Austin Journal of Endocrinology and Diabetes

Austin Publishing Group

Open Access Full Text Article

Research Article

The Association of Chlamydia Pneumoniae IgG Seropositivity with an Atherogenic Lipid Profile in a General Population: The Persian Gulf Healthy Heart Study

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Received: August 08, 2014; **Accepted:** September 23, 2014; **Published:** September 29, 2014

Abstract

Regarding the controversial contributory role of chronic Chlamydia pneumonia infection in an atherogenic lipid profile and limited studies in women, we investigated the independent association of C. pneumoniae IgG seropositivity with an atherogenic lipid profile in a large-scale, community-based study. Sera of 1754 participants of the Persian Gulf Healthy Heart Study, a cohort study of men and women aged ≥25 years, were evaluated for IgG antibodies against C. pneumoniae and high-sensitivity C-reactive protein (hsCRP) using enzyme-linked immunosorbent assay. Serum total cholesterol, triglyceride, and high-density lipoprotein cholesterol (HDL-C) levels were measured using enzymatic methods. A total of 714 (40.7%) subjects (45.7% of the men and 35.8% of the women; $p < 0.0001$) had IgG antibodies against C. pneumoniae. In multiple logistic regression analyses, age- and sex-adjusted C. pneumoniae infection did not show a significant association with high low-density lipoprotein cholesterol and high triglyceride. However, C. pneumoniae IgG seropositivity showed significant association with low HDL-C after controlling for age, sex, body mass index, hypertension, type 2 diabetes mellitus, smoking status, and circulating hsCRP levels (odds ratio = 2.12; 95% confidence interval = 1.72–2.62, $p < 0.0001$).in conclusion, there was a strong association between C. pneumoniae IgG seropositivity and low HDL-C. This association was independent of classical cardiovascular risk factors and circulating hsCRP levels in both men and women.

Keywords: Chlamydia pneumoniae; High-density lipoprotein cholesterol; Atherosclerosis; Cardiovascular risk factors, Lipid profile

Introduction

A growing body of evidence has demonstrated a contributory role for Chlamydia pneumoniae in the pathogenesis of coronary artery disease, stroke, and peripheral atherosclerosis [1-4]. Despite these rapidly growing numbers of studies about the involvement of C. pneumoniae infection in the initiation and progression of atherosclerotic processes, the pathogenic mechanisms are not fully understood. However, this obligate intracellular human respiratory pathogen can affect chronic processes, such as atherosclerosis, through augmentation of the inflammatory system, signaling pathways, and oxidative stress [5].

Beyond the described complex mechanisms of the cardiovascular risk in C. pneumoniae infection, it has been suggested that this bacterium may play a role in atherosclerosis through simpler processes, such as induction of an atherogenic lipid profile in the host [6].

The persistent (and probably chronic) presence of C. pneumoniae particles and their lipopolysaccharides (LPSs) in macrophages and endothelial cells of atherosclerotic lesions may induce continuous enhanced expression of numerous proinflammatory cytokines, including TNF and IL-1, and thus lead to an atherogenic lipid profile similar to one that promotes atherosclerosis [7-10].

In fact, elevated triglyceride and total cholesterol levels and decreased high-density lipoprotein cholesterol (HDL-C) levels were reported for subjects with antibodies against C. pneumoniae, indicating that a chronic infection with this microorganism induces an atherogenic lipid profile [6, 8, 10]. Chronic infection with C. pneumoniae may also aggravate the proatherogenic properties of lipoprotein(a) through the formation of circulating immune complexes containing C. pneumoniae–specific IgG antibodies [11]. Elevated apolipoprotein B levels were found in healthy subjects who were positive for C. pneumoniae IgG and IgM when compared with those who were negative [12]. In a cross-sectional study of patients who underwent coronary artery bypass grafting, patients with positive C. pneumoniae DNA in their atherosclerotic plaques had more hypercholesterolemia and low HDL-C levels than patients who were PCR negative [13]. Among patients with acute coronary artery disease, C pneumoniae-specific IgG was positively correlated with hsCRP, cholesterol and HDL-C [14]. However, no associations between seropositivity with C. pneumoniae and an atherogenic lipid profile were reported by other investigators [15, 16].

Citation: Vahdat K, Dadjou H, Hadavand F, Kalantarhormozi MR, Ostovar A, Assadi M, et al. The Association of Chlamydia Pneumoniae IgG Seropositivity with an Atherogenic Lipid Profile in a General Population: The Persian Gulf Healthy Heart Study. Austin J Endocrinol Diabetes. 2014;1(6): 1026.

Regarding the existing discrepancies in medical literature reports of chronic C. pneumoniae infection in relation to an atherogenic lipid profile, we investigated the independent association of C. pneumonia IgG seropositivity with an atherogenic lipid profile in a large-scale, community-based study with both men and women.

Material and Methods

Community sampling and baseline examinations

We conducted the present study as part of the Persian Gulf Healthy Heart Study, which was a prospective population-based cohort study initiated in 2003 based on male and female subjects aged ≥ 25 years. The Persian Gulf Healthy Heart Study was designed to determine the risk factors for cardiovascular diseases among the northern Persian Gulf population and to develop community-based interventional projects to change the lifestyles of the population and present the rising threat of cardiovascular diseases in the region. The design of this study encompasses two major components: phase I is a cross-sectional prevalence study of unhealthy lifestyle, ischemic heart disease (IHD), and associated risk factors; phase II is a multiple interventional project for reduction of cardiovascular diseases in the region. Detailed information about the methods and procedures of this study is available elsewhere [4]. The study was approved by the Medical Ethics Committee of Bushehr University of Medical Sciences, and all participants signed an informed consent form.

In an ancillary study to the Persian Gulf Healthy Heart Study, a total of 1754 subjects were selected through a stratified multistage design from major ports of the Bushehr Province (an Iranian province with the longest border with the Persian Gulf). All subjects were asked to fast and be present at the survey center between 7:30 a.m. and 9:30 a.m. After a 15-min rest in the sitting position, blood pressure was assessed twice on the right arm using a standard mercury sphygmomanometer. After the subjects removed their heavy outer garments and shoes, their height and weight were measured using a stadiometer. Body mass index (BMI) was calculated. Next, a resting 12-lead electrocardiogram (ECG) was performed.

Biochemical and serological measurements

A fasting blood sample was taken. All samples were promptly centrifuged and separated, and analyses were carried out at the Persian Gulf Health Research Center on the day of blood collection using a Selectra 2 autoanalyzer (Vital Scientific, Spankeren, The Netherlands).

Glucose was assayed by the enzymatic (glucose oxidase) colorimetric method using a commercial kit (Pars Azmun Inc., Tehran, Iran). Serum total cholesterol and HDL-C were measured using a cholesterol oxidase phenol aminoantipyrine method, and triglycerides were measured using a glycerol-3 phosphate oxidase phenol aminoantipyrine enzymatic method. Serum low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula; LDL-C was not calculated when the triglyceride concentration was >400 mg/dl.

Measurement of C-reactive protein (CRP) was performed using a high-sensitivity CRP (hsCRP) assay, the CRP HS ELISA (DRG International Inc., USA). The minimum detectable concentration of the CRP HS ELISA assay was estimated to be 0.1 mg/l. Additionally, the functional sensitivity was determined to be 0.1 mg/l also (as determined by inter-assay % CV <20%).

IgG antibodies against C. pneumoniae were measured by a commercial test kit (DRG Instruments GmbH, Germany). The principle of the kit was based on an indirect solid-phase enzyme immunoassay with horseradish peroxidase as a marker enzyme; the positivity threshold was enzyme immunounits> 45.

Definitions

By using the American Diabetes Association criteria, a fasting plasma glucose of ≥126 mg/dl or the use of anti diabetic measures was defined as diabetes [17]. The cutoff points of serum total cholesterol, HDL-C, and LDL-C distributions that were used to assign subjects to different levels of risk were those derived from the National Cholesterol Education Program guidelines in the USA (Adult Treatment Panel III) [18]. A subject was considered hypertensive if the blood pressure measurement was ≥140/90 mmHg. Smoking was considered to be present when the participant smoked cigarettes or used a shisha (water pipe) daily.

ECGs were coded on the basis of the Minnesota code criteria [19]. Codes 1.1 and 1.2 was classified as myocardial infarction; codes 1.3, 4.1–4.4, 5.1–5.3, and 7.1 were classified as ischemia. An ECG with evidence of IHD (IHD ECG) was defined as myocardial infarction and ischemia together.

Statistical methods

Normal distribution of the data was controlled with the Kolmogorov–Smirnov test. The significance of the difference in the results of any two groups was determined by chi-square analysis using 2×2 contingency tables for categorical variables and ANOVA for continuous variables. A two-tailed t-test was used to compare the mean values across groups. We found that log transformation of hsCRP gave a better fit to a Gaussian distribution. The geometric mean for hsCRP was defined as the arithmetic mean of the log-transformed data ±2SD, raised to the power of 10.

Binary logistic regression models were used to assess the association between IgG seropositivity to C. pneumoniae and an atherogenic lipid profile (as dependent variables in different models). Further, the models were adjusted for BMI, hypertension, smoking, log-transformed CRP levels, type 2 diabetes mellitus, age, and sex. There were no significant interactions between seropositivitiy to C. pneumonia, cardiovascular risk factors and an atherogenic lipid profile. Therefore, we did not include these interaction terms in our final models. Probability values <5% were considered statistically significant. All statistical analyses were performed using the PASW Statistics GradPack 18 (SPSS Inc., Chicago, IL, USA).

Results

A total of 1754 participants (49.2% men, 50.8% women) aged 25–66 years were evaluated for associations of C. pneumoniae IgG seropositivity with an atherogenic lipid profile in serum. Mean age of participants was 40.79 (SD = 11.15) years.

A total of 714 (40.7%) subjects (45.7% of the men and 35.8% of the women; $p < 0.0001$) had IgG antibodies against C. pneumoniae. The prevalence of IgG antibodies against C. pneumoniae increased progressively with the increase in age ($p < 0.0001$).

Table 1: Clinical and laboratory characteristics of a random population of the northern Persian Gulf (the study population) according to Chlamydia pneumonia IgG seropositivity status.

	Chlamydia pneumoniae IgG seropositive	Chlamydia pneumoniae IgG seropositivity	P value
Body mass index (kg/m²)	27.42±5.29	27.11±5.36	0.227
Systolic blood pressure (mmHg)	128.58±41.21*	124.43±34.81	0.023
Diastolic blood pressure (mmHg)	81.17±39.97	79.92±32.95	0.476
Total cholesterol (mg/dl)	208.17±47.71	204.51±47.85	0.116
HDL-cholesterol (mg/dl)	41.17±25.07*	47.27±43.79	0.001
LDL-cholesterol (mg/dl)	131.33±47.19*	124.09±58.20	0.006
Triglyceride (mg/dl)	178.27±101.31*	165.66±103.26	0.011
Fasting blood glucose (mg/dl)	90.12±39.85	93.73±40.67	0.066
hsCRP (mg/l)#	2.25±4.14*	1.77±3.64	<0.0001

Values are mean ± standard deviation
#Geometric mean ± standard deviation
**P value <0.05*

Table 2: Prediction of low HDL cholesterol and high LDL cholesterol by Chlamydia pneumonia IgG seropositivity using multivariable odds ratios (OR) and their 95% confidence intervals (CI).

	Low HDL cholesterol			High LDL cholesterol		
	OR	CI	P value	OR	CI	P value
Unadjusted	2.19*	1.81-2.66	<0.0001	1.30*	1.03-1.65	0.027
Model	2.15*	1.76-2.63	<0.0001	1.24	0.97-1.58	0.079
Model 2	2.12*	1.73-2.60	<0.0001	1.19	0.93-1.53	0.152
Model 3	2.12*	1.72-2.62	<0.0001	1.17	0.91-1.51	0.218

**P value <0.05*
The cutoff points of serum HDL cholesterol and LDL cholesterol distributions that were used to assign subjects to low HDL cholesterol and high LDL levels of cardiovascular risk were those derived from the National Cholesterol Education Program guidelines in the USA (Adult Treatment Panel III) [18]
Model 1 included Chlamydia pneumonia IgG seropositivity, sex and age
Model 2 included Chlamydia pneumonia IgG seropositivity, age, sex, body mass index (BMI), smoking, type 2 diabetes mellitus and hypertension
Model 3 included Chlamydia pneumonia IgG seropositivity, age, sex, body mass index (BMI), smoking, type 2 diabetes mellitus, hypertension and hsCRP (high-sensitivity C-reactive protein)

Table 1 shows the general characteristics—including BMI, blood pressure, and biochemical parameters—of the seropositive subjects compared with the seronegative subjects.

There were no significant differences in BMI, diastolic blood pressure, total cholesterol, and fasting blood glucose between the seropositive group and the seronegative group. However, the seropositive group had statistically significant higher systolic blood pressure, hsCRP, LDL-C, and triglyceride levels than the seronegative group ($p < 0.05$, Table 1). By contrast, the seropositive group had lower serum HDL-C levels than the seronegative group ($p = 0.001$, Table 1).

A total of 206 (28.9%) and 304 (29.2%) subjects were smokers in the seropositive and seronegative groups, respectively ($p > 0.05$). None of the participants had a history of alcohol consumption.

Tables 2 and 3 show unadjusted and adjusted odds ratios (ORs) (95% confidence interval [CI]) between atherogenic lipid indices and C. pneumoniae IgG seropositivity. Unadjusted low HDL-C, high LDL-C, and high triglyceride were significantly associated with IgG antibodies against C. pneumoniae. However, in multiple logistic regression analyses, C. pneumoniae infection did not show a significant association with high LDL-C and high triglyceride after adjusting for sex and age (Model 1, Tables 2 and 3).

C. pneumoniae IgG seropositivity showed a significant association with low HDL-C levels after controlling for age, sex, BMI, hypertension, type 2 diabetes mellitus, and smoking status (Model 2, Table 2, $p < 0.0001$). This significant association was not lost with further adjustment for circulating hsCRP levels (Model 3, Table 2, $p < 0.0001$).

A total of 222 (12.7%) participants had ECGs with evidence of IHD. When excluding those with IHD in multiple regression analysis, age- and sex-adjusted C. pneumoniae infection remained significantly associated with low HDL-C levels after controlling for cardiovascular risk factors and hsCRP levels (OR = 1.79; 95% CI = 1.40–2.30; $p < 0.0001$).

Discussion

In this large-scale, population-based study, we showed a strong association between chronic C. pneumoniae infection and low HDL-C, independent of age, sex, circulating hsCRP levels, and classical risk factors for cardiovascular disease.

Table 3: Prediction of high total cholesterol and high triglyceride by Chlamydia pneumonia IgG seropositivity using multivariable odds ratios (OR) and their 95% confidence intervals (CI).

	High total cholesterol			High triglyceride		
	OR	95% CI	P value	OR	95% CI	P value
Unadjusted	1.23	0.98-1.55	0.070	1.29*	1.07-1.57	0.008
Model	1.16	0.92-1.48	0.197	1.19	0.98-1.44	0.079
Model 2	1.13	0.89-1.44	0.312	1.14	0.93-1.40	0.182
Model 3	1.14	0.89-1.47	0.285	1.16	0.99-1.43	0.163

**P value <0.05*
The cutoff points of serum cholesterol and triglyceride distributions that were used to assign subjects to high total cholesterol and high triglyceride levels of cardiovascular risk were those derived from the National Cholesterol Education Program guidelines in the USA (Adult Treatment Panel III) [18]
Model 1 included Chlamydia pneumonia IgG seropositivity, sex and age
Model 2 included Chlamydia pneumonia IgG seropositivity, age, sex, body mass index (BMI), smoking, type 2 diabetes mellitus and hypertension
Model 3 included Chlamydia pneumonia IgG seropositivity, age, sex, body mass index (BMI), smoking, type 2 diabetes mellitus, hypertension and hsCRP (high-sensitivity C-reactive protein)

In agreement with our study, specific IgG antibodies against C. pneumoniae in Finnish men were significantly associated with lower HDL-C, lower HDL-C/total cholesterol ratio, and higher triglyceride concentrations.[10] Laurila et al [8], in another study, reported that Finnish men with persistent antibodies against C. pneumoniae during a 3-year period showed a similar atherogenic lipid profile such as decreased HDL-C in addition to elevated triglycerides and total cholesterol levels, indicating that chronic infection with C. pneumoniae is associated with a serum lipid profile known to be a cardiovascular risk [8]. Similarly, in 199 male participants of the World Health Organization–MONICA (MONItering of Trends and Determinants in CArdiovascular Disease) population survey in Northern Ireland, Murray et al. [6] found lower HDL-C, lower HDL-C/total cholesterol ratio, and higher total cholesterol levels in seropositive men than in men who were seronegative for IgG antibodies against C. pneumoniae. They also found similar findings when the comparisons were adjusted for age, measures of socioeconomic status, smoking habit, alcohol consumption, BMI, and season of screening. Hence, the existence of an association between chronic C. pneumoniae infection and an atherogenic lipid profile in men was suggested [6].

The most prominent limitation for the studies of Laurila and et al[8] as well as Kaftan and Kaftan [20] that showed a robust association between C. pneumoniae infection and lipid levels was the lack of adjustment for variable confounders in their analyses. However, Jaworowska and Bazylak [9] showed that chronic and persistent C. pneumoniae infection can affect serum lipid profile indices in overweight and obese women when potential confounders such as age, BMI, and lifestyle factors are considered in multivariate regression analysis. In the current study, we observed significant differences in the LDL-C and triglyceride levels in subjects who were C. pneumoniae IgG seropositive compared with those who were seronegative. However, these significant associations did not persist after adjustment for age, sex, and cardiovascular risk factors in multivariate analyses.

There are scarce studies about the association between chronic infection with C. pneumoniae and lipid alterations in women. Murray et al [6] reported that C. pneumoniae IgG seropositivity was not significantly associated with an atherogenic lipid profile in women. However, Jaworowska and Bazylak [9] found, for the first time, the significant association between double-positive C. pneumoniae serology (IgG+/IgA+) and lipid profile alterations among obese females. In our study, the association between C. pneumoniae IgG seropositivity and low HDL-C levels was independent of sex.

Smoking status has a correlation not only with C. pneumoniae [21] but also with low HDL-C levels [22]. Previously, we reported that concurrent elevated hsCRP and chronic infection with C. pneumoniae was associated with coronary artery disease [23]. In current study, subjects who were seropositive had higher hsCRP levels than subjects who were seronegative. Therefore, we considered both smoking status and circulating hsCRP levels in the logistic regression analysis to elucidate the independent association of C. pneumoniae IgG seropositivity with low HDL-C. This significant association between C. pneumoniae IgG seropositivity and low HDL-C remained when we excluded subjects with prevalent IHD in the logistic regression analysis, indicating that this association is beyond the observed link between chronic C. pneumoniae infection and IHD [1-3].

The precise mechanism or mechanisms by which infection with C. pneumoniae might reduce HDL-C are unknown. It is theoretically possible that chronic C. pneumoniae is related to alterations in the serum lipid profile, especially low HDL-C levels, through mechanisms other than the suggested chlamydial LPS-induced proinflammatory cytokines production [7-10].

Chlamydia species, as obligate intracellular pathogens, replicate in a dynamic lipid-containing membrane-bound compartment called an inclusion. They have evolved efficient mechanisms, such as recruiting lipid modifying enzymes and activating signaling transduction pathways, to acquire essential host cell lipids (e.g., glycerophospholipids, sphingolipids, and cholesterol) to fulfill their lipid needs [24].

ATP -binding cassette transporter A1 (ABCA1) mediates reverse cholesterol transport through influencing the efflux of cellular cholesterol and phospholipids to lipid-free apoA-1 to initiate the formation of HDL-C [25, 26]. It has been shown that C. pneumoniae infection decreases ABCA1 expression in epithelial cells [27]. Of interest, recently, Cox et al [26] demonstrated that C. trachomatis alters the intracellular trafficking of multiple components of the host cell lipid transport system involved in the formation of HDL, including ABCA1, CLA1, and apoA-1, to acquire a source of phospholipids that are necessary for its growth within infected cells. The recruitment of the host HDL biogenesis machinery to the inclusion of chlamydia-infected cells may provide clues to explain the observed decreased levels of HDL-C in humans.

Undoubtedly, to understand better the mechanisms for a chlamydia-induced atherogenic lipid profile, the complex interaction of the mechanisms behind C. pneumoniae–induced acceleration of atherosclerosis and chlamydia-induced macrophage foam cell formation—such as inhibitory effects on human cholesterol 7α-hydroxylase (CYP7A1) gene transcription [28], activation of toll-like receptor (TLR) 2 [29], activation of TLR-mediated innate immune and liver X receptor α (LXRα) signaling pathways [30], activation of the lectin-like oxidized LDL receptor-1 [31], upregulating acyl-coenzyme A :cholesterol acyltransferase 1 [32], disturbance in cholesterol homeostasis via JNK -PPARgamma in macrophages [33], MAPK-PPARα/γ reciprocal signal pathways [34],activity of hepatic cholesterol 7α-hydroxylase (CYP7A1) promoter [35], upregulation of the expression of scavenger receptor A, cluster of differentiation 36, acyl-coenzyme A: cholesterol acyltransferase 1 mRNA and proteins in LDL-treated human umbilical vein endothelial cells [36] should be considered through an interdisciplinary approach.

To the best of our knowledge, the current study was the largest population-based study for serological investigation of C. pneumoniae in relation to an atherogenic lipid profile in both men and women. However, we acknowledge the study limitations. The present cross-sectional study does not allow for inferring causality from the results. Future research should include longitudinal studies of the alteration in lipid indices, proinflammatory biomarkers, and evidence of serological markers of C. pneumoniae to determine the temporal sequence of any relationship. We assessed C. pneumoniae IgG seropositivity with single measurements; the changes in this serological marker over time could not be reflected in the current

study. We did not measure IgA or IgM titers for C. pneumoniae infection. However, currently, there is no valid marker to show the presence of chronic C. pneumoniae infection in seroepidemiological studies [37]. In addition, it has been reported that there is a significant relationship between organism-specific DNA or antigens in coronary arteries obtained at autopsy and levels of pre-existing C. pneumoniae–specific IgG antibody titers but not IgA or IgM titers [38].

In conclusion, in a large representative sample of a general population, we showed a strong association between C. pneumoniae IgG seropositivity and low HDL-C. This association was independent of known traditional cardiovascular risk factors and circulating hsCRP levels in both men and women. However, a large prospective cohort study is warranted to determine whether C. pneumoniae infection is a robust predictor of low HDL-. Clearly, more works on the complex molecular mechanisms and signaling pathways involved in C. pneumoniae–induced acceleration of atherosclerosis and chlamydia-induced macrophage foam cell formation are needed to clarify pathogenetic mechanisms of a chlamydia-induced atherogenic lipid profile in humans. The effective administration of antichlamydial agents in the treatment of chronic C. pneumoniae is only the beginning of a new approach in the management of low HDL -C levels. Hence, the future of low HDL therapy promises to be exciting and groundbreaking.

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Citation: Vahdat K, Dadjou H, Hadavand F, Kalantarhormozi MR, Ostovar A, Assadi M, et al. The Association of Chlamydia Pneumoniae IgG Seropositivity with an Atherogenic Lipid Profile in a General Population: The Persian Gulf Healthy Heart Study. Austin J Endocrinol Diabetes. 2014;1(6): 1026.