Arterial Stiffness and Plasma Lipids: Triglycerides are a Strong and Independent Predictor of Peripheral Artery Stiffness in Women

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Structured Abstract

Objectives: This study was designed to study whether standard measurements of plasma lipids and apolipoproteins will predict compliance measurements in the thigh and calf of men and women.

Background: An increase in arterial stiffness or compliance is a known risk factor for the presence of atherosclerosis. The relationship between arterial stiffness and measurements of plasma lipoproteins and plasma apoliproteins has not been determined in detail.

Methods: A cohort of 337 men and women were selected for this study. The cohort was divided equally between men and women and was selected to represent a wide range of cardiovascular risk as determined by Framingham Risk Assessment. None of the subjects have had a clinical diagnosis of any form of atherosclerotic disease.

Results: Fasting plasma triglyceride levels were the most important predictor of compliance results in women. To a lesser extent, body weight, plasma Apo_B, and content of ApoCIII in low density lipoprotein particles were predictive of compliance. In contrast, the only significant predictor of compliance in men was body weight. Non of the standard lipid and apolipoprotein measurements were predictive of compliance results in men.

Conclusions: The major predictor for arterial stiffness in women is fasting plasma triglyceride levels. These results are similar to previous studies that have identified fasting triglyceride levels as being a more important risk factor in women.

Condensed Abstract

A cohort of 337 men and women of varying cardiovascular risk were studied to determine the predicitive value of plasma lipid and apolipoprotein measurements on arterial stiffness. Fasting plasma triglyceride levels were the most significant predictor of stiffness in women. In contrast none of the standard lipid measurements were predictive of arterial stiffness in men. These results suggest that triglycerides are a more important risk factor in women.

Abbreviations:

Clinically evident peripheral vascular disease (PVD) is known to be associated with generalized arteriosclerosis and predicts acute arterial events in the coronary and cerebral circulation(1 ,2,3). Cigarette smoking (4) and diabetes (5-7) are particularly strong predictors of PVD but high blood pressure(8-10) and plasma cholesterol as well as low HDL cholesterol are also documented risk factors(8). Diagnosis of PVD is usually made after obstructive lesions are present causing ischemic symptoms or a reduction in the ratio of blood pressure in the lower leg compared to that in the arm. Abnormalities of endothelial function are thought to precede the development of significant accumulations of the inflammatory cells and collagen that characterize arteriosclerosis.(11-14) Abnormal endothelial function due to impaired release of nitric oxide (NO) is reflected in abnormal responses to stimuli such as acetylcholine infusion or flow enhancement following hypoxic dilation of resistance vessels. Recently, chronic tone in the media of muscular arteries has also been shown to be dependent on NO and therefore the stiffness or compliance of these arteries is recognized to be a function of this endothelial function(15-16).

There are few studies of peripheral vascular compliance in apparently health individuals without symptoms or signs of vascular disease. Using a recently developed device which measures the compliance of the arterial system in the thigh and calf of humans (17-19), we have studied individuals with a spectrum of risk factors as defined by NCEP (ATPIII) criteria but without peripheral, cerebral or coronary artery disease, The relationships between arterial compliance and fasting blood lipids (and lipoprotein components) appear to confirm certain of those noted in earlier studies of baseline lipid

measures and the incidence of clinical events. Of particular interest are the differences in the strength of these relationships in men versus women.

Methods:

The patient cohort- The protocol for the study and the recruitment process were approved by the Institutional Review boards of each of the sites involved in the study. The intent of this study was to relate potential lipoprotein predictors in men and women to measures of the early phase of vascular disease manifest by vascular compliance abnormalities. Evidence of vascular disease in any arterial distribution or the use of lipid lowering drugs was cause for exclusion. We defined populations of equal numbers of men and women with age ranges of 45 to 69 years and 55 to 79 years respectively. Using NCEP (ATPIII) criteria (20), cells defined by three risk groups of approximately equal numbers were recruited. All met age criteria for having this major risk factor. The cells contained those with predicted 10 year risk of coronary death or myocardial infarction of: (1) <10%, (2) 10 to <20% or (3) ≥20% (21). Patients with Type II Diabetes Mellitus were included if they met the other criteria. Completion of a treadmill exercise test without ECG or ultrasound evidence of CAD was required (see below). No criteria for triglycerides or other risk factors were applied in the initial exclusion criteria..

A total of 164 women and 173 men were initially enrolled in this study. The original group included subjects with known coronary disease and subjects on lipid lowering medications who were excluded from the present analysis. An additional 7 subjects were excluded because of abnormalities on the electrocardiogram or abnormalities of wall

motion on the echocardiogram during the treadmill stress test. After these exclusions there were 111 women and 112 men remaining for data analysis.

Laboratory Analysis

At the first visit, Framingham Risk and eligibility for the study was determined by history, physical examination, and blood analyses. Blood tests included ALT, AST, TSH, BUN, creatinine, complete blood count, hsCRP. Fasting plasma was available for lipid/apolipoprotein determinations. The Emory Lipid Research Laboratory, a participant in the Center for Disease Control (CDC)/NHLBI Lipid Standardization Program, performed all plasma lipid analyses from freshly isolated EDTA plasma on the Beckman CX7 chemistry autoanalyzer. Total triglycerides and cholesterol were determined by enzymatic methods (Beckman Coulter Diagnostics, Fullerton, CA). Direct high-density lipoprotein (HDL) and direct low-density (LDL) cholesterol were obtained using homogeneous assays (Equal Diagnostics, Exton, PA).Plasma concentrations of apo-B and Lp(a) were determined by immunoturbidometric method (DiaSorin, Stillwater, MN). ApoC-III in whole plasma and isolated llipoprotein fraction was determined by immunoturbidometric method (Wako Chemicals) Triglyceride-rich lipoproteins (TRL) were isolated by preparative ultracentrifugation at density 1.020 g/ml using the 50.4Ti rotor (Beckman Coulter, fullerton, CA). The supernate is quantitatively collected by aspiration into vomumetric tubes for the determination of lipid and apolipoprotein levels.

The high sensitivity CRP assays were performed on a Beckman LX-20 analyzer (Beckman Coulter, Brea, California) using an "Ultra CRP" assay manufactured by Polymadco, Inc. (Cortlandt Manor, NY). Plasma homocysteine (Hcy) is determined by

Treadmill exercise testing

All subjects had screening for coronary disease using a standard treadmill exercise test using the Bruce Protocol and Echocardiography. A resting electrocardiogram and echocardiogram was first obtained. Transthoracic echocardiography was performed according to the guidelines of the American Society of Echocardiography(22) with a Hewlett-Packard Sonos 1000 or equivalent machine. A standard Bruce protocol was used and the exercise was stopped when the predicted 85% maximal heart rate was obtained. Echocardiography was done within 60 secvonds of stopping the treadmill. Follow up electrocardiograms were also done until the pulse rate had returned to baseline.All subjects with significant ST changes on the electrocardiogram(>1mm of ST depression) or segmental wall motion abnormalities on the echocardiogram were excluded from the analysis. For consistency the exercise tests from all centers were read at Columbia Medical Center.

Measurement of Arterial Compliance

Arterial compliance was assessed on three visits within a 1 month period. On the third visit duplicate measurements were taken 20 minutes apart. Peripheral arterial compliance was measured with a fully automated computer- controlled air plethysmograph designed for clinical use (Vasogram ™). The device consists of an air pump, calibration chamber, and high-resolution pressure transducer. The interface with the patient is via standard blood pressure cuffs. The cuffs are placed at the thigh and calf and measurements at these levels are taken independently.

For this study, cuff pressures were inflated to 30 mmHg below diastolic pressure and segmental limb volume change as a function of time during the cardiac cycle was recorded. The cuff pressure was then increased in 10 mmHg increments and the process repeated until the peak cardiac cycle dependent volume change was reached. At each cuff pressure, during early diastole, a calibration volume of 0.65 mL was rapidly introduced to calibrate the system. To determine the local arterial compliance, the maximum volume change (MaxV) was divided by the subject's brachial pulse pressure. This value was normalized to a 50mmHg pulse pressure (MaxV50) to facilitate comparison among patients. Higher scores for MaxV50 correspond to more compliant arteries.

Based on the data used for analysis, the correlation between paired measures of Calf and Thigh MaxV50 obtained during the first and second visit were 0.77, $p < 0.0001$ and 0.76, $p < 0.0001$ respectively. The correlation between the 2 vasograms performed on visit 3 were 0.68 ($p < 0.0001$) for the replicated calf Max V50 and 0.91 ($p < 0.0001$) for the replicated Thigh Max V50. To calculate the mean Calf/Thigh Max V50 we used measurements from visits 1 and 2, and the first of visit 3 measurements

Statistical Analysis

Simple descriptive statistics were used to describe the characteristics of the study population. ANOVA was used to compare study population characteristics across risk groups within gender. The Pearson correlation coefficient and scatterplots overlayed with regression lines and 95% prediction confidence intervals were used to evaluate the

relation between anthropometric and lipid variables and mean arterial compliance. Additional sex-specific multivariable general linear models of mean arterial compliance were used to describe the relation between measures of arterial compliance and CHD risk group after adjusting for important covariates. The sex-specific multivariable general linear models were created using stepwise variable selection based on a variable set that included all variables in Table 2 as well as age, BMI, LPA, and HCY. All statistical analyses were performed using SAS Version 8.02 (Cary, NC).

Results:

Table 1 lists clinical characteristics of the subjects separated on the basis of gender. The women were slightly older by design to partially compensate for the fact that women have clinical arteriosclerosis at more advanced age than men. The women still had a lower average Framingham risk than men. The men were larger than the women.

Table 2 shows the values for standard lipid parameters in women and men. On average women had significantly higher levels of total cholesterol and HDL-cholesterol as expected..

Table 3 shows the additional values for the women and men. Women had higher hs-CRP than men and slightly lower ratio of apo-CIII per particle of low density lipoproteins that contain LDL,VLDL, and IDL (apo-CIII/B ratio). Levels of Apo-Ai, apo-B, homocysteine, and LDL size were not significantly different between men and women.

Figure 1 shows scatter plot of MaxV50 versus weight in women and men. There is a significant increase in calf compliance as weight increases. Women had a r=.21, p=0.03

and men had a r=0.45, p<0.001. There is less increase in thigh compliance as weight increases in both genders. This relationship is small in males (r=0.23 ,P=0.02) and disappears in females.

Figure 2 shows the relationship between compliance (MaxV50) and triglycerides in men and women. In women there is a significant decrease in compliance at both the calf (r=-0.30 , p=0.001) and thigh (r= -0.39 , p< 0.001) as triglycerides increase. In men there was no significant relationship between triglyceride levels and compliance.

Table 4 shows the relationship of various lipid parameters and the MaxV50 in univariate analysis. In women the MaxV50 correlated inversely with apo-B and non-HDL cholesterol but most strongly with the triglyceride concentration (r=-0.39 , p<.001). In men, none of the traditional lipid parameters was significantly related to compliance. However, hs-CRP was inversely related to compliance at the calf but not the thigh in men. Apo AI, HDL-cholesterol, apo-CIII, and the ratio of apo-CIII/apo-B in triglyceride rich lipoproteins were not significantaly correlated with compliance in either sex in univariate analysis.

Table 5 shows results of multivariate analysis of the anthropometric and lipid parameters as predictors of compliance. In males only size parameters were correlated with compliance individually (weight and BMI). With weight as the minimal model there was a slight increase in predictive value by adding Apo-CIII levels at the calf but not the thigh. No other parameters added predictive values in the males. In females the minimal

model for calf based on demographic and traditional lipid parameters included weight and triglyceride levels. With this model levels of Apo-B, apo-CIII/apo-B in triglyceride rich particles, and homocysteine added predictive values. This increased the R^2 value from 0.16 to 0.31 at the calf. At the thigh only apo-CIII/apo-B ratio added predictive value to the minimal model, which included only triglycerides. It was interesting that the ratio of CIII/B was significant only in the presence of triglycerides and not alone. The non-HDL cholesterol did not add to predictive value when triglycerides were considered.

Discussion:

Reduced compliance assessed by ultrasound techniques, pulse velocity and pulse wave analysis correlates with measures of atherosclerosis (23-29). The method of measuring compliance at the thigh and calf used in this publication has been shown to predict the extent of coronary artery disease measured by angiography (18) and the wall area of the abdominal aorta as assessed by magnetic resonance imaging (19) . In our studies, the thigh and calf Max50 was found to have a correlation coefficient of ___ for thigh and ___ for calf with the Framingham risk calculations using classical risk factors (21). The work described in this publication was done to determine if patients with a range of classical risk factors but without any clinical evidence of vascular disease would show relationships between lipoprotein parameters and the stiffness of thigh or calf arteries as measured by this air plethysmographic device. The study designed allowed comparison of cohorts of women and men of equivalent size and comparable risk as calculated by the Framingham risk functions.

The most striking finding in this study was the very strong and independent relationship between fasting triglyceride concentrations and reduced compliance in the arteries of the thigh and the calf in women but not in men. This relationship in women appears to be confirmed by significant correlations of the MaxV50 in the thigh and calf with non-HDL cholesterol and with total plasma apo-B. Plasma apo-CIII, another indicator of increased triglyceride rich lipoproteins also correlated with decreased compliance in the thigh in women. Other studies have reported similar findings with elevation of triglycerides providing stronger risk prediction for vascular disease in women than in men. This has been suggested in meta-analysis of clinical trials (30), the Framingham Heart Study (31), the PROCAM study in Europe (32) and the Evans County Study in Georgia (33). The weak correlation between HDL cholesterol or LDL size was surprising since these tend to be inversely related to triglyceride concentrations. This may be due to the small numbers of subjects in this study compared to the community based data sets which have defined these relationships. The unexpected positive but weak correlation ($p = 0.03$) of homocysteine and compliance in the calf of women may not be reproducible for similar reasons.

In devising a model for multivariate analysis, it was necessary to consider body weight and obesity. The strong relationship between the Vmax50 and body weight in men is not unexpected since the air plethysmograph is designed to measure the change in volume produced by each pulse wave within the arterial tree confined by the surrounding cuff. On average, larger men have larger arteries and hearts and therefore the absolute value of the pulse volume would be larger. However, the BMI was found to be much less strongly correlated with compliance than body weight. Weight is a function of lean body mass and

body fat. Artery size correlates with the former much more strongly than the latter. Since body fat, probably acquired after growth of body structures, is known to produce risk factors for vascular disease, an increasing BMI (primarily reflecting body fat in men of equal height) would be expected to reduce the Vmax 50. Since women have a larger percentage of body fat, this negative influence may essentially neutralize the positive effect of body size on the Vmax50. As a result of these relationships, it was found necessary to place body weight as an important component of the model in the multivariate analysis for men. For women weight had less influence in the calf and none in the thigh.

The increased prevalence and incidence of peripheral vascular disease in diabetes and the common occurrence of elevated triglycerides in this metabolic disorder raised the question of whether the relationship between triglycerides and reduced compliance might be attributable to the inclusion of diabetics in this cohort. On exclusion of the __ women with diabetes, there was no significant reduction in the correlation of the Vmax50 in either thigh or calf with triglyceride concentrations (data not shown). The absolute values of the Vmax 50 in the calf were higher in the diabetic women than in those without diabetes. This remains unexplained but may be related to the selection of diabetics with fewer risk factors since this diagnosis and being in the age range of 55 to 79 years was sufficient to include them into the highest risk group as a CAD equivalent syndrome. Another potential confounder was body weight. Increasing obesity is well known to associate with higher plasma triglyceride concentrations. On adjustment for either body weight or BMI, the correlation with compliance remained strongly related to

the triglyceride concentration in women. In the men a possible decrease in compliance related to triglycerides may have been confounded by the increase in compliance associated with increased weight that was much more evident in men than women.

On application of the multivariate model, the apo-CIII per particle composition (apo-CIII/apo-B ratio) of the triglyceride rich lipopoproteins added significant predictive power to total plasma triglyceride concentration in women for reduced compliance in both thigh and calf. Enrichment of apo-CIII in apo-B containing lipoproteins has been found to be a risk factor for vascular disease in cohorts of patients in clinical trials whether treated with placebo or cholesterol lowering drugs(34-36). This is believed to be a marker of circulating remnants of the triglycerides rich lipoproteins after partial hydrolysis of the lipids by lipoprotein lipase. In women, apo-B also correlated with reduced thigh Vmax50 in the multivariate model but is no longer significant when compliance is measured in the calf. Another inconsistent finding from the multivariate analysis was the positive relationship between homocysteine and compliance only in the calf and only in women.

By choosing populations of healthy middle aged men and women with comparable cardiovascular risk by classical risk factor analysis, we have completed a comparative study for effects of additional lipoprotein factors on measures of vascular compliance in the two genders. The striking finding was the strong and independent impact of triglyceride rich lipoproteins in women but not in men. The data is consistant in that

arteries of both thigh and calf illustrate this selective effect. Other measures consistent with remnants of VLDL are also correlated with this vascular measure only in women.

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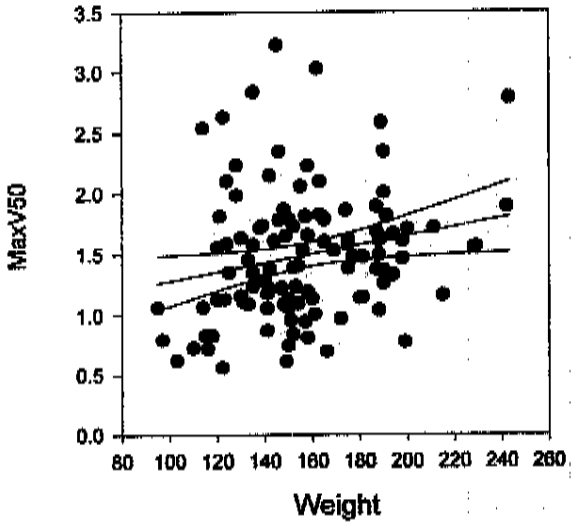
Figure Legends:

Figure 1. shows scatter plots of compliance measurements (MaxV50) in the thigh and calf versus weight in pounds. The upper 2 panels are for women and the lower 2 panels are for men. Standard regression lines and 95% confidence limits are shown.

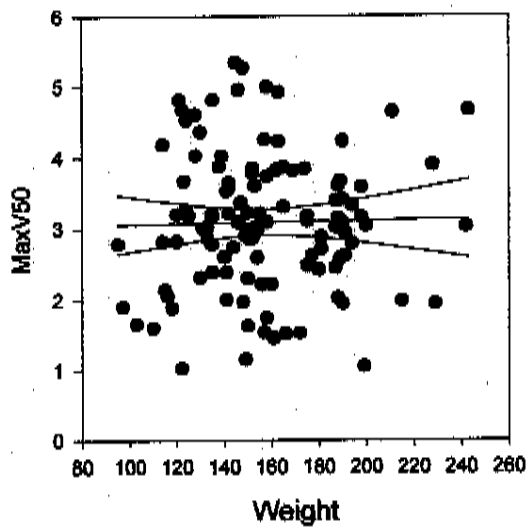
Figure 2 shows scatter plots of compliance measurements (MaxV50) in the thigh and calf versus fasting triglyceride levels (mg/dl). The upper 2 panels are for women and the lower 2 panels are for men.. . Standard regression lines and 95% confidence limits are shown

Figure1:

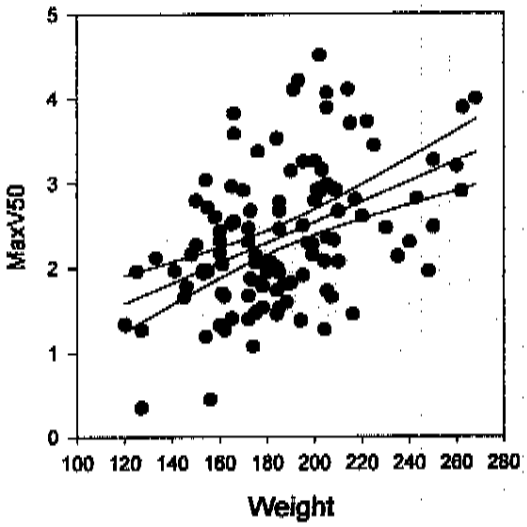
Mean Calf MaxV50 vs Weight
Women



Mean Thigh MaxV50 vs Weight
Women



Mean Calf MaxV50 vs Weight
Men



Mean Thigh MaxV50 vs Weight
Men

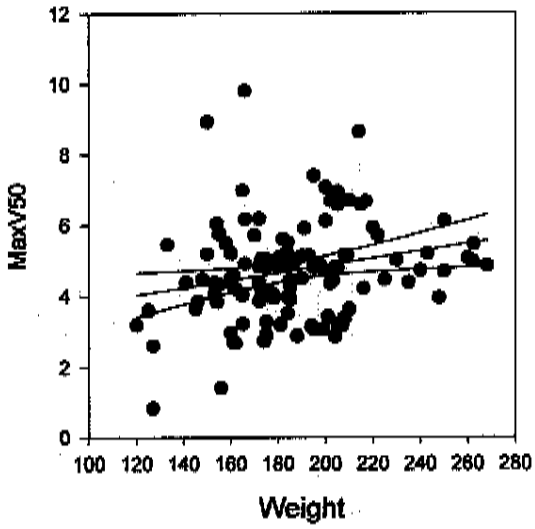
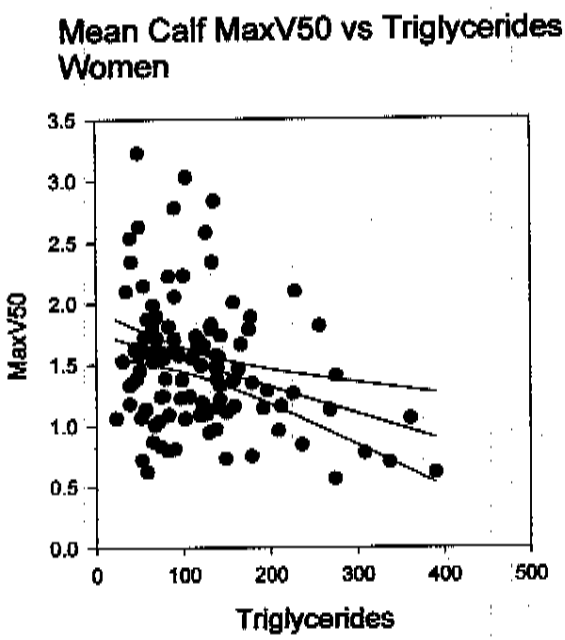


Figure2:


Mean Calf MaxV50 vs Triglycerides
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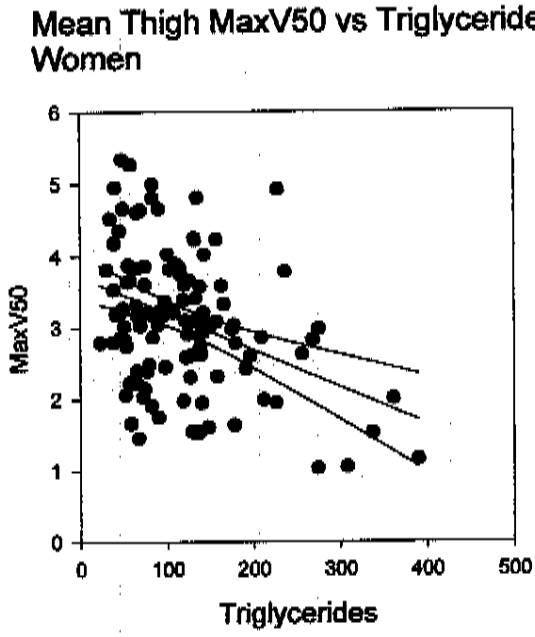
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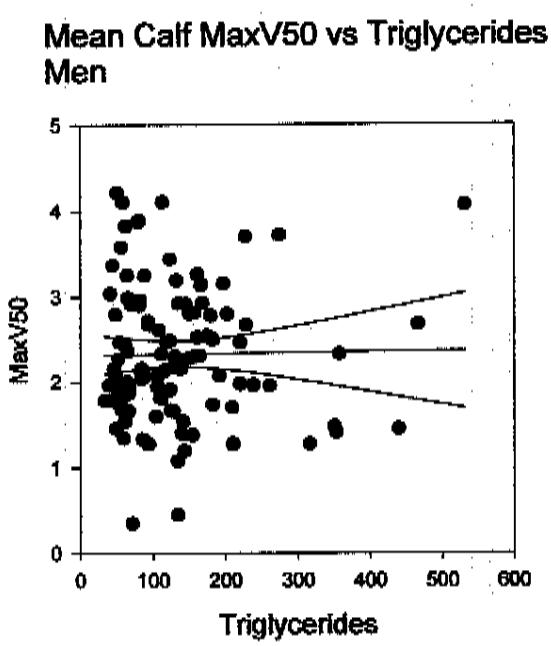
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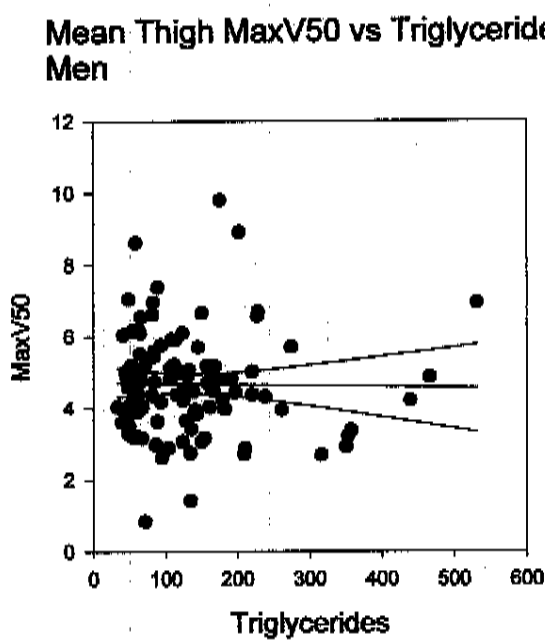
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Table 1

Clinical Characteristics of Subjects by Gender

Gender	Age	Systolic BP	Diastolic BP	Weight	BMI	Framingham Risk
Females	59.7 ± 8.9	134.8 ± 20.8	74.7 ± 11.5	157.2 ± 30.5	27.3 ± 4.8	9.6 ± 6.7
Males	53.7 ± 9.0	128.9 ± 16.8	76.3 ± 10.2	186.3 ± 31.1	26.9 ± 4.2	12.9 ± 8.8
Gender Comparison (P-value)	<0.001	0.02	0.27	<0.001	0.46	0.002

Table 1 shows results for average age, blood pressure, weight, BMI, and Framingham risk calculations for the men and women.

Table 2

Traditional Lipid Analysis of Subjects by Gender

Subject Gender	Total Chol (mg/dL)	HDL (mg/dL)	LDL (mg/dL)	Non HDL	TG (mg/dL)
Females	203.9 ± 34.1	52.6 ± 14.2	131.3 ± 32.4	151.4 ± 36.6	119.2 ± 72.9
Males	192.3 ± 36.2	43.2 ± 11.0	129.3 ± 34.7	149.1 ± 36.3	131.4 ± 92.8
Gender Comparison (P-value)	0.02	<0.001	0.66	0.65	0.28

Table 2 shows the average results of traditional lipid analysis for the women and men in the study.

Table 3

Additional Lipid Analysis of Subjects by Gender

Subject Gender	CRP	ApoCIII	C3_B	ApoB	ApoAI	LPA	HCY	LDL Size
Females	4.3 ± 5.4	22.3 ± 6.0	0.25 ± 0.16	131.3 ± 20.0	141.0 ± 31.5	29.2 ± 30.3	8.9 ± 3.7	25.3 ± 0.8
Males	2.0 ± 2.1	21.0 ± 5.8	0.31 ± 0.19	127.3 ± 20.9	124.4 ± 27.8	29.8 ± 30.0	9.1 ± 2.8	25.2 ± 1.1
Gender Comparison (P-value)	<0.001	0.12	0.02	0.15	< 0.001	0.88	0.67	0.19

Table 3 shows average results of hsCRP, Apo-CIII, Apo-B, Apo-AI, Lp(a), homocysteine, and LDL size in nm for the men and women.

Table 4
Univariate Correlations with Compliance

	Variable	N	CalfMaxV50		ThighMaxV50	
			Corr	Pval	Corr	Pval
F	APOA_I	111	-0.05	0.62	-0.02	0.85
	APOB	112	-0.26	0.01	-0.28	0.003
	CHOL	112	-0.17	0.08	-0.17	0.08
	HCY	112	0.20	0.03	0.06	0.54
	HDLC	112	0.15	0.12	0.19	0.05
	HSCRP	112	0.08	0.42	0.02	0.85
	LDLC	112	-0.12	0.20	-0.07	0.48
	LPA	112	0.03	0.79	0.12	0.22
	NON_HDLC	112	-0.22	0.02	-0.23	0.02
	TG	112	-0.30	0.001	-0.39	<0.001
	WEIGHT	113	0.21	0.03	-0.01	0.86
	APOCIII	112	-0.10	0.30	-0.24	0.01
	LDL SIZE	110	0.02	0.82	0.01	0.91
	C3_B	106	-0.04	0.69	-0.05	0.61
M	APOA_I	104	-0.11	0.26	0.03	0.77
	APOB	104	0.04	0.67	-0.01	0.90
	CHOL	107	-0.04	0.69	-0.01	0.93
	HCY	106	-0.10	0.32	-0.04	0.70
	HDLC	107	-0.15	0.11	-0.004	0.97
	HSCRP	106	-0.21	0.03	-0.04	0.69
	LDLC	107	-0.12	0.21	0.001	0.99
	LPA	107	-0.12	0.21	-0.08	0.39
	NON_HDLC	107	0.01	0.94	-0.01	0.94
	TG	106	0.01	0.91	-0.02	0.83
	WEIGHT	111	0.45	<0.001	0.23	0.02
	APOCIII	106	-0.10	0.30	-0.06	0.55
	LDLSIZE	106	-0.08	0.39	0.04	0.67
	C3_B	98	0.09	0.36	0.08	0.45

Table 4 shows the results of Univariate Analysis of the Lipid Values in Women and Men. The Pearson coefficient is shown with the p-value for compliance at the thigh and calf.

Table 5

Multivariate Analysis of Compliance

	Variables in Minimal Model	R^2 of Minimal Model	Additional Significant Variables	ΔR^2	P-value
Male Calf MaxV50	Weight	0.20	ApoCIII	0.02	0.04
Female Calf MaxV50	Weight & TG	0.16	ApoB, C3_B, HCY	0.15	< 0.001
Male Thigh MaxV50	Weight & BMI	0.10	***None***		
Female Thigh MaxV50	TG	0.15	C3_B	0.06	0.009

Table 5 shows the results of multivariate analysis of the lipid values. The minimal model in women included triglycerides only at the thigh and weight and triglycerides at the calf. In men the minimal model included weight at the calf and weight and BMI at the thigh..