Development of Type-2 Diabetes Mellitus is associated with Low Levels of ApoA1

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Abstract

Aims: Type-2 diabetes mellitus (T2DM) has become a major public health crisis in China. We examined the incidence of new T2DM over 4 years for association of clinical factors and lipids with development of T2DM in a community-based population.

Methods: We included 923 Chinese subjects who participated in community-organized health checkout in both 2009 and 2013. Health history was collected; physical examination was performed; biochemistry, lipids and glucose were measured. Of 923, 819 were confirmed without T2DM in 2009 and included in the analysis.

Results: Sixty-five subjects without T2DM in 2009 were identified as having new T2DM in 2013, 8% (65/819) over 4 years. These 65 subjects, compared to those 754 without new T2DM, were older, more likely to be male and smokers. They had higher BMI, fasting glucose, blood pressure and triglycerides, and lower levels of HDL-C and ApoA1. Multivariate logistic regression identified larger BMI (OR=1.7, 95%CI 1.22-2.39, p=0.002), higher fasting glucose (OR=4.2, 95%CI 2.90-6.19, p<0.001) and low levels of ApoA1 (OR=0.51, 95%CI 0.33-0.76, p=0.002) were independently associated with development of T2DM over 4 years. ROC curves for new T2DM showed that AUC improved from 0.87 to 0.89 when adding ApoA1 to the Framingham Diabetes Risk Model and from 0.85 to 0.89 when adding ApoA1 to a Chinese model.

Conclusions: This study showed a high incidence of new T2DM at 8% over 4 years among Chinese and demonstrated a significant and independent association of higher BMI and glucose levels, and lower levels of ApoA1 with development of T2DM.

Introduction

Type-2 diabetes mellitus (T2DM) has become a major public health issue with strong socioeconomic impact worldwide [1,2]. The prevalence of T2DM in China has increased substantially over recent decades with more than 100 million Chinese people estimated to have this condition [3]. Previous studies demonstrated that the most commonly identified risk factors for development of T2DM include older age [4], positive family history of diabetes [5], higher body mass index (BMI) [4], abdominal obesity [6], smoking [7], hypertension [8], higher fasting glucose level [9], physical inactivity [10] and metabolic syndrome [11]. There have been inconsistent reports on associations of ApoA1 and HDL-C with development of T2DM [12-18]. We examined the incidence of new T2DM over 4 years for association of clinical factors and lipids with development of T2DM among Chinese subjects who participated in a community-organized health checkout in both 2009 and 2013.

Material and Methods

Study population

Among 983 subjects who participated in the community-organized health checkout in 2009 at Beijing Xihongmen Community Hospital in China, 923 had a repeat checkout in 2013. The community-organized health checkout was funded by the local government and performed by the certified health care providers. It was offered to all community members aged ≥ 18 years. At the health checkout, health history was

collected; a physical examination was performed; liver and renal functions, biochemistry, lipids and glucose were measured.

As shown in Figure 1, among the 923 subjects, 104 were identified as having T2DM or fasting glucose levels ≥ 7 mmol/L in 2009 and excluded from the study. The remaining 819 were selected for this analysis of examining risk association of development of T2DM over 4 years.
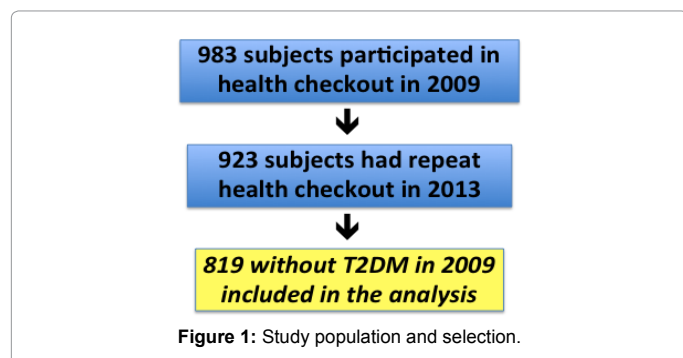
Clinical evaluations and laboratory measurements

Height (m) and weight (kg) were measured. BMI was calculated as weight in kilograms divided by the square of height in meters. Blood pressure (BP) was measured using an automatic manometer with an appropriate cuff size on the right arm after a resting period of ≥5 minutes. Blood sample was collected after fasting for a minimum of 9 hours and subsequently analyzed for concentrations of glucose, lipids, and liver enzymes by a certified laboratory at Beijing Xihongmen Community Hospital. Renal function and other biochemistry were also measured.

Figure 1: Study population and selection.

Definition of new T2DM

In 2013, positive T2DM was identified using the fasting plasma glucose (FPG) ≥ 7.0 mmol/L or if subjects were receiving active treatment for T2DM.

Statistical analyses

Descriptive statistics were expressed as the mean ± SD for continuous variables and the relative frequency (%) for categorical variables. In addition, the median and the inter-quartile range were calculated for highly skewed continuous variables. The demographic and biochemical characteristics of the study population were compared between patients with and without new T2DM using the two-sample t-test or the Wilcoxon rank sum test for continuous characteristics (the latter was used for highly skewed characteristics) and the chi-squared test for categorical characteristics. Unadjusted and adjusted logistic regression models were used to estimate the effects of biochemical characteristics on the risk of T2DM development (with the odds ratios and their 95% confidence intervals presented). Odds ratios for continuous risk factors are presented for a 1SD increase. The adjusted models were adjusted for age, gender, BMI and smoking and also adjusted for multiple comparisons. Receiver operating characteristics (ROC) curves were generated to demonstrate the sensitivity and specificity of risk factors predicting development of T2DM. Area under the curve (AUC) was calculated for the model with the seven variables (age, gender, BMI, fasting glucose, blood pressure, triglycerides and HDL−C) used in Framingham Diabetes Risk Scoring Model (FDRSM) [12] and for the recently published model for rural Chinese with four variables (age, BMI, fasting glucose and triglycerides) [19] and for the adjusted models for ApoA1 or HDL-C. All statistical analyses were performed using R, version 3.1.3 (R Foundation for Statistical Computing, Vienna, Austria). A p-value of <0.05 was considered statistically significant.

Results

Frequency of new T2DM

Sixty-five subjects without T2DM in 2009 were identified as having new T2DM in 2013, 8% (65/819) over 4 years.

Clinical and laboratory characteristics in subjects with and without new T2DM

As described in Table 1, the 65 subjects with new T2DM, compared to those 754 without, were more likely to be male (46% vs. 27%, p<0.001) and smokers (38% vs. 23%, p=0.02), they were older (mean ± SD 51 ± 10 vs. 47 ± 10 years, p=0.004), had larger BMI (28.8 ± 4.3 vs. 26.2 ± 3.9 kg/m², p<0.001), higher fasting glucose levels (5.99 ± 0.67 vs. 5.17 ± 0.53 mmol/L, p<0.001) and BP (131 ± 19 vs. 123 ± 17

mmHg for systolic BP, p=0.003; 86 ± 10 vs. 81 ± 11 mmHg for diastolic BP, p<0.001), also had higher ALT and creatinine levels in 2009. Interestingly, HDL-C and ApoA1 in 2009 were significantly lower in subjects with new T2DM than those without in 2013 (1.4 ± 0.3 vs. 1.5 ± 0.4 mmol/L, p<0.001) and (1.3 ± 0.2 vs. 1.4 ± 0.3 mmol/L, p<0.001). Triglycerides were higher (2.0 ± 1.1 vs. 1.6 ± 1.2 mmol/L, p<0.001), while total-C, LDL-C and ApoB did not differ significantly (5.0 ± 1.1 vs. 4.8 ± 0.9 mmol/L, p=0.2), (2.7 ± 1.1 vs. 2.5 ± 0.8 mmol/L, p=0.14) and (0.9 ± 0.2 vs. 0.8 ± 0.2 mmol/L, p=0.2) (Table 1).

Factors associated with development of T2DM

Unadjusted logistic regression analysis showed that blood pressure, fasting glucose levels, renal function, liver enzyme, triglycerides, HDL-C and apoA1 were significantly associated with new T2DM whereas TC, LDL-C, and ApoB were not as shown in Table 2. However, after adjustment for age, gender, BMI and smoking, only fasting glucose (OR=3.99, 95%CI 2.82-5.84, p<0.001) and ApoA1 (OR=0.56, 95%CI 0.38–0.80, p=0.002) remained statistically significantly associated with development of T2DM (Table 2).

Association of ApoA1 with development of T2DM

As presented in Table 3, multivariate logistic regression identified larger BMI (OR=1.7, 95%CI 1.22-2.39, p=0.002), higher levels of fasting glucose (OR=4.2, 95%CI 2.90-6.19, p<0.001) and low levels of ApoA1 (OR=0.51, 95%CI 0.33-0.76, p=0.002) were independently associated with development of T2DM over 4 years.

HDL-C, as expected, was highly correlated with ApoA1 (Pearson correlation = 0.69) as shown in Figure 2. However, compared to ApoA1, HDL-C was non-statistically associated with development of T2DM (Tables 2 and 3).

Furthermore, ROC curves for multivariate models showed an AUC of 0.87 with the FDRSM model including age, gender, BMI, fasting glucose, BP, triglycerides and HDL−C, AUC improved to 0.89 when

	New T2DM (+) N=65	New T2DM (-) N=754	P-value*
Age, years, mean ± SD	51.1 ± 10.0	47.2 ± 10.4	0.004
Male gender, %	46%	27%	<0.001
BMI, kg/m², mean ± SD	28.8 ± 4.3	26.2 ± 3.9	<0.001
Smoking, %	38%	23%	0.02
Systolic BP, mmHg, mean ± SD	130.6 ± 19.1	123.0 ± 16.5	0.003
Diastolic BP, mmHg, mean ± SD	85.7 ± 9.5	81.3 ± 10.7	<0.001
ALT, mg/dl, mean ± SD (median/IQR)	32.6 ± 38.0 (21/14)	22.1 ± 20.8 (18/12)	0.002**
AST, mg/dl, mean ± SD (median/IQR)	26.9 ± 27.2 (21/8)	21.3 ± 14.2 (19/7)	0.2**
Fasting Glucose, mmol/L	5.99 ± 0.67	5.17 ± 0.53	<0.001
Creatinine, μmol/L	86.9 ± 12.5	82.0 ± 13.5	0.01
Total cholesterol, mmol/L	5.0 ± 1.1	4.8 ± 0.9	0.2
Triglycerides, mmol/L (median/IQR)	2.0 ± 1.1 (1.6/1.5)	1.6 ± 1.2 (1.3/1.1)	<0.001**
LDL-C, mmol/L	2.7 ± 1.1	2.5 ± 0.8	0.14
HDL-C, mmol/L	1.4 ± 0.3	1.5 ± 0.4	<0.001
ApoA1, mmol/L	1.3 ± 0.2	1.4 ± 0.3	<0.001
ApoB, mmol/L	0.9 ± 0.2	0.8 ± 0.2	0.2

*The two-sample t-test for continuous variables or the chi-squared test for categorical variables (gender and smoking), unless stated otherwise
**The non-parametric Wilcoxon rank sum test
IQR = intra-quartile range

Table 1: Comparison of baseline clinical and laboratory characteristics between subjects with and without new T2DM.

	Unadjusted			Adjusted for age, gender, BMI and smoking			
	OR*	95% CI	P-value	OR*	95% CI	P-value	P-value**
Systolic BP	1.50	1.18, 1.90	<0.001	1.19	0.87, 1.60	0.3	0.5
Diastolic BP	1.48	1.15, 1.89	0.002	1.11	0.79, 1.54	0.5	0.8
Creatinine	1.41	1.08, 1.84	0.01	1.00	0.64, 1.54	1	1
log(ALT)	1.52	1.21, 1.90	<0.001	1.37	0.99, 1.87	0.053	0.2
log(AST)	1.32	1.07, 1.61	0.008	1.19	0.87, 1.57	0.3	0.5
Fasting glucose	3.93	2.97, 5.32	<0.001	3.99	2.82, 5.84	<0.001	<0.001
log(triglycerides)	1.50	1.17, 1.93	0.001	1.25	0.90, 1.71	0.2	0.4
Total cholesterol	1.21	0.95, 1.52	0.11	1.00	0.75, 1.33	1	1
LDL cholesterol	1.23	0.97, 1.55	0.07	1.02	0.77, 1.34	0.9	1
HDL cholesterol	0.57	0.42, 0.75	<0.001	0.71	0.48, 1.01	0.06	0.2
ApoA1	0.48	0.35, 0.64	<0.001	0.56	0.38, 0.80	0.002	0.01
ApoB	1.22	0.96, 1.53	0.1	1.02	0.75, 1.35	0.9	1

*Odds are presented per 1 SD increase in the independent variable.
**Adjustment for multiple comparisons using the FDR method.

Table 2: Unadjusted and adjusted models for new T2DM predicted by clinical and laboratory variables in Table 1.

A. Model with age, gender, BMI, smoking, fasting glucose and ApoA1	OR	95% CI	P-value
Age, per 1 SD	0.98	0.68, 1.41	0.9
Male gender	1.53	0.62, 3.75	0.3
BMI, per 1 SD	1.70	1.22, 2.39	0.002
Smoking (+)	2.07	0.83, 5.16	0.12
Fasting glucose, per 1 SD	4.16	2.90, 6.19	<0.001
Apo A1, per 1 SD	0.51	0.33, 0.76	0.002
B. Model with age, gender, BMI, smoking, fasting glucose and HDL-C			
Age, per 1 SD	0.99	0.68, 1.43	0.9
Male gender	1.77	0.71, 4.43	0.2
BMI, per 1 SD	1.68	1.21, 2.35	0.002
Smoking (+)	1.82	0.73, 4.53	0.2
Fasting glucose, per 1 SD	3.95	2.79, 5.79	<0.001
HDL-C, per 1 SD	0.72	0.47, 1.09	0.13

Table 3: Multivariate logistic regression models for new T2DM (N = 646).

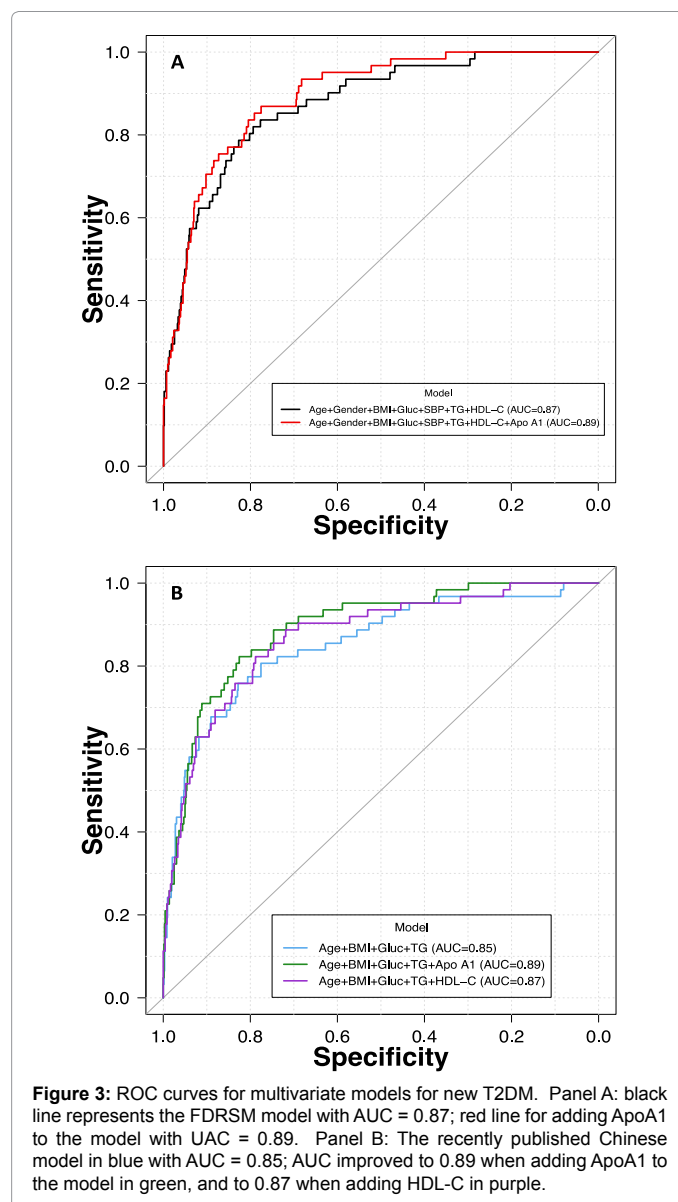**Figure 2:** Apo A1 vs. HDL-C by new diabetes status. Pearson correlation = 0.69, p<0.001.
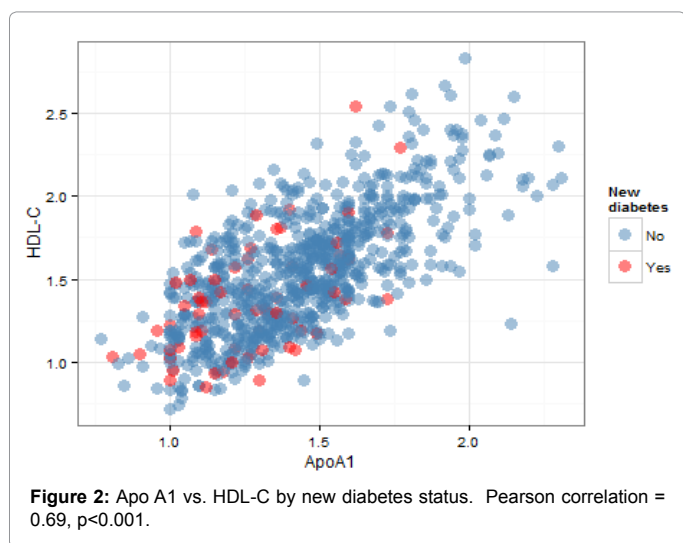
adding ApoA1 to the model (Figure 3A). Similarly, when ApoA1 was added to the Chinese model including age, BMI, fasting glucose and triglycerides, the AUC improved from 0.85 to 0.89, however, AUC only increased to 0.87 when adding HDL-C to the model (Figure 3B).

Discussion

Type-2 diabetes mellitus has become a major public health crisis in China with rapid urbanization, decreased physical activity, unhealthy diet and many other social and environmental factors [2,3]. In our community-based urban population, conservatively, 8% was found to have new T2DM over 4 years. This incidence was higher than 5.8% over 7.7 years In the PREVEND study [19], 6.9% over 4 years in healthy Korean men [20], 4.3% over 5 years in male Japanese workers [21] and 6% over 6 years among rural Chinese [19]. The higher incidence of new T2DM seen in this study is consistent with the overall substantial increase in the prevalence of T2DM in China [3].

Similar to that identified in the previous studies, older age, male gender, smoking, larger BMI, higher blood pressure, higher fasting glucose level and dyslipidemia with high triglycerides and low levels of HDL or ApoA1 were associated with new T2DM [4-11], however, after adjustment for age, gender, BMI and smoking, only fasting glucose and ApoA1 remained a statistically significant association

Figure 3: ROC curves for multivariate models for new T2DM. Panel A: black line represents the FDRSM model with AUC = 0.87; red line for adding ApoA1 to the model with UAC = 0.89. Panel B: The recently published Chinese model in blue with AUC = 0.85; AUC improved to 0.89 when adding ApoA1 to the model in green, and to 0.87 when adding HDL-C in purple.

with development of T2DM. Furthermore, multivariate analysis showed that higher BMI, increased fasting glucose levels and lower levels of ApoA1 were significantly and independently able to predict new onset of T2DM over 4 years in our study. We found that each SD (approximately 0.55 mmol/L) higher in fasting glucose levels increase the risk of developing T2DM by more than 4 folds (OR=4.2, 95%CI 2.90-6.19, p<0.001), and each SD (approximately 4 kg/m^2) increase in BMI almost doubled the risk (OR=1.7, 95%CI 1.22-2.39, p=0.002). These results strongly support the importance of weight and glucose control through exercise and a healthy diet in prevention of T2DM in a community-based population.

Our study demonstrated that each SD (0.25 mmol/L) decrease in ApoA1 independently led to a 97% increased risk of new T2DM (OR=1/0.51=1.97, p=0.002) over 4 years among the community-based urban Chinese subjects who are relatively healthy and without multiple risk factors for T2DM. However, this association has not been found to be consistent in previous studies [22-25] although previous research suggested that ApoA1 affects glucose metabolism via multiple mechanisms, including enhanced insulin secretion [26], increased insulin-independent glucose uptake in muscle and adipose tissues [27,28], improved insulin sensitivity [29], and reversed adipocyte dysfunction [30] and restored adiponectin expression and insulin sensitivity [31] with ApoA1 mimetic peptide. Furthermore, genetic studies suggested that genetic variation in ABCA1 has been associated with the increased risk of T2DM [32], and one study suggested that loss-of-function mutations in ABCA1 were associated with impaired b-cell function, but not with the development of T2DM [33]. Further investigations in both prospective population based studies and mechanistic basic science research including genetic studies are needed to confirm and establish the roles that ApoA1 plays in development of T2DM.

Our study also found that HDL-C, compared to ApoA1, had a much weaker association with development of T2DM although HDL-C is closely correlated with ApoA1. The data presented in Table 3 and Figure 3B indicated that HDL-C should not be considered as a substitute for ApoA1 in risk prediction for new T2DM. In addition to a growing body of evidence suggesting that HDL-C concentration does not accurately reflect the heterogeneous HDL particles and the HDL's vascular protective function [34,35], a recently published Mendelian randomization study [18] showed that low levels of HDL-C due to genetic variation do not increase risk of T2DM in the general population, which suggesting that the previously observed association between low levels of HDL-C and development of T2DM may be due to reverse causation of a state of prediabetes [18]. Similarly, a Mendelian randomization study showed that raised triglyceride levels were not causally associated with the risk of T2DM [36]. These results together indicate that the dyslipidemia with low HDL-C and high triglycerides has existed long before clinical diagnosis of T2DM and question HDL-C increasing therapy for reducing risk of new T2DM.

Furthermore, ApoA1 appeared to improve the risk prediction of new T2DM comparing to the existing risk prediction models. In the FDRSM model including age, gender, BMI, fasting glucose, BP, triglycerides and HDL–C [12], AUC improved from 0.87 to 0.89 when adding ApoA1 to the model (Figure 3A). In the recently published Chinese model including age, BMI, fasting glucose and triglycerides [19], AUC improved from 0.85 to 0.89 when adding ApoA1 to the model (Figure 3B).

Statistically, developing a multivariate logistic regression model requires at least 20 events per independent variable [37]. Others have argued for a less strict rule that 10 events per independent variable would be sufficient [38]. Our analysis included 5 independent variables for a total of 65 subjects with new T2DM (13 events per independent variable), which is adequate by the less strict rule. In order to confirm the reliability of the estimated odds ratios and their confidence intervals and p-values, we performed a sensitivity analysis for the multivariate models in Table 3 that used models with only 3 independent variables (adjustments for the relatively weaker effects of age, gender and smoking were excluded) following the stricter rule. The results of the sensitivity analysis showed virtually unchanged estimate of the ApoA1 and HDL-C effects and supporting our confidence in the results shown in Table 3.

Limitation

Hemoglobin A1C was not measured and oral glucose tolerance test was not performed in our study, which may result in an underestimation the true incidence of new T2DM over 4 years. Also, data on parental history of T2DM was not collected. Nevertheless, our analysis including the community-based urban population who participated in health-check up demonstrated an alarming rate of new T2DM, and higher BMI, increased fasting glucose levels and lower levels of ApoA1 were independently associated with development of T2DM among Chinese living in Beijing.

Conclusions

In conclusion, our analysis showed a high incidence of new type-2 diabetes at 8% over 4 years among middle aged urban Chinese and demonstrated a significant and independent association of larger BMI, higher fasting glucose levels and lower levels of ApoA1 with future development of type-2 diabetes. Future prospective studies are needed to investigate the roles that ApoA1 may play in the development of type-2 diabetes.

Funding Source

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