Does Elevated Plasma Triglyceride Level Independently Predict Impaired Fasting Glucose?

The Multi-Ethnic Study of Atherosclerosis (MESA)

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OBJECTIVE—Elevated plasma triglycerides (TGs) have been included in diabetes risk prediction models. This study examined whether elevated TGs predict risk for impaired fasting glucose (IFG).

RESEARCH DESIGN AND METHODS—This study used the baseline and longitudinal follow-up data from the Multi-Ethnic Study of Atherosclerosis (MESA). The analysis included non-Hispanic whites, African Americans, Hispanics, and Chinese Americans 45–84 years of age who had fasting glucose <100 mg/dL at baseline and who did not have clinically evident cardiovascular disease or diabetes. Cox proportional regression models were used to examine the association of elevated TGs with incidence of IFG adjusting for central obesity, low HDL cholesterol, elevated blood pressure, baseline fasting glucose, and BMI. Area under the receiver operating characteristic curve (AUC), sensitivity, and specificity of elevated TGs in predicting IFG were calculated.

RESULTS—The incidence rate of developing IFG was 59.1 per 1,000 person-years during the median 4.75 years of follow-up. African Americans and Hispanics had a higher incidence rate of IFG compared with non-Hispanic whites among people with normal TG concentrations. Elevated TGs (>150 mg/dL) at baseline were independently associated with the incidence of IFG with an adjusted hazard ratio of 1.19 (95% CI 1.04–1.37). However, its predictive value for identifying people at risk for IFG was poor, with <57% AUC. Interactions of elevated TGs with race/ethnicity in predicting IFG were not statistically significant.

CONCLUSIONS—Elevated TGs were moderately associated with risk for IFG, and it was a poor risk prediction tool for IFG.

Diabetes Care 36:342–347, 2013

Cardiometabolic risk factors such as obesity, hypertension, elevated triglycerides (TGs), low HDL cholesterol (HDL-C), and high fasting glucose tend to coexist. A cluster of these risk factors, also called the metabolic syndrome, significantly increases risk for type 2 diabetes and cardiovascular diseases (CVDs) (1–3). Impaired fasting glucose (IFG) is defined as fasting glucose between 100 mg/dL (5.6 mmol/L) and 125 mg/dL (6.9 mmol/L), and impaired glucose tolerance (IGT) is defined as a 2-h value of the oral glucose tolerance test of 140 mg/dL (7.8 mmol/L) to 200 mg/dL (11.1 mmol/L) (4,5). People with IFG or IGT are considered to have prediabetes; IFG and IGT form the intermediate stage in the development of diabetes. Clinical trials have consistently demonstrated that lifestyle and pharmacological interventions can significantly reduce the risk of type 2 diabetes among individuals with prediabetes (6–11). There are ~79 million American adults with IFG, and 15–30% of them will develop type 2 diabetes within 5 years without lifestyle changes (12). One may speculate that early prevention of IFG may be an effective and important strategy to address the growing burden of diabetes.

IFG often coexists with other metabolic syndrome components and is included in the definition of the metabolic syndrome in epidemiological studies; nevertheless, the temporal association of other cardiometabolic risk factors, particularly elevated TGs with IFG has not been well examined. As people with normal fasting glucose can also have elevated TGs and other cardiometabolic risk factors (13,14), it is reasonable to assume that those with higher TGs and other cardiometabolic risk factors may have a greater risk of developing IFG. Elevated TGs have been used in diabetes risk prediction models (15–18), but little is known about whether elevated TG levels also increase the risk for IFG independently of central obesity, HDL-C, and elevated blood pressure (BP).

The primary objective of this study was to examine *1*) the association of elevated TGs with the development of IFG independently of other metabolic syndrome components (large waist circumference [WC], low HDL-C, and elevated BP) and *2*) the predictive value of elevated TGs with regard to IFG risk.

RESEARCH DESIGN AND METHODS

Multi-Ethnic Study of Atherosclerosis study population and the analytic sample

The Multi-Ethnic Study of Atherosclerosis (MESA) is a multicenter cohort study

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Received 20 February 2012 and accepted 22 July 2012.
DOI: 10.2337/dc12-0355
A complete list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.

of 6,814 men and women 45–84 years of age free of known CVD at baseline, recruited from six different communities: Baltimore City and Baltimore County, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; Northern Manhattan and Bronx, NY; and St. Paul, MN. Detailed information about MESA design is provided elsewhere (19). The current study used MESA baseline data collected between July 2000 and August 2002 and the follow-up exam 2, 3, and 4 data through 2007, and included MESA study participants with normal fasting glucose <100 mg/dL. Those with type 2 diabetes or fasting glucose between 100 and 125 mg/dL at baseline were excluded. As this study used IFG as the end point, the study also excluded 185 study participants who developed diabetes during the follow-up time. The final sample for this study was 4,489, including non-Hispanic whites (44.6%), African Americans (24.7%), Chinese Americans (11.1%), and Hispanics (19.6%).

Data collection and the study variables

Information about socioeconomic status, medical history, medication, and tobacco and alcohol use was obtained through a questionnaire. WC at the umbilicus was measured to the nearest 0.1 cm using a measuring tape. Height and weight was measured by a stadiometer and calibrated scale. BMI was calculated from height and weight as kg/m^2. Resting BP was measured three times, with participants in the seated position, with a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon); the average of the last two measurements was used in the analysis. Fasting TGs were measured in plasma after an 8-h fast using a glycerol-blanked enzymatic method (Trig/GB; Roche Diagnostics, Indianapolis, IN). HDL-C was measured in plasma by the cholesterol oxidase method (Roche Diagnostics) after precipitation of non–HDL-C magnesium/dextran. Serum glucose was measured using the glucose oxidase method on the Vitros analyzer (Johnson & Johnson, Rochester, NY).

The main outcome variable was incident IFG, defined as having fasting glucose between 100 and 125 mg/dL at one of the follow-up visits. The main independent predictor variable was elevated TGs at baseline, defined as TGs >150/mg/dL. Other risk factors included large WC (>102 cm for men and >88 cm for women), low HDL-C (<50 mg/dL for women and <40 mg/dL for men), elevated BP (determined by systolic BP >129 mmHg or diastolic BP >84 mmHg), or taking hypertension medication. These definitions were based on ATP III updated recommendations (20). For Chinese Americans, we used the International Diabetes Federation cutoff point for large WC, >90 cm for men and >80 cm for women (21). Age, sex, smoking status, education level, physical activity, lipid medication use, and baseline fasting glucose were also included as covariates in the analysis. Physical activity level was measured as the sum of minutes spent in all activity types multiplied by the metabolic equivalent (MET) and expressed as min/week · MET. The variable moderate and vigorous physical activity was used in the analysis. Alcohol use was coded as current, former, or never. Never smoking was defined as lifetime consumption of <100 cigarettes. Current smoking was defined as smoking cigarettes within the last 30 days, and former smoking was defined as not smoking during the last 30 days.

Table 1—*Characteristics of study participants with normal fasting plasma glucose concentration at baseline, MESA, 2000–2002*

	Total	TGs >150	TGs ≤150	
	N = 4,489	*n* = 1,142	*n* = 3,347	*P* value
Demographics				
Age (%)				0.02
45–64	60.3	63.2	59.3	
65–84	39.7	36.8	40.7	
Age (mean/SD)	61.1/10.3	60.5/9.8	61.3/10.4	0.02
Sex (%)				0.006
Female	54.8	51.3	56.0	
Male	45.2	48.7	44.0	
Race/ethnicity (%)				
White	44.6	48.5	43.2	<0.001
African American	24.7	11.3	29.3	
Hispanic	19.6	27.1	17.1	
Chinese American	11.1	13.1	10.4	
Education level (%)				<0.001
High school or less	31.4	38.9	28.8	
Some college	28.7	28.5	28.8	
Bachelor or graduate	39.9	32.7	42.4	
Behavioral variables				
Cigarette smoking status (%)				0.01
Never	50.4	50.0	50.4	
Former	36.7	34.6	37.4	
Current	13.0	15.4	12.2	
Alcohol use (%)				0.30
Never	18.9	20.2	18.4	
Former	21.5	20.4	21.9	
Current	59.6	59.4	59.7	
Physical activities (min/week-MET) (mean/SD)	5,948/5,834	5,676/5,776	6,030/5,852	<0.001
ATP III metabolic syndrome components				
Large waist (%)	52.1	64.5	47.9	<0.001
Low HDL-C (%)	31.3	58.6	22.0	<0.001
Elevated BP (%)	47.0	52.9	44.9	<0.001
Other Variables				
Use of lipid-lowering medications (%)	13.7	15.5	13.1	0.038
Fasting glucose (mg/dL) (mean/SD)	86/7	87.2/6.8	85.6/7.1	<0.001
Fasting glucose (91–99 mg/dL) (%)	28.6	33.4	27.0	<0.001
BMI (mean/SD)	27.5/5.1	28.6/4.8	27.1/5.1	<0.001

Statistical analysis

The incidence rate of IFG over time was calculated for the entire sample as well as for each ethnic group (non-Hispanic whites, Chinese Americans, African Americans, and Hispanics) who had normal fasting glucose and was free of diabetes at the baseline. The difference in IFG incidence rate was determined using Poisson regression to account for variable follow-up time. Cox proportional hazards regression models were used to examine the association of the baseline elevated TGs with IFG incidence during the follow-up exams. Unadjusted and adjusted hazard ratios (HRs) were estimated. The adjustments were made in model 1 for cardiometabolic risk factors (large WC, low HDL-C, and elevated BP), demographic variables, education level, use of lipid medication, smoking status, alcohol use, physical activity, and sites. An additional adjustment was made in model 2 for the baseline fasting glucose coded as 1 for a value between 91 and 99 mg/dL and 0 for a value <91 mg/dL. The rationale for this code was based on a study showing that fasting glucose between 91 and 99 mg/dL predicted diabetes (13). The final model (model 3) was further adjusted for BMI. Sensitivity and specificity of elevated TGs (>150 mg/dL) and area under the sensitivity versus 1-specificity curve (AUC) for predicting IFG were calculated. The significance level was set at <0.05. IBM-SPSS version 19 was used for the statistical analyses. Given the ethnic difference in the distribution of TG levels between African Americans and whites (22–24), we further tested whether there was heterogeneity across different ethnic groups with regard to elevated TGs in predicting IFG.

RESULTS—The characteristics of this study sample by TG status are presented in Table 1. Overall, 25.4% had elevated TGs. Those with elevated TGs appeared to be younger, more frequently males, current smokers, and less frequently African Americans and had a higher prevalence of the cardiometabolic risk factors as well as a higher BMI compared with those who had normal TG levels.

IFG incidence rates for the entire sample as well as for the subgroups are displayed in Table 2. The IFG incidence rate was 59.1 per 1,000 person-years during the median 4.75 years of follow-up among all groups. African Americans had a higher incidence rate of IFG (61.2 per 1,000 person-years) and Hispanics had a higher incidence rate of IFG (66.3 per 1,000 person-years) compared with non-Hispanic whites (44.6 per 1,000 person-years), among those with normal TG concentrations. No racial/ethnic differences in the incidence rate of IFG were observed among people with elevated TG concentrations.

Elevated TGs were independently associated with IFG among the study participants who had normal fasting glucose <100 mg/dL at baseline. The unadjusted HR of elevated TGs in predicting IFG was 1.46 (95% CI 1.28–1.65). In Table 3, after the adjustment for other metabolic syndrome components and other variables, the association was significant, with an HR of 1.27 (1.11–1.46) in model 1. After further adjustment for baseline fasting glucose, the association was still significant, with an HR of 1.20 (1.04–1.38) in model 2. In model 3, with the additional adjustment for the baseline BMI, the association of elevated TGs with IFG remained statistically significant, with an adjusted HR of 1.19 (1.04–1.37). Elevated BP and large WC were also significantly associated with the development of IFG. Low HDL-C was significantly associated with IFG in model 1 and was not significant in model 2, after the adjustment was made for baseline fasting glucose. The HR of large WC was 1.54 (1.34–1.76) in model 2; further adjustment for baseline BMI in model 3 reduced it to 1.27 (1.08–1.49). There was no significant heterogeneity across racial/ethnic groups; compared with non-Hispanic whites, *P* values for interaction were 0.315 for African Americans, 0.912 for Chinese Americans, and 0.306 for Hispanics.

The AUC of elevated TGs in identifying risk for IFG for the entire sample was 55%, with a sensitivity of 32% and specificity of 77%. As displayed in Table 4, the sensitivity of elevated TGs was low, with <50% among each ethnic group.

CONCLUSIONS—This study has shown that the incidence rate of IFG was 59.1 per 1,000 person-years during the follow-up years among the MESA participants who were free of type 2 diabetes and known heart disease and who had fasting glucose in the normal range. The American Diabetes Association lowered the threshold of IFG from 110 to 100 mg/dL (4) to optimize the identification of people at increased risk for type 2 diabetes. However, some concerns have been raised about the risk of developing diabetes or progression to diabetes among those with fasting glucose <100 mg/dL, a current threshold for IFG (13,25,26).

According to the findings from a study using the National Health and Nutritional Examination Survey (NHANES) data, the prevalence of IFG or IGT has not changed from 1988 to 2005–2006 in the U.S., but the prevalence of diabetes has increased significantly (27). This may indicate that the risk of developing diabetes among those with normal fasting glucose has also increased over these

Table 2—*Incidence rates of IFG in multiethnic groups according to baseline plasma TG concentration*

	Total				TGs ≤150			TGs >150		
	n	No. with IFG	Incidence per 1,000 person-years	Poisson regression *P* value	*n*/no. with IFG	Incidence per 1,000 person-years	Poisson regression *P* value	*n*/no. with IFG	Incidence per 1,000 person-years	Poisson regression *P* value
Non-Hispanic white	2,001	454	52.8	Reference	1,447/281	44.6	Reference	544/173	75.4	Reference
African American	1,109	289	63.7	0.1	980/244	61.2	0.005	129/42	67	0.8
Hispanic	882	267	72.3	<0.001	572/161	66.3	<0.001	310/106	83.1	0.5
Chinese American	497	110	52.1	0.8	348/69	46	0.9	149/41	83.8	0.5
Total	4,489	1,117	59.1		3,347/755	53.1		1,142/362	77.4	

Table 3—*Association of elevated plasma TGs and other metabolic syndrome components with incident IFG in the MESA*

	Model 1[1]			Model 2[2]			Model 3[3]		
	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
Elevated TG	1.27	1.11–1.46	0.001	1.20	1.04–1.38	0.01	1.19	1.04–1.37	0.01
Large Waist[4]	1.74	1.52–2.00	<0.001	1.54	1.34–1.76	<0.001	1.27	1.08–1.49	<0.001
Low HDL-C[5]	1.17	1.03–1.34	0.017	1.10	0.96–1.25	0.16	1.07	0.94–1.22	0.16
Elevated BP[6]	1.32	1.16–1.50	<0.001	1.18	1.04–1.34	0.01	1.16	1.02–1.32	0.01

[1]Model 1 adjusted for age, sex, race/ethnicity, education level, smoking status, alcohol use, physical activity, use of lipid-lowering medication, and sites. [2]Model 2 adjusted for age, sex, race/ethnicity, education level, smoking status, alcohol use, physical activity, use of lipid-lowering medication, sites, and baseline fasting glucose. [3]Model 3 adjusted for age, sex, race/ethnicity, education level, smoking status, alcohol use, physical activity, use of lipid-lowering medication, sites, baseline fasting glucose, and baseline BMI. [4]Large WC, >102 cm for men and >88 cm for women; for Chinese Americans large WC, >90 cm for men and >80 cm for women. [5]Low HDL-C, <50 mg/dL for women and <40 mg/dL for men. [6]Elevated BP determined by systolic BP >129 mmHg, diastolic BP >84 mmHg, or taking hypertension medication.

periods, and most likely this may also reflect the increased diabetes risk due to increased prevalence of obesity and other risk factors among those with normal fasting glucose. Our study has shown that cardiometabolic risk factors such as large WC, high BP, and elevated TGs are associated with incident IFG. The study findings highlight the importance of addressing these risk factors among people with normal fasting glucose.

Elevated TGs (>150 mg/dL) are considered a marker of insulin resistance, a strong predisposing condition of type 2 diabetes (15–18). Insulin resistance is not only linked to other metabolic risk factors, such as abdominal obesity, hypertension, and high fasting glucose, but also hypothesized as the underlying pathophysiology of the clustered metabolic risk factors (28). Very few epidemiological studies, however, have reported that elevated TGs predict risk for prediabetes (29–31). Our study found that elevated TGs moderately predict risk for IFG. However, our study also demonstrated the poor discriminative utility of elevated TGs for identifying people at high risk for prediabetes. No interactions were seen by race/ethnicity.

Given the increased risk of IFG with other cardiometabolic risk factors, a better screening tool for prediabetes risk may need to measure a range of risk factors and weigh each accordingly. As the underlying cause for the progression to IFG has not been well understood, people with fasting glucose lower than the current criteria for IFG can benefit from the management of clustered risk factors through lifestyle change and medications when necessary. This study found that abdominal obesity was significantly associated with the increased risk for IFG even among those with normal glycemia. The presence of both abdominal obesity and elevated TGs, sometimes also called hypertriglyceridemic waist, has been recommended as a screening tool to identify coronary artery disease risk in people with prediabetes or diabetes (32). However, more research is needed to understand the underlying structure of the clustered cardiometabolic risk factors and identify key risk factors that can be targeted for the optimal outcomes in diabetes prevention programs.

To our knowledge, this is the only large-population study that has examined the incidence of IFG among people of multiethnic groups despite the national data on ethnic differences in the prevalence of IFG and diabetes. Ethnic differences in the prevalence of IFG and diabetes are well documented. African Americans and Hispanics have a higher prevalence of IFG (33,34). Our study reported that African Americans and Hispanics had higher incidence rates of IFG compared with non-Hispanic whites among people within a normal range of TGs at baseline. This finding is not surprising as other studies have consistently reported that African Americans with normal TGs had higher insulin resistance and fasting glucose (22–24). The reasons for this TG paradox among African Americans have been extensively discussed (23,35,36). The greater activity of lipoprotein lipase, the enzyme that clears TG-rich lipid particles among African Americans, may play a role (23). Studies have raised the concern that using the current elevated TG cutoff point at 150 mg/dL in the definition of the metabolic syndrome may underdiagnose African Americans at high risk for type 2 diabetes and CVD (37,38). Therefore, interventions to reduce risk for prediabetes among African Americans with a normal TG level deserve special attention.

The current study has some limitations. IFG was based on one fasting glucose value from each follow-up exam, and thus it is subjected to regression dilution bias. However, this type of bias is a conservative one, which means that the strength of the associations may have been underestimated. Because glucose tolerance test data are not available in MESA, the association of elevated TGs with prediabetes among people with either IFG or IGT could not be examined, which may result in the underestimation of the relationship between elevated TGs and prediabetes.

Table 4—*Sensitivity and specificity of elevated plasma TGs and other metabolic syndrome components in predicting IFG in different ethnic groups in the MESA*

	Non-Hispanic white			African American			Hispanic			Chinese American		
	AUC	Sensitivity	Specificity	AUC	Sensitivity	Specificity	AUC	Sensitivity	Specificity	AUC	Sensitivity	Specificity
Elevated TG	0.57	0.38	0.75	0.52	0.15	0.90	0.53	0.40	0.67	0.55	0.37	0.72
Large waist	0.59	0.63	0.55	0.58	0.69	0.48	0.55	0.63	0.48	0.54	0.56	0.51
Elevated BP	0.55	0.50	0.60	0.59	0.75	0.43	0.53	0.47	0.59	0.54	0.47	0.61
Low HDL-C	0.57	0.40	0.74	0.52	0.31	0.73	0.54	0.45	0.62	0.49	0.33	0.66

In conclusion, elevated TGs are moderately associated with risk for incident IFG. Due to its poor utility, elevated TGs cannot be used as a screening tool for IFG. The prevention of prediabetes could benefit from addressing a range of cardiometabolic risk factors among people with a normal range of fasting glucose.

Acknowledgments—The MESA study was supported by contracts N01-HC-95159 through N01-HC-95169 from the National Heart, Lung, and Blood Institute.

No potential conflicts of interest relevant to this article were reported.

S.X.L. conceived and designed the study and researched data. I.B. researched data and participated in the writing of the manuscript. R.Y., C.T.S., P.S., M.S., and A.G.B. participated in the writing of the manuscript. Z.J. researched data. All authors reviewed and edited the manuscript. S.X.L. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

This study was presented in abstract form at the 72nd Scientific Sessions of the American Diabetes Association, Philadelphia, Pennsylvania, 8–12 June 2012.

The authors thank the other investigators, staff, and participants of the MESA study for their valuable contributions.

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