Turkish Journal of Endocrinology and Metabolism, (2002) 2 : 69-75 **ORIGINAL ARTICLE**

Triglyceride/HDL Cholesterol Ratio in Obese Women

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The aim of this study is to determine the relationships of triglyceride /HDL cholesterol ratio (THR) with ischemic heart disease (IHD) risk factors. 320 consecutive overweight and obese women were studied. Body mass index (BMI), waist/hip ratio (WHR), blood pressure, serum glucose, lipid profile, fasting insulin concentration, THR, and a surrogate of insulin resistance (homeostasis model assessment-HOMA) were determined. THR showed significant positive associations with total cholesterol, systolic blood pressure, WHR, BMI, insulin and HOMA. In multivariate regression analysis, total cholesterol, insulin and WHR were independent positive predictors of THR (R^2 of the model = 0.1381, $p<0.001$). Receiver-operating characteristic analysis indicated that cut-point of THR above which presence of previously defined risk factors will be increased was 4.5. Cut point of THR below which IHD risk will not be affected was 2.0. THR may be used as an indicator of the concurrent presence of IHD risk factors in obese women.

Key words: **Triglyceride/HDL cholesterol ratio, obesity, women, ischemic heart disease risk factors**

Introduction

Epidemiological studies revealed that elevated triglyceride concentrations are associated with increased ischemic heart disease (IHD) risk (1,2). This correlation may be direct or indirect. Recent data suggest that triglyceride concentrations are an independent risk factor for IHD (3-6). But adjustment for HDL cholesterol attenuated the correlation power between triglyceride concentrations and IHD risk. A meta analysis of previous population-based studies showed that an 88 mg/dl increase in plasma triglyceride levels was associated with an increased relative risk of cardiovascular disease of 30% in men and 75% in women. After adjustment for HDL cholesterol, multivariate relative risk estimates decreased to +14% in men and +37% in women (4). In Framingham Heart Study subjects with high triglyceride and low HDL cholesterol concentrations were at increased risk for IHD. The relative risk was even higher in women than in men. In this study, numerous subjects with increased triglyceride-low HDL cholesterol concentrations had normal total and LDL cholesterol levels suggesting that high triglyceride-low HDL cholesterol profile may indicate increased IHD risk even if total and LDL cholesterol levels are normal (7). Copenhagen Male Study showed that a steadily increased IHD risk was found with increasing triglyceride concentrations within each level of HDL cholesterol, when triglyceride concentrations were stratified by HDL cholesterol levels (5).

Although it is quite clear that elevated triglyceride concentrations are IHD risk factor regardless of HDL cholesterol concentrations, these findings suggest that high triglyceride-low HDL cholesterol lipid profile is a potent risk factor for cardiovascular disease regardless of LDL and total cholesterol levels (3,4,6). The aim of this study is to determine the validity of triglyceride /HDL cholesterol ratio

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(THR) as an indicator of the concurrent presence of CVD risk factors in obese women and to identify the relationships of THR with other well-defined risk factors for IHD.

Materials and Methods

Study population

320 consecutive overweight and obese women admitted our outpatient Obesity clinic between September 1993 and November 2000 participated in the study. All subjects had a body mass index (BMI) > 27 kg/m^2. The mean age and mean BMI of the subjects were found as 35.32 ± 9.10 years (range 19-62) and 36.24 ± 6.83 kg /m^2 (27.1-59.68) respectively. None of the subjects had previous diagnosis of IHD or signs/symptoms suggesting IHD.

Methods

A standardized clinical evaluation was performed to all subjects. This included assessment of daily eating and physical activity patterns, smoking and alcoholic drinking habits, pharmacological drug use, family history, electrocardiogram, thyroid function tests and overnight dexamethasone suppression test where necessary. A general physical examination involved the measurement of height (to the nearest cm, without shoes), weight (to the nearest 0.1 kg, without coats), waist circumference (as the minimum value between iliac crest and the lateral costal margin) and hip circumference as the maximum value over the buttocks) (8). Body mass index (BMI) was calculated as the ratio of weight (kg) divided by height (m) squared. Waist to hip ratio (WHR) was calculated as waist circumference (cm) divided by hip circumference (cm). A WHR ≥ 0.8 was chosen as a measure of central adiposity.

Systolic and diastolic blood pressures were measured on the right arm of the subject in an upright sitting position after at least 5 min rest using a mercury sphygmomanometer with appropriate cuff size. Two readings were recorded for each individual. The average of two readings was defined as the subject's blood pressure.

Blood samples were drawn between 8 am and 9 am after a 12- 14- hour overnight fast for biochemical (glucose, total and HDL cholesterol, triglyceride concentrations) determinations and basal insulin measurement. All biochemical analyses were performed using the Technicon DAX-72 auto analyzer (Tehnicon, Bayer Corporation, Tarrytown, New York, USA) in the Central Biochemistry Laboratory, Istanbul Faculty of Medicine. HDL cholesterol concentrations were measured using RA-XT autoanalyzer (Technicon, Bayer Diagnostics, Dublin) after phosphotungstic acid and magnesium chloride precipitation. Insulin concentrations were measured by RIA using commercially available kits (Diagnostic Systems laboratories, Webster, Texas, USA).

Conventional IHD risk factors were determined as follows (9-11):

Diabetes mellitus as fasting serum glucose ≥ 7.00 mmol/l; hypercholesterolemia as serum total cholesterol concentration ≥ 5.18 mmol/l; hypertension as systolic blood pressure ≥ 140 and/or diastolic blood pressure ≥ 90 mmHg or concurrent drug treatment for hypertension and hyperinsulinemia as fasting insulin concentration ≥ 13 μU/ml.

Insulin resistance was calculated by a computer derived formula (12):

HOMA (homeostasis model assessment) = insulin (μU/ml) /22.5 x $e^{-\ln \text{(fasting glucose mmol/l)}}$

Statistical Methods

Descriptive statistical results are presented in the tables as the means ± standard deviations. Since insulin and HOMA distributions significantly deviated from a normal distribution, measurements were log-transformed for analysis. However since the differences in the results were extremely small for between-groups comparisons, we presented the results using untransformed means ± standard deviations. Study subgroups were compared using Student's unpaired-t test. For comparison amongst more than two groups of variables, one way-ANOVA was used. Correlations were performed using simple and multiple linear regression analysis. Significance was taken as $p<0.05$.

Receiver-operating characteristic (ROC) analysis was used to develop THR cut-points associated with increased or decreased risk profile for IHD using previously defined four-IHD risk factor analysis (13). Four-IHD risk factor analysis comprised diabetes mellitus, hypercholesterolemia, hypertension

and hyperinsulinemia. The distribution of THR was divided into segments and the relative frequency of subjects with or without at- least one of the 4 risk factors were determined at each segment. Upper and lower cut-points were identified by calculating and comparing the likelihood ratios for the positive results, i.e. presence of at-least one of the four-IHD risk factors and negative results i.e. absence of any of the four-IHD risk factors. Upper and lower cut-points were identified as the highest likelihood ratio [sensitivity/(1-specificity)] for positive results and lowest likelihood ratio [(1-sensitivity)/specificity] for negative results.

The data of the subjects were recorded using "Dbase IV V2.0" (Borland International Inc., USA) software. All analyses were conducted by "SPSS/PC+ V 3.0" statistical software (Statistical package for Social Sciences, SPSS Inc., Chicago, Illinois, USA) (14).

Results

The mean THR of the study group was found to be 3.84 ± 2.57 (range 0.48-17.96). Mean serum triglyceride concentration was 1.82 ± 0.94 mmol/l (range 0.36-6.27) and mean HDL cholesterol concentration was 1.19 ± 0.27 mmol/l (range 0.52-2.22).

Subjects were divided into different groups according to the levels of the conventional risk factors. Triglyceride/HDL cholesterol ratio was significantly higher in hypercholesterolemic group (total cholesterol ≥ 5.18 mmol/l) than normocholesterolemics (4.35 ± 2.72 vs 3.27 ± 2.28, p<0.001); in subjects with central adiposity (WHR ≥ 0.8) than subjects with peripheral fat distribution (4.36 ± 2.78 vs 3.31 ± 2.24, p<0.001); in hyperinsulinemics (fasting insulin ≥ 13 μU/mL) than normoinsulinemics (4.34 ± 2.76 vs 3.40 ± 2.37, p=0.001). THRs were not significantly different between subjects with hypertension and normotension and between subjects with hyperglycemia and normoglycemia.

Significant correlations were observed between THR and IHD risk factors except for diastolic blood pressure, age and glucose, although the correlation coefficients were relatively weak (Table 1).

Multiple regression analysis where THR was the dependent variable and total cholesterol, glucose, insulin, HOMA, systolic blood pressure, diastolic blood pressure, WHR, BMI and age were independent variables revealed that cholesterol, insulin and WHR were significant independent predictors of THR in obese women. This multivariate regression model explained the 14% of overall variability of THR.

Table 1. Pearson's correlation coefficients (r) between triglyceride/HDL cholesterol ratio and study parameters.

	r	p
Cholesterol	0.2782	<0.001
HDL cholesterol	-0.5671	<0.001
Triglyceride	0.8984	<0.001
Systolic blood pressure	0.1232	<0.05
Diastolic blood pressure	0.0924	NS
WHR	0.1966	0.001
BMI	0.1251	<0.05
Age	0.0785	NS
Glucose	0.0485	NS
Insulin	0.2327	<0.001
HOMA	0.2307	<0.001

Simple regression analysis was used to determine correlation coefficients.

WHR: waist to hip ratio

BMI: body mass index

HOMA(homeostasis model assessment): insulin (μU/ml) /22.5 x e^{-ln} (fasting glucose mmol/l)

NS: not significant

ROC analysis indicated that the upper cut-point of THR for the presence of at-least one of the previously defined four IHD risk factors was 4.5 and lower cut-point for the absence of these risk factors was 2.0. The proportion of false positives (the proportion of those identified at-risk but are not at-risk) above the cut-point of 4.5 was 11% for 4-risk factor analysis. The proportion of false negatives (proportion of those identified not at-risk but are at-risk) below the cut-point of 2.0 was 13 % for 4-risk factor analysis. The area under curve for ROC curve of THR for 4-IHD risk factor analysis was 0.6612 (p<0.0001).

Table 2. Multiple linear regression analysis: standardized regression coefficients between triglyceride/HDL cholesterol ratio and study parameters.

Dependent variable	Independent variable	Standard coefficients	P
THR	Cholesterol	0.2428	<0.001
	Insulin	0.1814	0.001
	WHR	0.1385	0.01

Multiple R^2 0.1381, p<0.001

WHR: waist to hip ratio

Table 3. Receiver-operating characteristics (ROC) analysis for triglyceride/HDL cholesterol ratio (THR).

THR	Non-risk cumulative frequency	At risk cumulative frequency	Sensitivity	Specificity	Positive likelihood	Negative likelihood
>6.0	4	45	0.1691	0.9259	2.2838	0.8972
>5.5	5	55	0.2067	0.9074	2.2330	0.8741
>5.0	6	62	0.2330	0.8888	2.0977	0.8627
>4.5	**7**	**81**	**0.3045**	**0.8703**	**2.3490**	**0.7990**
>4.0	9	99	0.3721	0.8333	2.2330	0.7533
>3.5	12	124	0.4661	0.7777	2.0977	0.6863
>3.0	15	148	0.5563	0.7222	2.0030	0.6142
>2.5	22	173	0.6503	0.5925	1.5963	0.5899
>2.0	**31**	**212**	**0.7969**	**0.4259**	**1.3883**	**0.4766**
>1.5	40	232	0.8721	0.2529	1.1774	0.4930
>1.0	50	250	0.9398	0.0740	1.0115	0.8120
>0.5	52	256	0.96241	0.0370	0.9994	1.0150
>0	54	266				

Non-risk. Absence of previously defined 4 risk factors.

At-risk. Presence of at least one of the previously defined 4 risk factors for individual subjects

Equations:

Sensitivity= cumulative frequency at-risk/total at-risk

Specificity= 1-(total not at-risk cumulative frequency/total not at-risk)

Positive likelihood=sensitivity/(1-specifity), Negative likelihood= (1-sensitivity)/specificity

Table 4. Comparison of subjects with triglyceride/HDL cholesterol ratio (THR) <2, between 2 and 4.5 and > 4.5

Variables	THR<2 n=69	THR 2-4.5 n=167	THR>4.5 n=84
Age (years)	33.97 ± 9.51	34.90 ± 8.80	36.75 ± 9.27
BMI (kg/m^2)	32.76 ± 5.37	36.81 ± 6.56*	37.53 ± 7.41*
WHR	0.78 ± 0.06	0.80 ± 0.08	0.82 ± 0.06*
Cholesterol (mmol/l)	4.85 ± 0.77	5.35 ± 0.91*	5.70 ± 1.02*,**
Systolic BP (mm Hg)	128.7 ± 21.5	137.1 ± 23.9*	142.5 ± 28.3*
Diastolic BP (mm Hg)	84.2 ± 15.1	88.4 ±13.5*	91.2 ± 17.4*
Glucose (mmol/l)	5.41 ± 0.72	5.47 ± 0.71	5.58 ± 0.79
Insulin (mU/ml)	10.8 ± 9.2	15.5 ± 12.8*	22.5 ± 19.3*,**
HOMA	2.70 ± 2.39	3.89 ± 3.54*	5.81 ± 5.17*,**

Values are mean ± standard deviation.

Comparisons amongst three groups were determined by ANOVA and subsequently Student's unpaired t-test was used to determine statistical significance between two-groups.

*significantly different from subjects with THR<2

** significantly different from subjects with THR 2-4.5

BMI: body mass index

WHR: waist to hip ratio

HOMA(homeostasis model assessment): insulin (mU/ml) /22.5 x $e^{-\ln \text{(fasting glucose mmol/l)}}$

Table 4 indicated the comparison of risk factors for women with THR <2, between 2-4.5 and above 4.5. Women with THR > 4.5 and between 2-4.5 had elevated risk factors compared with women THR <2 except for serum glucose concentrations.

Discussion

Our data indicates that THR is associated with a number of well-known IHD risk factors. Triglyceride/HDL cholesterol ratio may be used to estimate the IHD risk factor status in obese women. Values above a selected cut-off point (4.5)

may indicate the concurrent presence of at-least one of the previously defined 4-IHD risk factors enclosing diabetes mellitus, hypertension, hyper-cholesterolemia and hyperinsulinemia which are commonly linked to insulin resistance syndrome (9,10).

Increased IHD risk revealed by increased THR may reflect an altered metabolic state. It has been suggested that elevated triglyceride and decreased HDL cholesterol concentrations are all secondary to resistance to insulin-stimulated glucose uptake (15). Lamarche et al. (16) investigated three groups of male subjects (normal triglyceride with low HDL cholesterol concentrations, high triglyceride with normal HDL cholesterol concentrations and high triglyceride with low HDL cholesterol concentrations). During an oral glucose tolerance test, only men with high triglyceride low HDL cholesterol concentrations-i. e., men with the highest THR- showed fasting hyperinsulinemia and higher plasma insulin levels compared with normolipemic subjects. Another study by Laws & Reaven (15) included 18 non-diabetic, moderately overweight sedentary men aged 25-50 years. According to their steady-state plasma glucose levels, men in highest tertile had significantly higher fasting and post oral glucose challenge insulin concentrations, higher fasting triglyceride and lower fasting HDL cholesterol concentrations-indicating a higher THR than men in the lowest and middle tertile. They concluded that insulin resistance has an effect on the modulation of plasma insulin, triglyceride and HDL cholesterol concentrations. Haffner et al.(17) evaluated the 195 subjects converted to type 2 diabetes during the 7-year follow-up of San Antonio Heart Study. Insulin resistance was determined by HOMA IR and only the converters who were insulin resistant had higher blood pressure and triglyceride levels and lower HDL-cholesterol levels-pointing towards a higher THR- than non-converters. Relationship of THR with IHD risk factors may reflect the clustering of metabolic abnormalities associated with the complex metabolic state responsible for insulin resistance in obese women (9). In our study, THR correlated positively with a number of parameters including surrogates of insulin resistance i.e., fasting insulin and HOMA as indicated by others (16). In multiple regression analysis, total cholesterol, fasting insulin and WHR were significant and independent predictors of THR. Lack of an independent correlation between THR and HOMA in multiple regression analysis can not exclude the associations of THR with more direct measures of insulin sensitivity. However assessment of insulin sensitivity by insulin clamp or other techniques is very difficult to achieve in large series. It therefore might be postulated that the association between elevated THR and increased IHD risk is partly mediated by insulin resistance/hyperinsulinemia. Furthermore, central fat distribution have a significant and fasting hyperinsulinemia-independent effect on THR. Our data points towards that in obese women, a THR above an upper cut-point might be the another expression of an insulin resistant state. A recent review also indicated that an elevation of very low density lipoprotein triglyceride and a reduction in high density lipoprotein cholesterol is characteristic dyslipidemia of the insulin resistance phenotype (18). In addition, in type 2 diabetic patients, progression of microalbuminuria -a risk factor for cardiovascular disease- was correlated independently and significantly with THR (19).

The variability of THR was explained by serum cholesterol to a slightly greater extent than WHR and fasting hyperinsulinemia. Total cholesterol concentrations may reflect VLDL cholesterol concentrations and more prominent association between total cholesterol and THR may be explained by increased VLDL cholesterol associated with increased triglyceride concentrations. This point should be addressed in future studies.

Predictive power of the univariate correlations observed in this study seems to be relatively low. Overall variability of THR explained by multivariate regression model was 13%. None of the women in this study had previous diagnosis of IHD or signs/symptoms indicating IHD. These findings suggest that the associations between THR and total cholesterol, insulin and WHR may exist before clinical manifestations of IHD have developed in obese women. Previous epidemiological studies investigating the relationships of various parameters with cardiovascular risk factors in relatively healthy subjects showed that the correlation coefficients between these variables were relatively weak and variances explained by multivariate model were within 1-12 % (20). It is possible that a similar study including larger number of subjects would identify some of the previously non-significant

variables as significant. Alternatively other unidentified genetic/metabolic factors or factors not included in this analysis might explain the residual variability.

Our results indicate that women with THR between 2.0-4.5 are at moderate IHD risk. Women in this category had significantly higher BMI, cholesterol, insulin, HOMA, systolic and diastolic blood pressure than women with THR <2.0 (Table 4). In addition women with THR >4.5 had higher BMI, WHR, cholesterol, systolic and diastolic blood pressure, insulin and HOMA than women in the lowest category, but only cholesterol, insulin and HOMA measurements were significantly higher than women with THR between 2-4.5.

The major limitation of our study is that the our study group is confined merely to obese women. It is suggested that women are particularly sensitive to the direct/ indirect atherogenic effects of serum triglyceride levels (4,7). Triglyceride values are significant to predict cardiovascular events with a relative risk of 1.37 for women compared with 1.14 for men (4). In the secondary prevention setting, most of the adverse effects of triglyceride on cardiovascular events after coronary artery bypass grafting were observed in women (21). These observations could be explained by the gender differences in insulin resistance and associated metabolic abnormalities (21,22). Therefore caution is required when extrapolating the results of the obese women to non-obese subjects and men in general. In addition whether a THR above the selected high cut-off value is an accurate indicator for future cardiovascular events cannot be determined on the basis of current study results.

Finally it is concluded that THR may be used as an indicator of the concurrent presence of IHD risk factors which are predominantly associated with insulin resistance in obese women. Whether THR can reflect the risk factor status in general population including men and non-obese subjects or values above a selected cut-point are satisfactory markers for future cardiovascular events should be clarified by further studies.

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