Serum lipid profiles with and without CAD: Jordan Hyperlipidaemia and Related Targets Study (JoHARTS-1)

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مرتسمات شحميات المصل من المصابين بمرض الشريان التاجي ومن غيرهم: الدراسة الأردنية لفرط شحميات الدم والأهداف المرتبطة بها

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الخلاصة: قام الباحثون في هذه الدراسة بقياس الكوليسترول الكلي، والغليسريدات الثلاثية، ومستويات الكوليسترول البروتيني الشحمي المنخفض الكثافة LDL-C والمرتفع الكثافة HDL-C في أمصال 5000 فرد مأخوذة على الريق. وكان مرض الشريان التاجي موجوداً في 31٪ منهم. وتميَّز الذكور بانخفاض متوسط الكوليسترول الكلي، والكوليسترول البروتيني الشحمي المنخفض الكثافة والمرتفع الكثافة، وبارتفاع متوسط المركبات الثلاثية الغليسريد، وذلك بالمقارنة مع الإناث. وكان المستوى الأمثل من الكوليسترول الكلي موجوداً في 46٪ فقط من الذكور، و41٪ من الإناث؛ والمستوى الأمثل من الغليسريدات الثلاثية في 42٪ من الذكور و50٪ من الإناث. وكان مستوى الكوليسترول البروتيني الشحمي المرتفع الكثافة أعلى من 60 مغ/دل في 3٪ من الذكور و12٪ من الإناث. ولم يختلف متوسط الكوليسترول الكلي في المصابين بمرض الشريان التاجي عن غير المصابين به، في حين كان متوسط الغليسريدات الثلاثية أعلى بشكل يعتد به إحصائياً لدى مرضى الشريان التاجي، ومتوسط الكوليسترول البروتيني الشحمي المرتفع الكثافة أقل بشكل يُعْتَدُّ به فيهم. وكان انخفاض مستوى الكوليسترول البروتيني الشحمي المرتفع الكثافة في كل الفئات العمرية أكثر انتشاراً بين الذكور والإناث المصابين بمرض الشريان التاجي.

ABSTRACT We measured fasting serum total cholesterol (TC), triglycerides (TG), and low- and high-density lipoprotein cholesterol (LDL-C and HDL-C) levels in 5000 individuals. Coronary artery disease (CAD) was present in 31%. Compared with women, men had lower mean TC, LDL-C and HDL-C and higher mean TG. Optimal TC level was observed in only 46% of men and 41% of women, and optimal TG in 42% of men and 50% of women. Only 3% of men and 12% of women had HDL-C > 60 mg/dL. Mean TC was not different in CAD patients and those without CAD, but mean TG was significantly higher and mean HDL-C was lower. In all age groups, low HDL-C was more prevalent among men and women who had CAD.

Profil lipémique de coronariens et non coronariens : l'étude JoHARTS-1 (Jordan Hyperlipidaemia and Related Targets Study – étude jordanienne de l'hyperlipidémie et des cibles associées)

RÉSUMÉ Nous avons mesuré le cholestérol total (CT), les triglycérides (TG) et le cholestérol des lipoprotéines de basse et haute densité (respectivement C-LDL et C-HDL) dans le sérum de 5000 sujets. La présence d'une maladie coronarienne a été confirmée chez 31% d'entre eux. Par comparaison avec les femmes, les hommes présentaient des taux moyens de CT, de C-LDL et de C-HDL plus faibles et un taux moyen de TG plus élevé. Un taux optimal de CT n'a été observé que chez 46 % des hommes et 41 % des femmes, et une triglycéridémie optimale chez 42 % des hommes et 50 % des femmes. Seuls 3 % des hommes et 12 % des femmes avaient un taux de C-HDL > 60 mg/dL. Par rapport aux sujets indemnes de maladie coronarienne, les patients coronariens présentaient un cholestérol total moyen comparable, tandis que les TG moyens étaient significativement plus élevés et le C-HDL moyen plus bas. Dans toutes les tranches d'âge, la prévalence d'un faible taux de C-HDL était plus importante chez les hommes et les femmes coronariens.

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Introduction

Dyslipidaemia [elevated levels of serum total cholesterol (TC), triglycerides (TG) and low-density lipoprotein cholesterol (LDL-C) and low levels of high-density lipoprotein cholesterol (HDL-C)] is a major modifiable risk factor for cardiovascular disease. All components are associated with increased incidence of coronary artery disease (CAD). Intensive treatment of dyslipidaemia stabilizes atherosclerosis and promotes its regression, and reduces all-cause and cardiovascular mortality in patients with CAD [*1–8*]. Previous studies on dyslipidaemia in the countries of the Eastern Mediterranean, including Jordan, were limited by the relatively small number of participants and not all of them compared serum lipoproteins in individuals with and without cardiovascular disease, including those with acute coronary syndrome (ACS) [*9–14*].

In the Jordan Hyperlipidaemia and Related Targets Study (JoHARTS), we aimed to determine the prevalence of dyslipidaemia in a large sample of adults by studying their lipid profiles. We also studied the effect of several variables, including age, sex, smoking and diabetes on serum lipoprotein levels.

Methods

The study was conducted during the period July 2003–January 2005. Individuals ≥ 18 years of age were enrolled in the study on a consecutive basis as they presented for routine check-up or for management of coronary disease-related admission until the predetermined number (n = 5000) was met. Patients with acute illnesses and endocrinopathies that could affect serum lipoprotein levels were excluded from the study as well as those with secondary causes of dyslipidaemia, users of lipid-lowering medication and those with severe systemic illness that could potentially affect serum lipoprotein levels.

All participants agreed to have their lipid profile measured by the study investigator as part of their management and for the data to be used in the study. There were no refusals to participate. The study was approved by the ethics committees in the participating hospitals: the Islamic Hospital, Jordan University Hospital and Khalidi Hospital, all in Amman.

Venous blood levels of TC, TG, LDL-C and HDL-C were measured. Measurements were made on the day of collection after 8–12 hours of fasting or upon admission of patients with ACS. Serum levels of TC, HDL-C and TG were measured using fully enzymatic methods.

The TC method is based on the principle first described by Stadtman and later adapted by others involving the hydrolysis of cholesterol esters [*15,16*]. The chromophobe that is later produced was measured using a polychromatic technique. The concentration of HDL-C was directly measured by accelerating the reaction of cholesterol oxidase with non-HDL-C unesterified cholesterol and dissolving HDL-C selectively using a specific detergent. TG concentration was measured by converting into free glycerol and fatty acids using a lipoprotein lipase enzyme. This was further broken down and the resulting quinoneimine was quantitatively assayed using a bichromatic technique. Values for LDL-C were calculated using the Friedewald formula when TG levels did not exceed 300 mg/dL and otherwise using direct quantitative homogenous enzymatic assay.

Reference values for optimal and high levels of serum lipids were based on the National Cholesterol Education Program [*17*] as follows: optimal TC < 200 mg/dL,

borderline 200–239 mg/dL, high ≥ 240 mg/dL; optimal TG < 150 mg/dL, borderline high 150–199 mg/dL, and high > 199 mg/dL; for HDL-C, we used 40 mg/dL as the cut-off for both sexes. Regarding LDL-C, for patients with cardiovascular disease or diabetes optimal level was < 100 mg/dL, for individuals with ≥ 2 risk factors this was < 130 mg/dL and for individuals with ≤ 1 risk factors it was < 160 mg/dL (note: the study was done before optimal LDL for vascular and diabetic patients was reduced to < 70 mg/dL).

Coronary artery disease was diagnosed based on the presence of angina and electrocardiographic, echocardiographic and coronary angiographic studies or prior percutaneous or surgical coronary revascularization. Acute coronary syndrome was defined as the presence of unstable angina or acute myocardial infarction on admission. In the absence of ACS, patients with CAD were classified as chronic CAD patients. Definition of risk factors was similar to criteria set in the Euro Heart Survey for patients with acute coronary syndromes [*18*]. Current smoking was defined as smoking up to 1 month before enrolment. Hypertension was defined as prior diagnosis by a physician, current use of blood pressure lowering medications, or known blood pressure values of ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic on ≥ 2 occasions. Diabetes was defined as prior diagnosis by a physician or current use of hypoglycaemic medications.

Statistical methods

Data are presented as mean plus standard deviation (SD) or median values for continuous variables and as absolute and relative frequencies for categorical variables. Calculations of the mean values excluded the extremely high values of TC (> 350 mg/dL), TG (> 500 mg/dL), or LDL-C (> 280 mg/dL). No exclusions were made when the median values were determined. Comparisons between groups were performed using the chi-squared test to compare frequencies, the Student *t*-test to compare mean values of 2 groups, and analysis of variance to compare mean values of more than 2 groups.

Multiple regression analyses were applied for serum lipoproteins as dependent variables and age, sex, diabetes, hypertension and smoking as independent variables. Results were classified according to 6 age groups for men and women. Optimal and elevated lipoprotein levels were defined according to standard guidelines [*17,18*].

Results

Clinical features of the 5000 individuals enrolled in the study are shown in Table 1. There were 3308 men (66%) and 1692 women (34%); CAD was present in 1534 (31%) individuals, 1202 men, mean age 55.5 (SD 11.1) years, and 332 women, mean age 60.8 (SD 10.1) years. ACS was

Table 1 **Clinical features of men and women participating in the study (*n* = 5000)**

Variable	Men (*n* = 3308)		Women (*n* = 1692)	
	No.	%	No.	%
CAD	1202	36	332	20
ACS	781	24	206	12
Diabetes mellitus	863	26	547	32
Hypertension	1273	38	963	57
Smoking	1209	37	124	7
Age (years) mean (SD)	50.1 (12.1)		54.1 (11.5)	

P ***< 0.001 for all variables.***
CAD = coronary artery disease; ACS = acute coronary syndrome; SD = standard deviation.

present in 987 patients (64% of CAD patients), 781 men and 206 women. Diabetes and hypertension were more prevalent in women than men, but smoking was more prevalent in men.

Table 2 shows mean and median levels of serum lipids in men and women. Women had significantly higher levels of TC, LDL-C and HDL-C and lower TG.

Optimal serum TC level (< 200 mg/dL) was present in less than half the men (47%) and women (41%). Optimal TG level (< 150 mg/dL) was found in 42% of men and 50% of women. Low LDL-C level (≤ 100 mg/dL) was found in 22% of men and 21% of women. Low HDL-C level (≤ 40 mg/dL) was found in 63% of men and 34% of women ($P < 0.001$), and high HDL-C level (> 60 mg/dL) was also found in more women than men (12% and 3% respectively, $P < 0.001$).

In the 6 age groups, for both sexes, median levels of TC, TG, and LDL-C increased with age and peaked around 50 years of age in men and around 60 years in women (Table 3). At a younger age (< 45 years), men had higher levels of TC, TG, and LDL-C than women. Beyond this age, TC and LDL-C levels were significantly higher in women than in men. HDL-C levels were, however, significantly higher in women than in men in each age group, and did not significantly change in either sex with age.

Multiple regression analyses (Table 4) showed that sex influenced all lipid levels; diabetes influenced TC, TG and HDL-C levels; age influenced TG and HDL-C; and smoking only influenced HDL-C. Hypertension, however, had no effect on serum lipid levels.

In those with CAD, only 22% (19% of men and 27 % of women) had elevated TC levels (> 200 mg/dL), and 55% had elevated TG (> 150 mg/dL). Low HDL-C (≤ 40 mg/dL) was found in 45% (54% of men and 27% of women, $P < 0.001$).

Mean TG level was significantly higher in patients with chronic CAD compared with individuals who did not have CAD; mean HDL-C was significantly lower in chronic CAD patients (Table 5). On the other hand, ACS patients had lower mean TC and HDL-C levels, but similar mean TG and LDL-C levels compared with those without CAD. They also had significantly lower TC, LDL-C and TG levels compared with individuals who did not have CAD.

Table 2 **Serum lipid profile in men and women participating in the study (n = 4850[a])**

Variable	Men		Women		*P*-value
	Mean[b] (SD)	Median	Mean[b] (SD)	Median	
TC (mg/dL)	207.6 (43.7)	205	213.6 (46.6)	210	< 0.001
TG (mg/dL)	173.4 (78.7)	169	161.7 (75.0)	150	< 0.001
LDL-C (mg/dL)	131.0 (38.3)	129	134.1 (41.2)	131	0.0129
HDL-C (mg/dL)	39.0 (14.6)	38	46.5 (13.1)	46	< 0.001

[a]Data presented for 4850 patients (150 patients did not have LDL-C or HDL-C values for analysis).
[b]47 individuals (1%) were excluded from calculation (TC > 600 mg/dL).
SD = standard deviation.
TC = total cholesterol; TG = triglycerides; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol.

Table 3 **Median values of serum lipids in men and women in 6 age groups**[a]

Age (years)	Men						Women						*P*-value
	No.	%	TC	TG	LDL-C	HDL-C	No.	%	TC	TG	LDL-C	HDL-C	
< 30	125	3.9	194	146	118	38	29	1.8	156	80	93	46	< 0.0001
30–45	1073	33.6	207	177	130	37	361	21.9	201	131	125	46	< 0.0001[b]
46–55	960	30.0	207	177	131	38	525	31.8	214	153	132	46	< 0.001[c]
56–65	735	23.0	204	170	130	38	491	29.7	222	162	140	45	< 0.0001[d]
66–75	250	7.8	199	139	126	40	200	12.1	207	160	127	44	< 0.03[e]
> 75	55	1.7	184	138	119	40	46	2.8	204	143	125	48	< 0.037[f]
P (ANOVA)			< 0.0001	< 0.0001	0.013	0.163			< 0.0001	< 0.0001	< 0.0001	0.2930	–

[a]Data presented for 4850 patients (150 patients did not have LDL-C or HDL-C values for analysis).
[b]Significant for TC and LDL-C only.
[c]Significant for LDL-C only.
[d]Significant for TC, LDL-C and HDL-C.
[e]Significant for TC, TG and HDL-C.
[f]Significant for TC, LDL-C and HDL-C.
HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides. All lipid values expressed as mg/dL.
ANOVA = analysis of variance.

Table 4 **Multiple linear regression analyses of serum lipoproteins according to selected variables**

Variable	B	β	*P*
LDL-C			
Age	0.0088	0.0020	0.891
Sex	3.3170	0.0340	0.033
Diabetes	–2.4690	–0.0240	0.127
Smoking	0.8000	0.0080	0.626
Hypertension	2.8170	0.0310	0.056
	R^2 = 0.0100; ***P*** (ANOVA) < 0.0001		
TC			
Age	–0.0314	–0.0080	0.643
Sex	6.3960	0.0610	< 0.001
Diabetes	3.8970	0.0350	0.023
Smoking	1.2940	0.0110	0.459
Hypertension	2.9380	0.0290	0.058
	R^2 = 0.0040; ***P*** (ANOVA) = 0.013		
HDL-C			
Age	0.0553	0.0460	0.006
Sex	6.8080	0.2200	< 0.001
Diabetes	–2.2350	–0.0690	< 0.001
Smoking	–1.4220	–0.0430	0.005
Hypertension	–0.6040	–0.0210	0.187
	R^2 = 0.0700; ***P*** (ANOVA) < 0.0001		
TG			
Age	–0.9030	–0.0660	< 0.001
Sex	–30.1090	–0.0870	< 0.001
Diabetes	52.3050	0.1430	< 0.001
Smoking	8.7640	0.0240	0.124
Hypertension	1.6340	0.0050	0.747
	R^2 = 0.0290 ***P*** (ANOVA) < 0.0001		

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides.
B = unstandardized regression coefficient.
β = standardized regression coefficient.
ANOVA = analysis of variance.

Discussion

Epidemiological studies in various regions of the world have demonstrated marked variations in the prevalence of dyslipidaemia between countries or even between regions in the same country (e.g. rural versus urban and inland desert versus temperate highlands) [*19–21*]. These variations are not only related to genetic and environmental factors, but also to the definition of "optimal" serum lipoprotein levels, which is an arbitrary definition and reflects population studies from the more developed countries that might not necessarily apply to other regions, including the Eastern Mediterranean.

In this study, high levels of serum cholesterol and triglycerides were present in at least half the participants. Only one fifth of CAD patients had hypercholesterolaemia, and about half of them had elevated triglycerides.

Low levels of HDL-C were present in 63% of all men and 54% of men with CAD, and in 34% of all women and 27% of women with CAD. In a previous local study, the prevalence of low HDL-C was 45% in men and 23% in women [*10*], similar to that in Lebanon (47% in men and 15% in women) but lower than that in the Islamic Republic of Iran (57% in men and 47% in women) [*21*], and higher than that in Saudi Arabia (28%) [*12,13*] and the United States of America (18% in men and 6% in women) [*22*].

Mean HDL-C levels in our study were 39.0 mg/dL in men and 46.5 mg/dL in women, much higher than those observed in the Islamic Republic of Iran (34.5 mg/dL in men and 39.0 mg/dL in women) [*21*] but lower than those in some European Mediterranean countries (46.2 mg/dL in Italy, 46.6 mg/dL in Spain and 51.1 mg/dL in France) [*23*].

The fact that more than 80% of men and 73% of women with CAD in our study had optimal or borderline cholesterol levels is consistent with other studies and implicates

Table 5 **Mean serum lipids in individuals with no coronary artery disease (CAD), with chronic CAD and with acute coronary syndrome (ACS)**

Variable	No CAD (*n* = 3466) Mean (SD)	Chronic CAD (*n* = 1534) Mean (SD)	ACS (*n* = 987) Mean (SD)	*P*[a]	*P*[b]	*P*[c]
TC	209.9 (44.5)	212.5 (42.9)	204.7 (45.2)	0.213	0.002	0.002
TG	169.1 (77.4)	176.6 (74.4)	166.5 (80.1)	0.045	0.380	0.020
LDL-C	132.0 (39.2)	135.4 (38.7)	130.7 (38.7)	0.071	0.387	0.031
HDL-C	42.6(13.8)	39.8 (11.6)	38.9 (17.4)	< 0.0001	< 0.0001	0.262

[a]No CAD and chronic CAD.
[b]No CAD and ACS.
[c]Chronic CAD and ACS.
HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides.
SD = standard deviation.

the coexistence of other risk factors that predispose to cardiovascular disease and might be more important than hypercholesterolaemia, namely diabetes mellitus and cigarette smoking [*24*]. In fact, diabetes and smoking were more prevalent among chronic CAD and ACS patients (51% and 41% for diabetes, and 28% and 43% for smoking, respectively) than among individual who did not have CAD (21% for diabetes and 23% for smoking). Moreover, the presence of atherogenic lipoproteins that are not routinely measured, such as small, dense LDL-C and oxidized LDL-C, can contribute to the pathogenesis of atherosclerosis despite normal LDL-C levels, especially among people with diabetes [*25–27*].

Chronic CAD patients had higher TG and lower HDL–C levels compared with those without CAD. Other studies from the region also found that CAD patients had significantly higher TG and TC, and lower HDL-C levels than individuals with no CAD [*14,28*]. Low HDL-C and high TG are recognized as independent coronary risk factors, and these may potentially play a more important role in the pathogenesis of atherosclerosis in this region of the world than hypercholesterolaemia, although larger, longitudinal studies would be needed to show this.

Our finding that ACS patients had lower TC, TG, and LDL-C levels compared with those with chronic CAD may be related to the increased catabolic state associated with myocardial necrosis and the consumption of serum lipid in myocardial cell repair at the infarction site [*29*], especially if there was considerable delay in presentation of patients to the hospital.

Due to the fact that dyslipidaemia is prevalent and coexists with other coronary risk factors in individuals with and without CAD [*24*], and because it is difficult to predict which individual with dyslipidaemia will develop CAD; early detection, evaluation and aggressive treatment are vital components of the strategies to control CAD in this region, including achieving very low LDL-C levels (i.e. < 70 mg/dL) in high risk groups such as diabetics and vascular patients [*30*].

The study has some limitations. The participants may not represent Jordanian society as a whole because enrolment of individuals was not based on a community survey, but rather through consecutive, hospital-based evaluation. The only cut-off value that did

not follow the National Cholesterol Education Program reference values [*17*] was optimal HDL-C for women, we defined it as > 40, rather than > 50 mg/dL which would lead to an underestimation of the number of women with low HDL-C.

Healthy individuals in Jordan frequently seek medical advice for primary care issues at a tertiary care level by non-primary care physicians. Actually, 1626 (33%) individuals in the whole group did not have diabetes, hypertension or CAD.

We believe that the large sample size in the study could overcome some of these limitations.

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