Triglyceride levels and risk of type 2 diabetes mellitus: a longitudinal large study

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ABSTRACT

The relationship between triglyceridemia and diabetes mellitus remains unclear. This study evaluated the risk of diabetes and impaired fasting glucose associated with a wide range of triglyceride levels. A longitudinal retrospective study was carried out employing data from a screening center between the years 2000 and 2012. Inclusion criteria were absence of diabetes at baseline and attendance at the center at least twice over a 5-year period. Participants were divided by fasting blood glucose level (normal/impaired) at the first visit. A total of 5085 participants were eligible for the study. Of the 4164 normoglycemic participants at baseline, 40 (0.96%) had diabetes and 998 (24%) had impaired fasting glucose by the end of the study. On stepwise logistic regression analysis, every 10 mg/dL increase in triglyceride level significantly increased the risk of diabetes by 4% and of impaired fasting glucose by 2% ($p<0.001$). This association held true even when rising triglyceride levels remained within the accepted normal range (<150 mg/dL, $p<0.001$). Sustained increments in serum triglyceride level, even within the accepted normal range, are an independent risk factor for diabetes mellitus and impaired fasting glucose in normoglycemic participants.

Significance of this study

What is already known about this subject?

- The relationship between triglyceridemia and diabetes mellitus remains unclear.
- There is no consensus that elevation in triglyceride levels increases the risk for diabetes.
- Studies have reported a link between high serum triglyceride levels and insulin oversecretion in apparently healthy people.

What are the new findings?

- We evaluated the relationship between diabetes and the increment in triglyceride levels within the normal range.
- Our results suggest that sustained increments in rising triglyceride level, even within the accepted normal range, might pose a cumulative risk for the development of DM and IFG.
- To our knowledge there are, as yet, no studies of the potential relationship between normal-range triglyceride levels and risk of DM and IFG.

How might these results change the focus of research or clinical practice?

- Triglyceride levels may serve as a therapeutic target to reduce the risk for diabetes and IFG.
- Our findings have important implications for the conceptual and practical approach to the management of what is currently considered normal triglyceride levels and may serve a premise for the formation of new methods of diabetes risk evaluation.
- Individualized risk stratification may be preferable to setting a standard general threshold for normal triglyceride levels.

INTRODUCTION

Type 2 diabetes mellitus (DM) is a multifactorial disease involving a genetic predisposition and various environmental factors.[1 2] It tends to be associated with other components of the metabolic syndrome, namely obesity, hypertriglyceridemia, low level of high-density lipoprotein (HDL) cholesterol, and hypertension, which together promote the development of atherosclerosis and increase the risk of cardiovascular disease.[3]

A characteristic pattern of diabetes-associated dyslipidemia, consisting of disturbances in the production and clearance of plasma lipoproteins in the presence of low levels of HDL cholesterol, increased levels of triglycerides, and postprandial lipemia, has also been documented in people with insulin resistance and normal plasma glucose levels.[4–7] Furthermore, studies have reported a link between high serum triglyceride levels and insulin oversecretion in apparently healthy people.[8–11] Nevertheless, the cause–effect relationship between hypertriglyceridemia and insulin resistance remains controversial.[12] Insulin resistance may be responsible for most of the components of the metabolic syndrome, or it may be a consequence of precedent hypertriglyceridemia. The latter possibility is supported by the study of Steiner[13] where reducing serum triglyceride levels in participants with hypertriglyceridemia led to a decrease in serum insulin levels and in the incidence of type 2 DM. In another study, changes in triglyceride levels were accompanied by changes in the

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incidence of type 2 DM.[14] However, the possible risk of diabetes in individuals with apparently normal triglyceride levels is not clear.

A better understanding of the pathophysiological mechanisms underlying the development of type 2 DM at different triglyceride levels could lead to improvements in primary prevention of the disease and changes in the approach to treating hypertriglyceridemia. The aim of the present study was to evaluate the risk of diabetes and prediabetes in the presence of a wide spectrum of triglyceride levels.

METHODS

A retrospective longitudinal study was carried out employing data from a screening center at the Rabin Medical Center in Israel between the years 2000 and 2012. The screening center provides regular health assessments for male and female employees aged 20–80 years from different companies. Each person undergoes a comprehensive physical examination in addition to a panel of blood and urine tests, chest X-ray, ECG, exercise stress test, and lung function test. People may return once a year for a repeat investigation.

Included in this study were all participants who had no evidence of diabetes and a fasting plasma triglyceride level of 24–1130 mg/dL at their initial visit and had attended the clinic at least twice over a 5-year period.

All participants with a prior diagnosis of diabetes and/or participants who received any medication for diabetes before their first visit were excluded.

Tests of 12 h fasting glucose and triglyceride levels were performed with a Beckman Coulter AU 2700 analyzer and the results were quantified by enzymatic ultraviolet or enzymatic color assay, respectively. Impaired fasting glucose (IFG) was defined as a plasma glucose level of ≥100 and ≤125 mg/dL, according to the 2003 criteria of the American Diabetes Association,[15–17] while levels above 125 mg/dL were diagnosed as DM. Hypertriglyceridemia was defined as a plasma triglyceride level of ≥150 mg/dL, according to the criteria of the National Cholesterol Education Program III,[18 19] while lower levels were considered normal. Participants were divided into two groups by fasting glucose level at baseline (normoglycemic/IFG), and univariate and multivariate analyses were performed to determine the association of triglyceride level with risk of development of diabetes and IFG.

The study protocol was approved by the Helsinki Committee of the Rabin Medical Center.

Statistical methods

Continuous variables are expressed as mean±SD, and categorical variables as numbers and percentages. Analysis of variance (ANOVA) was used to compare baseline values between participants with normal glucose levels and IFG, and Pearson's χ^2 test or Fisher's exact test was used, as appropriate, for discrete variables. ORs and 95% CIs for contracting hypertriglyceridemia or diabetes were derived using Stepwise Logistic Regression. A p value of ≤0.05 was considered significant. All statistical analyses were performed using BMDP Statistical Software (1993) (Chief Editor: WJ Dixon, University of California Press, Los Angeles, USA).

RESULTS

Participants and baseline values

A total of 5085 participants met the inclusion criteria, with 3746 (74%) men and 1339 (26%) women of mean age 42.8±9.0 years. The mean duration of follow-up was 7.58 ±1.98 years. The characteristics of the participants are presented in table 1.

The division of the study population by fasting glucose levels at the first visit yielded 4164 normoglycemic participants (82%) and 921 participants with IFG (18%). Normal blood triglyceride levels were found in 3722 participants (73%) and hypertriglyceridemia in 1363 participants (27%). By the end of the study, DM was diagnosed in 170 participants (3.3%). Their characteristics are presented in table 2.

Relationship between triglyceride level and diabetes risk: normoglycemic participants

DM developed in 40 of the 4164 participants with normal fasting glucose levels at their initial visit (0.96%). A significant association was found between the baseline triglyceride level and diabetes risk in normoglycemic participants. On stepwise logistic regression analysis including age, sex, family history of diabetes, body mass index (BMI), Tg/HDL ratio, and hypertension, every increase of 10 mg/dL in the triglyceride level increased the risk of diabetes by 4% (OR 1.04, CI 1.02 to 1.07). Triglyceride level was the

Table 1 Characteristics of 5085 participants without diabetes attending a health screening center

	Men n=3746	Women n=1339	Total N=5085	p Value
Age (years), mean±SD	42.6±8.9	43.5±9.3	42.8±9	0.001
Follow-up (year), mean±SD	7.7±2.0	7.3±1.9	7.6±2.0	<0.001
BMI (kg/m^2), mean±SD	26.8±3.7	24.8±4.4	26.3±3.96	<0.001
Impaired fasting glucose, n (%)	764 (20.4%)	157 (11.7%)	921 (18.1%)	<0.001
Hypertriglyceridemia, n (%)	1181 (31.5%)	182 (13.6%)	1363 (27%)	<0.001
Hypertension, n (%)	168 (4.5%)	41 (3.1%)	209 (4.1%)	0.025
Family history of diabetes, n (%)	795 (21.3%)	300 (22.6%)	1095 (21.6%)	0.33
HDL cholesterol (mg/dL), mean±SD	45.8±9.6	60±13.7	49.5±12.5	<0.001
LDL cholesterol (mg/dL) mean±SD	127.3±0.4	119.1±30.7	124.7±30.7	<0.001

BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 2 Baseline characteristics of participants diagnosed with DM by the end of the study

	DM n=170	No DM n=4915	p Value
Age (year), mean±SD	48.3±8.7	42.6±8.9	<0.001
Men, n (%)	139 (82%)	3607 (73%)	0.02
BMI (kg/m^2), mean±SD	29.1±4.3	26.2±3.9	<0.001
Impaired fasting glucose, n (%)	130 (76%)	791 (16%)	<0.001
Triglycerides (mg/dL), mean±SD	172.6±89.7	123.2±70.9	<0.001
Hypertriglyceridemia, n (%)	83 (49%)	1280 (26%)	<0.001
Hypertension, n (%)	21 (12.4%)	188 (4%)	<0.001
Family history of DM, n (%)	75 (44%)	1020 (21%)	<0.001
HDL cholesterol (mg/dL), mean±SD	44.3±9.3	49.7±12.6	<0.001
LDL cholesterol (mg/dL), mean±SD	129.9±31.4	124.6±30.7	0.048

BMI, body mass index; DM, diabetes mellitus; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

most significant risk factor for DM, followed by family history, BMI, and age (table 3). The Tg/HDL ratio was not found to be one of the most significant predictors. The diabetes rate increased significantly when rising triglyceride levels remained within the accepted normal range (p<0.001; figure 1).

Relationship between triglyceride level and diabetes risk: participants with IFG

DM developed in 130 of the 921 participants with IFG at their initial visit (14%). On logistic regression analysis including age, sex, BMI, hypertension, IFG, Tg/HDL ratio, and family history, the ratio was the most significant factor (OR 1.19, CI 1.09 to 1.30) followed by family history, age, and BMI. A rise of every10 mg/dL in the triglyceride level was not found to be a significant risk factor for DM in participants with IFG (table 4).

Relationship between triglyceride level and IFG risk: normoglycemic participants

IFG developed in 998 normoglycemic participants (24%) by the end of the study. Their characteristics are presented in table 5. On stepwise logistic regression analysis including age, sex, BMI, hypertension, Tg/HDL ratio, and family history, every 10 mg/dL increase in triglyceride level and the Tg/HDL ratio had a comparable predicting value for IFG following sex, age, family history, and BMI even though the OR of the Tg/HDL ratio was higher (1.05 CI 1.03 to 1.11) compared to (1.02 CI 1.01 to 1.03) of every 10 mg/dL increase in Tg levels (tables 6 and 7).

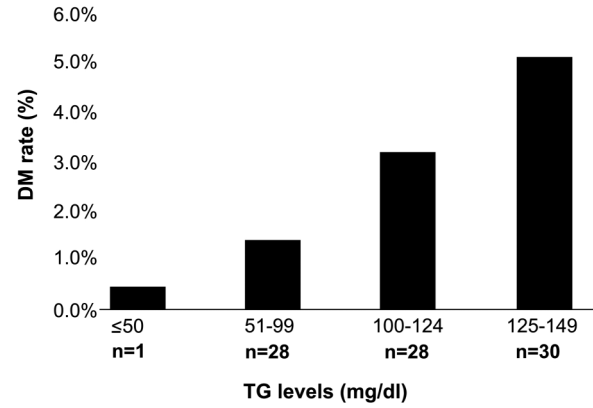

Figure 1 Diabetes mellitus (DM) rate with normal triglyceride levels after 7.6 years of follow-up.

A parallel significant increase in IFG rates associated with the increase in triglyceride levels within the accepted normal range is shown in figure 2 (p<0.001).

We did not find an association between high-density and low-density lipoprotein cholesterol levels and risk of diabetes or IFG.

DISCUSSION

The present large-scale longitudinal study demonstrates a significant association between increasing triglyceride levels, even within the accepted normal range, and risk of development of both type 2 DM and IFG.

To the best of our knowledge, there are as yet no studies of the potential relationship between normal range triglyceride levels and risk of DM. The few studies to date that have dealt with the association between triglycerides and DM have concentrated on abnormally high triglyceride levels,[20–25] and the results were conflicting. Longitudinal investigations in individual ethnic groups from Norway, Taiwan, and Japan[20–22] consistently found that hypertriglyceridemia is a significant risk factor for DM, taking between-study differences in diagnostic standards and methods into consideration. Another group showed that hypertriglyceridemia is an independent risk factor for diabetes in middle-aged British men.[23] By contrast, prospective studies of male Caucasian and Swedish cohorts and a white population in France reported no relationship between high triglyceride levels and DM after adjusting for conventional diabetes risk factors.[2 24 25] Furthermore,

Table 3 Results of stepwise logistic regression analysis of risk of diabetes mellitus in normoglycemic participants for all triglyceride levels

Variable/step number	OR	95% CI	p Value
Triglycerides/10	1.04	1.02 to 1.07	<0.001
Family history	3.19	1.69 to 6.03	<0.001
BMI	1.11	1.04 to 1.19	0.003
Age/10	1.45	1.02 to 2.06	0.044

AUC, area under the curve=0.77.
BMI, body mass index.

Table 4 Results of stepwise logistic regression for analysis of risk of diabetes mellitus in participants with impaired fasting glucose for all triglyceride levels

Variable/step number	OR	95% CI	p Value
Tg/HDL ratio	1.19	1.70 to 3.77	<0.001
Family history	2.56	1.02 to 1.07	<0.001
Age/10	1.59	1.24 to 1.93	<0.001
BMI	1.06	1.02 to 1.12	0.017

AUC, area under the curve=0.70.
BMI, body mass index; HDL, high-density lipoprotein.

Table 5 Baseline characteristics of participants with IFG by the end of the study, excluding those who had initial IFG and those who developed DM

	IFG n=998	No IFG n=3126	p Value
Age (years), mean±SD	44.7±8.8	41.1±8.6	<0.001
Men, n (%)	800 (80.2%)	2153 (68.9%)	<0.001
BMI (kg/m^2), mean±SD	27.1±3.8	25.5±3.7	<0.001
Triglycerides (mg/dL), mean±SD	134.8±80.4	115±66.5	<0.001
Hypertriglyceridemia, n (%)	321 (32.2 %)	672 (21.5%)	<0.001
Hypertension, n (%)	52 (5.2%)	73 (2.3%)	<0.001
Family history of DM, n (%)	244 (24.5%)	581 (18.7%)	<0.001
HDL cholesterol (mg/dL), mean±SD	47.9±11.4	50.7±13.1	<0.001
LDL cholesterol (mg/dL), mean±SD	127.6±30.7	122.1±30.4	<0.001

BMI, body mass index; DM, diabetes mellitus; HDL, high-density lipoprotein; IFG, impaired fasting glucose; LDL, low-density lipoprotein.

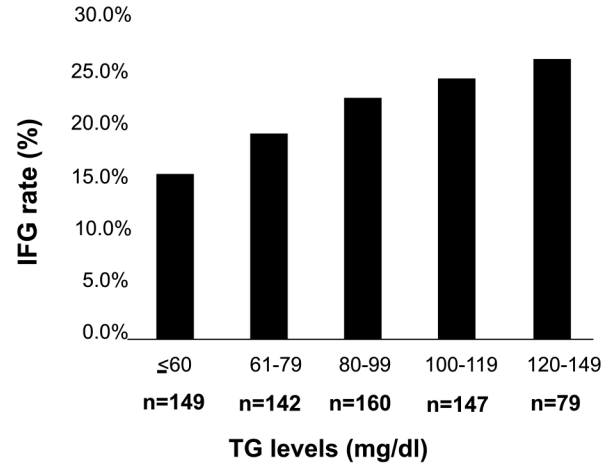

Figure 2 Impaired fasting glucose (IFG) rate with normal triglyceride levels after 7.6 years of follow-up.

unlike some of the longitudinal studies that evaluated specific categories of blood triglyceride levels over time,[14 26] we covered a very broad range of values. Our results show, for the first time, that the risk of DM is cumulative for even small changes in the triglyceride level along the whole continuum, including the presumably normal range, both in participants with initially normal glucose levels and those with IFG.

In our study, we compared the predictive value of the increase in triglyceride levels to predictors shown in other studies such as the Tg/HDL ratio and family history[27–30] and found that a slight increase in triglyceride levels is as good as the Tg/HDL ratio in predicting IFG and might be better than it in predicting diabetes in normoglycemic participants. In contrast, the Tg/HDL ratio was shown to be a better predictor than triglyceride levels in predicting DM in patients with IFG. Apparently, both tools could be useful in predicting DM development.

In our study, family history was a very significant predictor for DM as well as IFG. Our results are compatible with other conclusions.[30 31] Family medical history represents valuable genomic information because it characterizes the combined interactions between environmental, behavioral, and genetic factors.[31 32]

The use of family history as part of a comprehensive risk assessment for an individual can be crucial in the prevention, early detection, and treatment of type 2 DM.[31]

The association between triglycerides and IFG is controversial and has not been widely addressed. Hypertriglyceridemia was found to be a poor predictor of IFG in the prospective Multiethnic Study of Atherosclerosis (MESA),[33] and a good predictor in a longitudinal Japanese study.[22] To the best of our knowledge, our study is the first to reveal a consistent relationship between IFG risk and increased triglyceride levels within the normal range.

This study presents a new perspective in the relationship between triglycerides and DM, emphasizing the important impact of a slight increase in triglyceride levels even within the normal range. Even though it is an associative and not necessarily a causative relationship, our findings have important implications for the conceptual and practical approach to the management of what is currently considered normal triglyceride levels and may serve as a premise for the formation of new methods of diabetes risk evaluation. It is possible that doing so may lower the risk of both DM and IFG. Accordingly, individual risk stratification may be preferable to setting a standard general threshold for normal triglyceride levels.

The strengths of our study include a large cohort, a long follow-up of at least a 5-year period, inclusion of participants of both sexes who underwent the same medical assessment, and data collection in a registered database that

Table 6 Results of stepwise logistic regression for analysis of risk of impaired fasting glucose in normoglycemic participants for all triglyceride levels excluding Tg/HDL ratio

Variable/step no.	OR	95% CI	p Value
Gender (M)	1.69	1.37 to 2	<0.001
Age/10	1.57	1.44 to 1.70	<0.001
Family history	1.45	1.21 to 1.72	<0.001
BMI	1.08	1.06 to 1.10	<0.001
Triglyceride/10	1.02	0.01 to 1.03	0.001

AUC, area under the curve=0.69.
BMI, body mass index; HDL, high-density lipoprotein.

Table 7 Results of stepwise logistic regression for analysis of risk of impaired fasting glucose in normoglycemic participants for all triglyceride levels including Tg/HDL ratio

Variable/step number	OR	95% CI	p Value
Gender (M)	1.69	1.37 to 2.00	<0.001
Age/10	1.57	1.44 to 1.70	<0.001
Family history	1.45	1.21 to 1.72	<0.001
BMI	1.08	1.06 to 1.10	<0.001
Tg/HDL ratio	1.05	1.03 to 1.11	0.001

AUC, area under the curve=0.67.
BMI, body mass index; HDL, high-density lipoprotein.

lessened the chances of information bias. However, the voluntary nature of the participation in health screening may have posed a selection bias, as the population was composed mainly of individuals of high socioeconomic status with high health awareness.

In conclusion, our results suggest that sustained increments in rising triglyceride levels, even within the accepted normal range, might pose a cumulative risk for the development of DM and IFG. Triglyceride levels may serve as a therapeutic target to reduce these risks. Further prospective large-scale studies are needed to confirm our results.

Contributors AB and IK contributed to study design and writing of the manuscript. EC, EG and MG collected the data. PL was responsible for statistical analysis.

Competing interests None declared.

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