ORIGINAL ARTICLE

Seasonal Variability of Serum Lipids in Adults: Tehran Lipid and Glucose Study

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Summary

There are contradictory results regarding the pattern of seasonal variation of serum lipids. The aim of this study was to compare serum lipid levels in different seasons in participants of the Tehran Lipid and Glucose Study. This was a cross-sectional study among 2890 men and 4004 women 20-64 years old from the participants of Tehran Lipid and Glucose Study (TLGS) between 1999 and 2001. Mean values of serum lipids in different seasons were compared with Analysis of Covariance (ANCOVA) after adjustment for age, physical activity level, smoking, BMI and Waist-to-hip ratio. In men, there was a significant trend for change in the values of cholesterol, LDL-C and HDL-C in different seasons, with higher cholesterol and LDL-C values in winter than in summer ($P<0.05$). In women, only the mean values of triglycerides were significantly different between different seasons with values lower in winter than in summer. There was a 26.2% relative increase in the prevalence of hypercholesterolemia (≥ 240 mg/dl) in winter than in summer in men. The corresponding increase in the prevalence of high LDL-C (≥ 160 mg/dl) was 26.7% and 24.9% in men and women, respectively ($P<0.05$). The prevalence of high triglycerides (≥ 200mg/dl) in women significantly decreased (23.8%) in winter relative to summer ($P<0.001$). This study showed that there is seasonal variability in serum lipid values and this variability is greater in men than women. The increase in the prevalence of high LDL in winter in both sexes must be considered in population screening and in the follow-up of hyperlipidemic patients.

Key Words: Seasonal variation, Lipids, Adults

Introduction

During the past 60 years several longitudinal studies have reported the seasonal variation of serum lipids, but the mechanism of changes in the metabolism of lipids in relation to seasonal variables is not fully understood yet and there are considerable ambiguities about the consistency and validity of these findings [1-6].

Many studies suggest that cholesterol levels are higher in the fall and winter than spring and summer[1-4]. A longitudinal study of plasma lipid levels reported a mean seasonal change in plasma total cholesterol concentration of 7.4 mg/dl [5]. Some studies have suggested that low-density lipoprotein (LDL) appears to increase in the winter, as does HDL[4]. Although triglyceride may vary seasonally and may be lower in the winter than in summer, the variation in triglyceride does not appear to be related to the cholesterol variations[4]. These seasonal variations may result in large difference of the frequency of patients being labeled as hypercholesterolemic, hypertriglyceridemic or having high LDL at different times of the year[5]. Seasonal variation of serum lipids biases clinicians toward the treatment of dyslipidemia in different seasons, yet no standard guideline through it has been justified[5]. Since there is no consensus on the seasonal variation of serum lipids and its mechanisms and also this topic has not yet been studied in Iran, the present study was designed to evaluate that issue among healthy participants of the first phase of the Tehran Lipid and Glucose Study.

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Materials and Methods

This is a cross-sectional study in which the data of the first phase of Tehran Lipid and Glucose Study (TLGS) are used. Details of rationale and design of the TLGS have been published elsewhere [7]. A cluster random sampling technique was used to recruit 15005 people, aged over three years from district 13 of Tehran, the capital of the Islamic Republic of Iran. Using exclusion criteria, including ages over 64 and below 20 years, known cases of diabetes, Users of anti-hyperlipidemic drugs and those with chronic and debilitating disease, the database of 6894 (2890 men and 4004 women) participants in the first cross-sectional phase of the TLGS from February 1999 to August 2001, were used in this study.

All of the participants were examined on the morning after 12-14 hours of fasting and informed written consent obtained from them. Trained physicians according to a uniform protocol studied the participants. Demographic and lifestyle information (smoking and physical activity) as well as history of chronic diseases and anti-hyperlipidemic drug usage obtained by the use of a standard and validated questionnaire. Based on this questionnaire those who exercised or had vigorous physical activity at least three times a week were considered to be active and those who smoked currently were called smokers.

After completion of clinical examination including blood pressure, weight, height, waist and hip circumference measurement by a single trained physician, blood samples obtained for the measurement of serum lipids including total cholesterol (TC), Triglyceride (TG), LDL-cholesterol (LDL-C) and HDL-cholesterol (HDL-C). The samples were analyzed on the day of collection at the TLGS research laboratory[7]. The analyses of samples were performed using Selectra 2 auto-analyzer (Vital Scientific, Spankeren, Netherlands). Utilizing TC and TG kits (Pars Azmon Inc., Iran), TC and TG were assayed using enzymatic calorimetric tests with cholesterol esterase and cholesterol oxidase and glycerol phosphate oxidase, respectively. HDL-C was measured after precipitation of the apolipoprotein B containing lipoproteins with phosphotungistic acid. LDL-C was calculated from the serum TC, TGs, and HDL-C concentrations expressed in mg/dl using Friedwald formula if TG concentration was lower than 400 mg/dl [8]. Lipid standard (C.f.a.s, Boehringer Mannheim, Germany; cat. no. 759350) was used to calibrate the Selectra 2 auto-analyzer on all days of laboratory analyses. Inter- and intra-assay coefficients of variation were two and 0.5% for TC and 1.6 and 0.6% for TGs, respectively.

Body Mass Index (BMI) was calculated as weight (kg) divided by square of height (m). Waist-to-hip ratio (WHR) was also calculated by dividing the waist circumference to hip circumference both in centimeters. Overweight and obesity were defined in terms of BMI Based on WHO criteria as follows: overweight: 25.0-29.9 and obesity: BMI≥30kg/m2 [9]. W.H.R≥0.95 and W.C≥102 in men and W.H.R≥0.8 and W.C ≥88 in women were considered as abdominal obesity (central obesity)[9]. ATP III criteria were used to define high risk serum dyslipidemia as: total cholesterol ≥ 240, triglyceride ≥ 200 and LDL-C ≥ 160 mg/dl[10].

Statistical analysis was performed by SPSS 11.5 software package and data were presented as percent and mean ± SD. Since the values of TG were not normally distributed, they were log-transformed before statistical analysis and were back-transformed again before presentation. Analysis of Covariance (ANCOVA) was used to compare the mean levels of serum lipids in different seasons after adjustment for age, history of smoking, physical activity level, WHR and BMI. Also, the prevalence of dyslipidemia in the hottest and coldest seasons of the year was compared by chi-square test in the whole study population and in each sex.

Results

A total of 6894 subjects (2890 males and 4004 females) were studied. Baseline characteristics of the study population are given in Table I. The mean age of males and females was 39.4±11.6 and 38.3±11.3 years, respectively. The prevalence of overweight was higher in males than in females (42.6 vs. 38.4, P<0.001) and females were more obese than males (29.1 vs. 14.7%, P<0.001). 13.8% of the studied population was smoker with higher frequency in males (P<0.001). The mean serum lipid values were significantly different between males and females with total cholesterol, LDL-C and HDL-C higher in females and serum triglyceride higher in males (P<0.001). Serum lipid values were also highly correlated with all of the anthropometric measures (Table II).

The mean serum lipid values in different seasons of the year and their comparison between summer and winter,

which represent the hottest and coldest seasons, are shown in Table III. In men, there was a significant seasonal variation in the mean values of serum cholesterol and LDL-C with higher values in winter than summer (P<0.05). There was also statistically significant difference in serum HDL-C values in different seasons in men with the highest and lowest values in winter and spring respectively (P<0.05). On the other hand, the mean serum triglyceride value in women was highest in winter and lowest in summer (P<0.05). Among anthropometric measures WC and WHR in women and WHR in men had a significant seasonal variation. Physical activity was also found to be different between seasons in women but not in men.

The prevalence of dyslipidemia in different seasons is presented in Table IV. There was 4.8% relative increase in the prevalence of hypercholesterolemia in winter than in summer in the whole study population. This increase was higher in men than in women (26.2 vs. 7.6%, P<0.05). Similar pattern was observed for LDL-C with a 25.8% relative increase in the prevalence of high LDL-C in winter than in summer which was statistically significant in both sexes (26.7% in men and 24.9% in women). on the other hand, the prevalence of hypertriglyceridemia showed the overall 17.7% decrease in winter than in summer only in women (P<0.001).

Table I: Baseline characteristics, anthropometric variables and serum lipids of the study subjects stratified by sex.

Characteristic	Men (n=2890)	Women (n=4004)	P Value
Age (year)	39.4 ±11.6*	38.3±11.3	0.13
Education			
High school diploma or less	2221(78.7) †	3278 (87.5)	<0.001
Post-high school diploma	601(21.3)	469(12.5)	
B.M.I			
Normal (17.1-24.9)	1218(42.8)	1279(32.5)	<0.001
Overweight (25-29.9)	1211(42.6)	1512(38.4)	
Obese (≥ 30)	417 (14.7)	1145(29.1)	
WC(cm)			
Normal	2580(89.3)	2101(52.5)	<0.001
High	302(10.4)	1821(45.5)	
WHR			
Normal	2061(71.3)	1434(35.8)	<0.001
High	821(28.4)	2488(62.1)	
Smoking			
Yes	829(28.8)	124 (3.1)	<0.001
No	2053(71.2)	3876(96.6)	
Mean level of serum lipids (mg/dl)			
Cholesterol	203±43	207±45	<0.001

* Data are mean ± SD

† Numbers in parenthesis represent percent

Smoking: Do you smoke cigarettes now. High WC: ≥ 88 for women and ≥ 102 for men ,High WHR: ≥ 0.88 for women and ≥ 0.95 for men.

Table II: Pearson's correlation coefficients between anthropometric variables and lipid levels

	Cholesterol-C	Triglycerides	HDL-C	LDL-C
BMI(kg/m2)	.235	.182	.059	.189
Waist(cm)	.294	.266	.118	.238
WHR	.237	.280	.192	.197

All correlations were significant at the P <0.001 level.

BMI: body mass index; WHR: waist-to-hip ratio.

Table III: Seasonal variation of serum lipids, anthropometric indexes and physical activity in men and women

	Men					Women			
	Spring	Summer	Autumn	Winter	P for trend	Spring	Summer	Autumn	Winter
Serum lipids (mg/dl)									
Cholesterol	201±44*	200±41	206±45	207±41†	<0.001	201±44	208±45	210±45	208±48
LDL	130±36	126±35	131±37	133±33‡	<0.01	131±37	130±37	137±38	136±39
HDL	36.8±9.2	37.7±8.9	37.8±9.1	38.3±9.8	<0.05	43.0±10.9	44.1±11.1	45.1±10.8	44±11.7
Triglycerides	181±132	195±147	191±143	181±102	NS	138±93	173±96	154±120	138±88†
LDL/HDL ratio	3.5±1.3	3.3±1.1	3.3±1.2	3.5±1.1†	<0.005	3.0±1.2	3.0±1.1	3.0±1.2	3.1±1.3
Anthropometric indexes									
BMI(kg/mg2)	25.7±4.0	25.8±4.1	25.7±4.1	26.0±4.0	NS	27.1±5.5	27.3±5.0	27.6±5.3	27.3±5.8
Waist (cm)	87.8±10.8	88.4±11.3	88.0±11.5	87.6±11.2	NS	86.5±12.9	85.0±12.0	87.8±12.2	88.1±12.7
WHR	0.90±0.06	0.91±0.07	0.91±0.07	0.90±0.07	<0.05	0.83±0.08	0.81±0.07	0.82±0.07	0.83±0.07
Physical activity (**)									
Inactive or mild	43.1	44.9	42.1	39.2	NS	30.8	29.7	31.1	39.8
Moderate or Sever	56.9	55.1	57.9	60.8		69.2	70.3	68.9	60.2

* Data are mean ± SD and compared with ANCOVA after adjustment of age, smoking, physical activity, BMI and WHR

† and ‡: p<0.05 and P<0.01 respectively, winter-summer comparison

** Data in this section are percent (%) and compared by Chi square analysis. Moderate or sever activity was defined as exercising at least 3 times a week

BMI: Calculated as weight (kg) divided by the square of height (m); WHR: waist-to-hip ratio

NS: P>0.05

Discussion

In this study, as well as in early reports of T.L.G.S [11] the mean total cholesterol, LDLC and HDL-C level were higher in females and triglyceride levels higher in males. This study also showed a significant trend for change in the values of cholesterol, LDL-C and HDL-C in different seasons in men, with higher cholesterol and LDL-C values in winter than in summer (P<0.05). In women, only the mean values of triglycerides showed difference between the hottest and the coldest seasons.

Similar results was shown in the Pincherel study, a cross-sectional study of approximately 7000 men seen over a period of 2.5 years, which showed that cholesterol levels were higher in winter[12]. On the other hand Bleiler *et al,* in a study of 11 men and women in Iowa, found that cholesterol levels in summer comparing to winter were lower in men but higher in women. This study however, did not even span a complete year [13].

Summary of the major studies of winter-summer comparison of serum lipid levels are presented in Table V. There are some studies that have not reported a difference between men and women in the value of LDL-C between winter and summer [4, 14]. Most studies about the seasonal variation of serum LDL-C report similar results with increase in the serum values in winter and its decrease in the summer. Harlap *et al.* reported the highest value of LDL-C in the autumn in 5244 middle-aged men and women not prescribed a uniform diet [15], while Gordon *et al.* found that the seasonal variation of serum LDL-C was similar to the serum HDL-C [14]. He also demonstrated a highly significant synchronous sinusoidal seasonal cycle for LDL-C and HDL-C, peaking in the first month of winter[1].

Several studies have demonstrated that there is also a seasonal variation in the HDL-C value, with higher values in winter than in summer in both sexes [1, 5, 15], while some, like the current study, has reported no difference in HDL-C values between winter and summer in any sexes [4]. There are different reports about the seasonal variation of serum triglyceride. Some studies reported an irregular seasonal pattern, highest in mid-summer and late autumn [1,14]. Ocken *et al* found that the amplitude of the seasonal variation in rigyceride levels was significant only in women and that the peak occurred only during the fall [5]. Donahoo did not find a seasonal variation in the serum triglyceride, but higher fatty tissue lipoprotein lipase

Table IV: Prevalence of serum lipid disorders in summer and winter

	Serum lipid disorders (%)				
	Participants, No.	Summer	Winter	Relative difference	P value
Total Cholesterol level ≥ 240 mg/dl					
All	929	21.3	25.0	14.8	0.006
Men	320	16.7	22.6	26.2	0.003
Women	609	24.6	26.6	7.6	0.273
LDL Cholesterol level≥ 160mg/dl					
All	816	18.4	24.8	25.8	<0.001
Men	291	16.2	22.1	26.7	0.004
Women	525	20.0	26.6	24.9	<0.001
Triglyceride level ≥ 200mg/dl					
All	1142	30.1	24.8	17.7	<0.001
Men	549	34.0	30.7	9.8	0.166
Women	593	27.4	20.9	23.8	<0.001

Table V: Summary of the major studies of Winter-Summer comparison of serum lipid levels

Study	Study Design	Population studied	Winter vs. summer values			
			HDL-C	LDL-C	Triglyceride	Cholesterol
The present study	Cross-Sectional	2890 Men & 4004 Women		Higher in men	Higher in women	Higher in men
Gordon *et al.* [1]	Longitudinal (7-years)	1446 Men	Higher		Lower	
Ockene *et al.* [5]	Longitudinal (12-month)	517 Men & Women	Higher in both sexes			Higher in women
Pincherle *et al.* [12]	Cross-sectional	7000 Men				Higher
Bleiler *et al.* [13]	Cross-Sectional	11 Men & Women				Higher in men & Lower in women
Gordon *et al.* [14]	Longitudinal	1446 Men	Higher	Higher	Lower	
Harlap *et al.* [15]		5244 Men & Women	Higher	Higher		
Robinson *et al.* [16]	Cross-Sectional	170000 Men & 44000 Women				Higher
Rastam *et al.* [21]	Cross-Sectional	3377 Men & 3900 Women				Higher in men

activity was demonstrated in winter[4]. Hence, although the main mechanisms behind the seasonal variation of cholesterol have been the increase in liver production of LDL-C or decrease in the activity of LDL receptors in winter, but it seems that the increase in the activity of lipoprotein lipase is the main factor in increasing the metabolism of triglyceride containing particles in the cold seasons of the year[4].

There have been conflicting reports about the association of the weather temperature and plasma cholesterol levels in the studies that have evaluated the seasonal variation of serum lipids in addition to the measurement of the temperature of the environment. Robinson and Pincherle studies showed a negative association of cholesterol level with the environment temperature[12,16]. On the other hand, Fyfe *et al* found no association [17], while Bull *et al* found a positive association in this regard in men under 55 years of age[18]. The association of plasma cholesterol levels with the environment temperature could be the result of the direct effect of temperature on serum cholesterol or the effects of other seasonal parameters, which are strongly correlated with the temperature[15]. During summer, the increase in the environment temperature or physical activity, or most likely the combination of the two, could be contributing to a hemodilution effect with an accompanying decrease in serum lipid levels. The underlying mechanism could be mobilization of fluid from the interstitial to the intravalscular compartment [19,20]. We showed higher frequency of high serum cholesterol and LDL-C in winter than in summer in men. In women, there was a similar pattern for high LDL-C. On the other hand, the frequency of high serum triglyceride was lower in winter than in summer only in women. Others have sound similar results. Rastam et al, in a cross-sectional study on 3377 men and 3900 women, found a statistically significantly higher prevalence of hypercholesterolemia in winter (25.4%) than in summer (13.5%) only in men, but not in women[21].

Difference in the prevalence of hypercholesterolemia in different seasons could result in two major biases: first, individuals who have hypercholesterolemia during the winter months might have been misclassified and second, when patients who initiate drug therapy during the summer and have follow-up visit in winter, there is higher chance of seeing failure of therapy. These findings imply that clinicians should take season into account when diagnosing hyperlipidemia and evaluating apparent success or failure in its treatment. On the other hand, in a recent large longitudinal study including over 450,000 men and women, not only Total cholesterol but also blood pressure and body mass index showed pronounced seasonal variations with average levels significantly higher during the winter months in all age groups and both sexes, giving an estimated increase in CHD mortality risk of 6.8% in men and 3.6% in women[22]. Hence, seasonal differences of serum lipids could partly explain the Seasonal variation in cause-specific mortality and preventive strategies remains a public health challenge in this regard.

There are some limitations to the current study. First no adjustment for diet was made because of the lack of data. However, there are studies that suggest that the seasonal variations of serum lipids are probably induced by factors directly related to endogenous factors or seasonal rhythm and not to dietary factors [23,24]. Second, this study which was designed for evaluation of the seasonal variation of serum lipids was cross-sectional in nature, with different individuals being observed at different time-points. The longitudinal studies on this subject have the advantage of measuring serum lipids in sequence for each subject, although in most of these either the number of individuals studied is very small or the time-period over which the study was conducted is short [13].

One of the advantages of the current study, despite being cross-sectional, was the large sample size and also the meteorological situation of Tehran in which there is significant difference in the weather temperature throughout the year.

Conclusion

This study which is the first extensive cross-sectional study about seasonal variability of different serum lipids in Iran showed that men had higher values of cholesterol, LDL-C and HDL-C in winter. The prevalence of hypercholesterolemia in men and high LDL-C in both sexes was also higher in the winter. More extensive longitudinal studies with adjustment for other confounding variables like diet, environment temperature measurement, plasma volume or serum hemoglobin are needed in order to further investigate these results.

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