Published in final edited form as:

Diabetes Res Clin Pract. 2011 April ; 92(1): 124–127. doi:10.1016/j.diabres.2010.12.024.

Type 2 Diabetes Risk in Persons with Dysglycemia: The Framingham Offspring Study

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Abstract

Aims—Detection of risk of type 2 diabetes mellitus (T2DM) among adults with dysglycemia.

Methods—We used a nested case-cohort prospective design to estimate risk of new diabetes (diabetes treatment or FPG ≥ 7.0 mmol/l) among 1004 Framingham Heart Study Offspring with baseline dysglycemia [fasting plasma glucose (FPG) 5.4–6.9 mmol/l and/or 2-hour post glucose load level 7.8–11.0 mmol/l]. Using clinical characteristics previously shown to predict incident T2DM, we used logistic regression to estimate odds ratios (OR), p-values for predictors, and assessment of model discrimination.

Results—At the end of 7 yrs follow-up there were 118 incident T2DM cases. In a model that included age, sex, elevated blood pressure or blood pressure treatment, lipid-lowering treatment and elevated triglycerides, we found the following additional characteristics to be independently associated with new T2DM: parental history of diabetes (OR 2.28, $p=0.004$); excess adiposity (BMI ≥ 30 kg/m² or waist circumference ≥ 101.6 cm) (OR 2.04, $p=0.0005$), and low HDL-C [<1.0 (men) or <1.3 mmol/L (women)] (OR 2.77, $p<0.0001$). The multivariable c-statistic for this model was 0.701, and with glycemic category information included, $c=0.751$.

Conclusions—The key non-glycemic traits that predicted later T2DM in adults with dysglycemia were parental history of diabetes, excess adiposity and low HDL-C.

Introduction

Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) after an oral glucose load are well-recognized antecedents of the development of T2DM. The primary prevention of diabetes trial undertaken in the United States recruited persons with IGT and over a three year follow-up interval the authors reported that a lifestyle intervention reduced the incidence of new T2DM approximately 58%.¹ The incidence rate in the placebo arm of this clinical trial was approximately 11 per 100 person years of follow up.

In a community setting the incidence of new T2DM was approximately 0.8% per year (approximately 6.4% total over 8 years for both sexes combined) for the Framingham Offspring Study middle-aged adults in the interval 1992–2000. The risk of developing

T2DM in this setting has been shown to be proportional to the number of metabolic syndrome risk variables.² Risk of developing T2DM has been estimated to be about 1 per cent per year among Kaiser enrollees with normal fasting glucose,³ and there is considerable interest in identifying persons at high risk to develop T2DM in the community. Investigating the role of metabolic syndrome variables in persons known to have dysglycemia (impaired fasting glucose, IFG, or impaired glucose tolerance, IGT) has not been well studied. Analyses in Framingham and in other studies could provide insight into the role of non-glycemic variables in the development of T2DM, and identify subsets of dysglycemic patients at especially high risk of subsequent T2DM.

This study identifies the absolute and relative risks for the 8-year incidence of T2DM in middle-aged white persons according to dysglycemia and non-glucose risk factor status. The objective was to use simple clinical variables to identify the subset of dysglycemia subjects at highest risk of progressing to T2DM, with the aim to test the hypothesis that factors that predict risk of T2DM in all non-diabetic individuals also predict T2DM in individuals who would be eligible for T2DM prevention interventions based on inclusion criteria of prevention trials, that is, with baseline dysglycemia. 1· 13· 14

Methods

Examination 5 of the Framingham Offspring Study served as the baseline examination for this study, and it included a standard 75-gram oral glucose tolerance test (OGTT) with fasting and 2-hour glucose measurements in individuals who did not have T2DM at baseline. A fasting glucose level 5.4-6.9 mmol/L was defined as impaired fasting glucose (IFG), and a 2-hour glucose level 7.8-11.0 mmol/L was defined as impaired glucose tolerance (IGT), as described previously.^{2,4} Risk factor assessment at the baseline examination included parental history of diabetes mellitus, weight, height, blood pressure, blood pressure medication, cholesterol, HDL cholesterol, triglyceride levels, and medications used to lower lipids, as described previously.^{2,4} Baseline T2DM was defined as a fasting glucose level >7.0 mmol/L, a 2-hour glucose level >11.0 mmol/L or diabetes medication use, as described previously.^{2,4} Of 3,799 persons attending the baseline exam, 400 with T2DM, 46 missing MetS trait information and 226 taking angiotensin converting enzyme inhibitors were excluded, leaving 3,127 individuals in this analysis. Angiotensin converting enzyme inhibitor medication users were excluded, which in addition to lifestyle trials 1· 13 allowed comparisons to the DREAM trial participants 14”

The Framingham Offspring participants were followed 8 years for the development of T2DM, which was determined by a fasting glucose ≥ 7.0 mmol/L at either of the follow-up examinations conducted 4 years and 8 years after the baseline evaluation or if the participant started oral hypoglycemic agents or insulin therapy.

The metabolic syndrome traits were the key covariates considered as potentiators of T2DM risk. These factors include information on adiposity (waist girth, and alternatively, body mass index (BMI), blood pressure, and fasting measures of glucose, HDL cholesterol, and triglycerides. Each of these factors was considered in prediction models that separately developed analytical approaches that included models with continuous variables or dichotomous variables that employed expert-derived cutoff levels developed by the National Cholesterol Education Program (NCEP).

Logistic regression was used to test for the effects of IFG, IGT, and combined IFG and IGT as risk factors for the development of T2DM, with consideration of the potential effects of age, sex, parental history of T2DM, and the metabolic syndrome (MetS) trait burden. The MetS was considered according to the number of abnormal traits (dichotomous variable

approach) and in separate analyses by using the traits expressed as continuous variables in the prediction equations. The discriminatory capability of the models was assessed using the C statistic, or the area under the receiver operating characteristic curve. The overall purpose of this approach was to develop risk equations that predicted the development of T2DM based on IFT/IGT, with further consideration of non-glycemic MetS traits, among individuals from the community with characteristics similar to inclusion criteria of prevention trials. 1, 13, 14

Results

The 7-year risk of events according to glycemic status, IFG, IGT and normal glucose levels are seen in Table 1. Among persons without either dysglycemic abnormality the T2DM incidence over 7 years was 1.3%. Comparisons were made to this low risk population and to the IGT-only group.

Three different multivariable prediction models for T2DM are shown in Table 2. All persons in these analyses had at least IFG or IGT at the baseline evaluation. Model 1 does not include glycemic information, Model 2 includes IFG and IGT glycemic category information and Model 3 includes fasting and post-challenge glucose information from the OGTT testing. Model 2 shows that glycemic categories IFG and IGT are both important to categorize individuals at risk for T2DM over and above traditional non-glucose characteristics. An appreciable increase in the C-statistic from 0.727 to 0.764 is shown for this model. Model 3 that includes continuous measures of glucose using fasting and post-glucose load information provides the best overall model and the C-statistic is 0.820. In Model 2 and Model 3 that consider glycemic information, the key non-glycemic traits that predicted later T2DM in adults with dysglycemia were parental history of diabetes, excess adiposity and low HDL-C.

Discussion

This study shows that the risk of developing T2DM in middle-aged men and women with dysglycemia is related to the burden of metabolic traits. We developed a risk estimation model that included age, sex, IFT only, IGT only, both IFG and IGT, and non-glycemic metabolic syndrome traits. Others have used questionnaire data in cross-sectional studies to identify persons with undetected T2DM or to increase the yield of glucose testing, with the findings that greater age, higher BMI, and ethnicity were especially important predictors.^{5,6} Where investigated, hypertension history, physical activity, family history of diabetes have been shown to be predictive of an abnormal OGTT in this setting.⁷

We have previously reported that the metabolic syndrome variables efficiently identified subjects at elevated risk for incident T2DM, suggesting that clinical screening adds value beyond screening using personal knowledge.⁸ Other investigators have also focused on the role of metabolic factors that are easy to quantify in the office setting, and tested them as determinants of T2DM in cross-sectional and longitudinal studies, including the San Antonio Heart Study, Insulin Resistance Atherosclerosis Study, Rancho Bernardo, Munster cohorts.⁹⁻¹²

An analysis by investigators from the Atherosclerosis Risk in Communities that included more than 7900 adults 45-64 years of age showed a high degree of model discrimination of future T2DM cases during follow up when the NCEP metabolic syndrome variable count of 0 to 5 was used in the analysis (AROC=0.78).¹⁰ They concluded that rules based on the metabolic syndrome are reasonable alternatives to estimate risk for T2DM, similar to a

recent report from the Framingham experience in which the NCEP metabolic syndrome trait count was highly related to a greater risk to develop T2DM.²

The metabolic traits that constitute the metabolic syndrome are especially important in the determination of risk for T2DM. Previous research based on the Framingham Offspring experience has shown that an increasing number of any traits is an important determinant of risk for T2DM. In comparison to having no metabolic syndrome traits the presence of 1-2 traits increased risk for T2DM 2-3 fold and presence of ≥ 3 of the 5 traits increased risk approximately 25-fold.² The metabolic syndrome traits show similar effects when the relative risks are considered for combinations of traits.

Aside from a positive parental history of T2DM, it is possible to intervene directly or indirectly on all of the other traits that were predictive in our analyses. In particular, increased physical activity, weight loss, dietary changes, and medications may act through metabolic factors to favorably alter risk for T2DM, as evidenced by recent intervention trials such as the diabetes prevention program conducted in the United States and the lifestyle prevention of diabetes trial undertaken in Europe.^{1,13} Clinical identification of a parental history of diabetes and the presence of combinations of metabolic syndrome risk factors in persons with IFG or IGT should prompt consideration to prescribe these evidence-based strategies, especially therapeutic lifestyle change, to prevent or delay the onset of T2DM.

Abbreviations

HDL-C	high density lipoprotein cholesterol
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
OGTT	oral glucose tolerance test
T2DM	type 2 diabetes mellitus

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Table 1

Baseline Glycemic Testing and 7-Year Risk of Type 2 Diabetes Mellitus Experience of 3,127 Framingham Offspring

IFG	IGT	New Diabetes During Follow up			7-Year Cumulative Incidence of T2DM	Crude Odds Ratio Relative to Population Sample	Crude Odds Ratio Relative to IGT only Group
		No	Yes	Total			
No	No	2095	28	2123	1.3%	Referent	-----
No	Yes	157	7	164	4.3%	3.34	Referent
Yes	No	574	58	632	9.2%	7.57	2.27
Yes	Yes	155	53	208	25.5%	25.6	7.67

Table 2
Multivariable Prediction of Type 2 Diabetes Mellitus over 7 Years Framingham Offspring Experience

Characteristics	Model 1 No Glycemic Information		Model 2 IFG and IGT Categories		Model 3 Fasting and 2-hr OGTT Glucose Information	
	Odds Ratio	P Value	Odds Ratio	P Value	Odds Ratio	P Value
Age<50	Referent	--	Referent	---	Referent	---
Age 50-64	0.94	0.81	0.89	0.67	0.79	0.41
Age ≥65	0.91	0.80	0.76	0.41	0.53	0.08
Male sex	0.82	0.33	0.85	0.44	1.00	0.99
IFG No, IGT Yes	Not used	---	Ref	---	Not used	---
IFG Yes, IGT No	Not used	---	2.86	0.01	Not used	---
IFG Yes, IGT Yes	Not used	---	7.25	<0.001	Not used	---
Fasting Plasma Glucose (per SD=per 9.4 mg/dL)	Not used	---	Not used	---	3.42	<0.0001
2-hr OGTT Plasma Glucose (per SD=per 28.2 mg/dL)	Not used	---	Not used	---	1.50	0.0003
Parental T2DM	2.18	0.001	2.15	0.002	1.84	0.02
BMI > 30 kg/m ² or Waist > 40 in	1.83	0.004	1.68	0.02	1.42	0.13
BP ≥130/85 mm Hg or BP Therapy	1.52	0.004	1.46	0.12	1.25	0.39
Lipid Rx for HDL/Trig	1.47	0.08	1.47	0.23	1.30	0.45
HDL <50 (W) or <40 (M) mg/dl	2.28	0.0003	2.22	0.0006	2.08	0.004
Triglycerides ≥150 mg/dL	1.52	0.06	1.49	0.08	1.22	0.43
C-statistic	0.727		0.764		0.820	