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Letters

RESEARCH LETTER

Hypertriglyceridemia and Multiorgan Disease Among U.S. Adults

Severe hypertriglyceridemia, defined by serum triglyceride level ≥500 mg/dL, is a risk factor for atherosclerotic cardiovascular disease (ASCVD).[1] New triglyceride-lowering agents including apolipoprotein C-III inhibitors, angiopoietin-like (ANGPTL) 3 and ANGPTL 4 inhibitors, and fibroblast growth factor (FGF) 21 analogs are directed toward specific pathways, and these inhibitors markedly lower triglycerides.[1,2] In addition to lowering serum triglycerides, these medications may improve other chronic conditions including central obesity, diabetes, and metabolic dysfunction-associated steatotic liver disease (MASLD).[2] There are few data available on the prevalence of chronic conditions among adults with severe hypertriglyceridemia. Clinical trials of new triglyceride-lowering agents may be informed by enrolling patients with comorbidities in addition to severe hypertriglyceridemia and testing whether these other factors are improved with treatment.

We estimated the prevalence of chronic conditions and multiorgan disease among U.S. adults with severe hypertriglyceridemia, defined by serum triglycerides ≥500 mg/dL.[1] For comparison, we estimated the prevalence of comorbidities and multiorgan disease among U.S. adults with normal triglycerides and moderate hypertriglyceridemia, defined by serum triglycerides <200 and 200 to <500 mg/dL, respectively.

For the current study, we analyzed data from the U.S. National Health and Nutrition Examination Survey (NHANES). As a limited number of NHANES participants had severe hypertriglyceridemia, we pooled data from the NHANES 1999-2000 to 2017-2020 cycles to provide stable statistical estimates. Pooling NHANES cycles was done in compliance with the statistical guidance from the U.S. National Center for Health Statistics and provides prevalence estimates for the time period over which data were pooled.[3] The current analysis was restricted to nonpregnant adults, ≥18 years old, who fasted overnight prior to a morning study visit and had a valid triglyceride level (N = 24,518).

All participants completed a study interview and a medical examination. Of relevance to the current analysis, the examination included assessments of height, weight, waist circumference, and blood and urine collection. Chronic conditions included: 1) central adiposity; 2) diabetes; 3) chronic kidney disease (CKD); 4) MASLD; and 5) history of ASCVD. Central adiposity was defined by a waist circumference >88 cm for women and >102 cm for men. Diabetes was defined by fasting serum glucose ≥126 mg/dL, glycohemoglobin ≥6.5%, or self-reported diabetes with glucose-lowering medication use. CKD was defined by an estimated glomerular filtration rate <60 ml/min/1.73 m^2 or an albumin-to-creatinine ratio >30 mg/g. For participants without heavy drinking or hepatitis B or C, nonalcoholic fatty liver disease score was calculated, and MASLD was defined by having nonalcoholic fatty liver disease score ≥−0.64 and any of the following: overweight, diabetes, or normal weight with at least 2 metabolic abnormalities, including central adiposity, high serum triglycerides, low high-density lipoprotein-cholesterol, prediabetes, hypertension, and insulin resistance. The history of ASCVD was assessed by self-report.

Characteristics and the prevalence of chronic conditions were estimated for US adults with serum triglycerides <200 mg/dL, 200 to <500 mg/dL, and ≥500 mg/dL. Participants with ≥3 comorbidities were considered to have multiorgan disease. Poisson regression with robust variance estimators was performed to estimate prevalence ratios for other chronic conditions and multiorgan disease associated with serum triglyceride levels of 200 to <500 mg/dL and ≥500 mg/dL, each vs <200 mg/dL, after adjustment for age, race/ethnicity, and gender. Analyses incorporated the NHANES survey design and were weighted to represent the noninstitutionalized U.S. population.

Overall, 192.1 (95% CI: 185.0-199.2), 26.8 (95% CI: 25.1-28.5) and 2.3 (95% CI: 1.9-2.7) million U.S. adults had serum triglycerides <200 mg/dL, 200 to <500 mg/dL (moderate hypertriglyceridemia), and ≥500 mg/dL (severe hypertriglyceridemia), respectively. The prevalence of each chronic condition was higher among individuals with moderate

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TABLE 1 Characteristics and Prevalence of Chronic Conditions Among U.S. Adults by Serum Triglyceride Levels

	Serum Triglyceride Levels, mg/dL		
	<200 (n = 21,321)	200 to <500 (n = 2,956)	≥500 (n = 241)
U.S. adults			
Row % (95% CI)	86.8 (86.2-87.5)	12.1 (11.5-12.7)	1.0 (0.9-1.2)
Number (95% CI) in millions	192.1 (185.0-199.2)	26.8 (25.1-28.5)	2.3 (1.9-2.7)
Age in years, mean (95% CI)	45.8 (45.3-46.3)	49.6 (48.8-50.3)	46.2 (44.2-48.2)
Women, % (95% CI)	52.7 (51.9-53.4)	40.1 (37.8-42.4)	24.2 (17.0-32.6)
Race/ethnicity, % (95% CI)			
Non-Hispanic white	66.9 (64.8-69.0)	73.5 (70.6-76.2)	68.4 (61.1-75.1)
Non-Hispanic black	12.1 (10.9-13.4)	4.8 (3.9-5.7)	N/A
Hispanic	13.8 (12.4-15.4)	15.1 (13.0-17.5)	19.5 (14.0-25.9)
Other	7.1 (6.5-7.9)	6.6 (5.3-8.1)	8.0 (4.2-13.6)
Mean non-HDL-C (mg/dL)	133.6 (132.8-134.4)	175.0 (173.2-176.9)	233.4 (221.9-244.9)
Prevalence of chronic conditions, % (95% CI)			
Central adiposity	50.7 (49.5-51.8)	69.8 (67.6-72.0)	70.3 (61.7-77.9)
Diabetes	10.1 (9.6-10.7)	21.8 (19.8-23.8)	32.7 (25.9-40.0)
CKD	11.9 (11.3-12.5)	17.4 (15.8-19.2)	21.6 (15.9-28.2)
MASLD[a]	30.6 (29.7-31.5)	68.6 (66.0-71.1)	67.0 (59.5-73.9)
History of ASCVD	6.9 (6.4-7.5)	10.6 (9.3-12.1)	10.6 (6.3-16.3)
Multiorgan disease[b]	11.5 (10.8-12.1)	25.9 (23.8-28.2)	29.3 (23.7-35.5)
Prevalence ratio (95% CI)[c]			
Central adiposity	1.0 (ref)	1.39 (1.34-1.44)	1.57 (1.41-1.75)
Diabetes	1.0 (ref)	2.01 (1.83-2.22)	3.45 (2.79-4.27)
CKD	1.0 (ref)	1.40 (1.28-1.55)	2.19 (1.63-2.94)
MASLD	1.0 (ref)	2.13 (2.04-2.23)	2.12 (1.89-2.36)
History of ASCVD	1.0 (ref)	1.42 (1.25-1.62)	1.88 (1.19-2.98)
Multiorgan disease	1.0 (ref)	2.12 (1.94-2.31)	2.95 (2.43-3.59)

[a]For participants without heavy drinking (>14 drinks per week for men, >7 drinks per week for women) or hepatitis B or C, MASLD is defined by NAFLD score ≥−0.64 and 1 of: overweight; diabetes; or ≥2 metabolic abnormalities (central adiposity (waist circumference >94 cm in men and >80 cm in women); high triglycerides (≥150 mg/dL or self-reported lipid-lowering medication use); low HDL-C (<40 mg/dL in men and <50 mg/dL in women); hypertension (systolic blood pressure ≥130 mm Hg or diastolic ≥85 mm Hg or self-reported antihypertensive medication use); prediabetes (fasting plasma glucose ≥100 mg/dL, glycohemoglobin ≥5.7%); insulin resistance [fasting plasma insulin × fasting plasma glucose/405 ≥2.5]). [b]Multi-organ disease is defined as ≥3 chronic conditions including: 1) central adiposity; 2) diabetes; 3) chronic kidney disease; 4) MASLD; and 5) history of ASCVD. [c]Prevalence ratios are adjusted for age, gender, and race/ethnicity.

ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; HDL-C = high density lipoprotein cholesterol; MASLD = metabolic dysfunction-associated steatotic liver disease; N/A = results are not reliable due to small sample size; NAFLD = nonalcoholic fatty liver disease.

and severe hypertriglyceridemia vs triglycerides <200 mg/dL (Table 1). Among U.S. adults with severe hypertriglyceridemia, 70.3% had central obesity, 32.7% had diabetes, 21.6% had CKD, 67.0% had MASLD, and 10.6% had ASCVD. Among U.S. adults with serum triglycerides <200 mg/dL, moderate hypertriglyceridemia, and severe hypertriglyceridemia, 11.5%, 25.9%, and 29.3% had a multiorgan disease, respectively. After adjustment for age, race/ethnicity, and gender, and compared to U.S. adults with serum triglycerides <200 mg/dL, the prevalence ratio for multiorgan disease was 2.12 (95% CI: 1.94-2.31) and 2.95 (95% CI: 2.43-3.59) for those with moderate and severe hypertriglyceridemia, respectively.

In the current analysis, chronic conditions and multiorgan disease were more common at higher triglyceride levels. High triglyceride levels and the cholesterol content of triglycerides have emerged as causal contributors to ASCVD risk.[1,4] Moreover, evidence from Mendelian randomization studies suggests that therapies aimed at reducing certain pathways that modulate circulating triglycerides might reduce the risk for MASLD development and progression.[5]

Apolipoprotein C-III inhibitors, ANGPTL3 and 4 inhibitors, and FGF21 analogs may have cardiometabolic benefits beyond lowering triglycerides.[2] Some distinct differences in these triglyceride-lowering pathways include improvements in glycemia with ANGPTL4 inhibitors and reductions in hepatic fat with FGF21 analogs.[1,2] Given the high prevalence of chronic conditions and multiorgan disease among U.S. adults with hypertriglyceridemia identified in the current study, clinical trials with novel selective pathway inhibitors of triglyceride metabolism may benefit from directing enrollment toward those with specific comorbidities that align with the pathway being targeted.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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