUC	95%CI		Sensitivity (%)	Specificity (%)	*P*
Difference of MS diagnosis	0.69	0.64	0.73	66.25	71.40	0.00
Difference of MS component number	0.64	0.60	0.69	64.38	60.62	0.00
MS at baseline	0.58	0.54	0.63	39.38	77.19	0.00
Difference of FPG diagnosis	0.89	0.87	0.91	96.25	80.49	0.00
FPG diagnosis at baseline	0.67	0.62	0.72	54.38	79.73	0.00

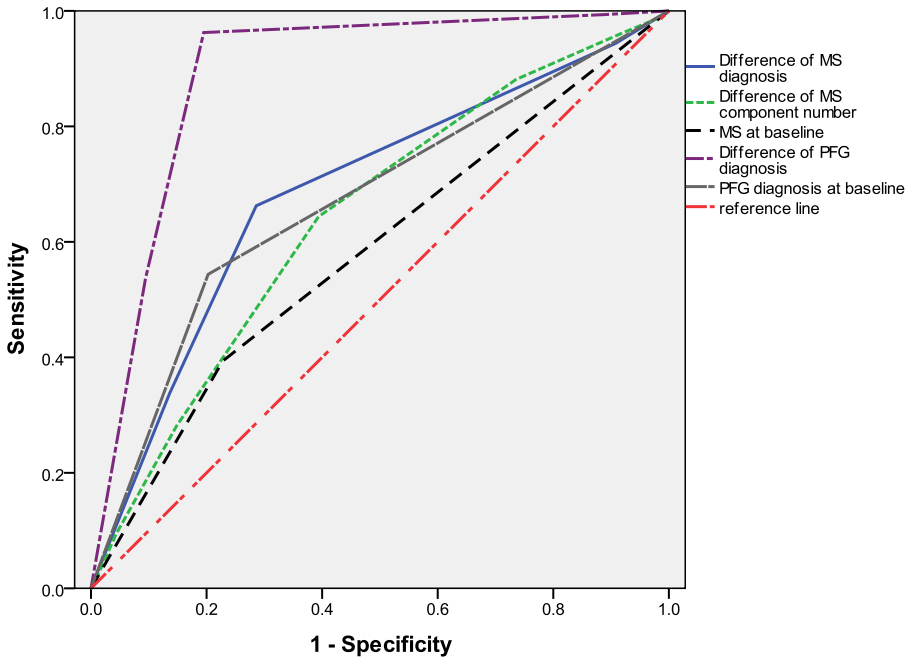

Fig. 1: Predictive power for T2DM by using dynamic change in MS, dynamic change in FPG and MS

Discussion

The results of the present study provide two major findings. First, the current analysis shows that Difference of MS diagnosis ($_a$RR 2.04) and dynamic change of FPG ($_a$RR 5.24) provides a superior assessment of diabetes risk compared to FPG and MS at baseline, separately.

The results from the previous studies suggested the similar results in different populations. A recent report based on the evaluation of National Health and Nutrition Examination Survey (NHANES) 2003–2006 estimated that over one third of the US adult population had MS and thus would be identified as being at risk for developing diabetes (25). Additionally, MS persons experienced a 4-fold greater risk for T2DM development than the general population in Scandinavian. A study of over 8 year cohort reported that the RR of incident T2DM was greatly increased (>4) in persons with MS at baseline (26). In WOSCOPS, the presence of MS conferred much greater risk for T2DM than for CHD in Framingham participants (RR 3.5) (27).

Furthermore, the relation between FPG and the increased risk of developing T2DM had been showed similarly in several articles. The Hoorn study investigators found that patients with FPG

and normal glucose tolerance had a similar risk of developing DM to those with IGT and normal fasting glucose (28). An important observation in several studies comparing IGT and FPG has been the increased risk of T2DM and cardiovascular disease among patients with both FPG and IGT (29). In addition, a study of serial measurements of fasting and two-hour insulin levels in Nauruans over several months found that FPG was strong predictors to T2DM, even after adjusting for insulin levels (30).

The second important finding of the present study is that, Dynamic change of FPG owns the largest AUC, highest Sensitivity and highest Specificity demonstrating that dynamic change of FPG can provide strongest predictive information to T2DM, dynamic change of MS comes second. Roc curve of dynamic changes indicators were higher than those at baseline, suggesting using dynamic changes indicators have found more T2DM patients. Elevated fasting glucose level was an important criterion for both of T2DM and MS diagnosis. Glucose cutoff value is 5.6mmol/L and 7.0mmol/L for MS and T2DM, respectively. And FPG can easily be measured in routine clinical practice. Although there were few reports compared with dynamic changes and baseline data, some results showed that MS components including FPG (5.6mmol/L - 7.0mmol/L) were the most important factor for diabetes predicting in MS patients in the previous study (31). However, other studies suggested that the traditional risk factors, such as the combination of family history, high blood sugar, insulin resistance, inflammatory markers, could predict T2DM more efficiently than MS or its components (32, 33). Moreover, Using subjects in the Inter99 cohort, a group of adult Danish subjects who were followed for at least five years, Tracy BS and colleagues have reported that PreDxH Diabetes Risk Score, a previously developed diabetes risk score, provided a more accurate assessment of risk for diabetes than MS (34).

Our study also had some limitations. Cox Proportional-Hazards Regression, sensitivity analysis and area under ROC curve (AUC) were used to evaluate the predictive power for T2DM by using dynamic change of MS, dynamic change of FPG, MS at baseline and FPG at baseline. In addition to FPG, Oral Glucose Tolerance Test and Glycated hemoglobin also are widely used to predict diabetes. Because our PMMJS study did not Oral Glucose Tolerance Test (OGTT) and Glycated hemoglobin(HbAlc) in the follow-up survey, we excluded the dynamic change of OGTT and HbAlc diagnostic from our study. Maybe in our future follow-up our study will measure these indicators.

Conclusion

Comparing among Dynamic Change of MS, Dynamic Change of FPG, MS at baseline and FPG at baseline, dynamic change of FPG was a most useful prediction factor for T2DM in Chinese population.

Ethical considerations

Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc) have been completely observed by the authors.

Acknowledgments

This work was supported by Scientific Research Fund of National Ministry of Health (Grant no. 2004-2-014) and the Priority Academic Program Development of Jiangsu Higher Education Institution. This study was supported in part by the CDC of Jiangsu province, Nanjing, China, for their direct and systems analysts to the study. The authors thank the local community health station for their dedication to first quality data collection and management. In addition, thank for the PMMJS interviewers for their contribution to the study. The authors declare that there is no conflict of interests.

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