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# Association of lipids with coronary heart disease in a saudi population

## *Associação de lipídios com doença cardíaca coronariana em população saudita*

Mohmed Elfatih Ashmaig<sup>1</sup>, Khalifa Ashmeik<sup>2</sup>, Atif Ahmed<sup>2</sup>, Samia Sobki<sup>3</sup>, Muheeb Abdulla<sup>2</sup>

### Abstract

**Background:** The Saudi population is known to have an unhealthy diet in addition to physical inactivity.

**Objective:** To investigate the lipid-mediated risk factors that might be associated with increased incidence of coronary heart disease in the Saudi population as this was found in Western populations.

**Materials and Methods:** Two hundred and twenty subjects suspected of having coronary heart disease underwent coronary angiography and blood draw following a 12-hour fast. Total and HDL cholesterol, triglycerides, Lp(a) and lipoprotein lipase were measured by standard methods. Small, dense LDL was measured by the iodixanol method with an ultracentrifugation of only 2.5 hours.

**Results:** One hundred and forty subjects were found to be positive for coronary heart disease while 80 subjects were shown to be negative for this disease. Statistically significant risk factors for coronary heart disease in the Saudi population were hypertriglyceridemia ( $1.93 \pm 0.95$  versus  $1.45 \pm 0.16$  mmol/L;  $p < 0.0001$ ); low HDL cholesterol ( $1.09 \pm 0.55$  vs  $1.33 \pm 0.63$  mmol/L,  $p = 0.0001$ ); high Lp(a) ( $46.8 \pm 45.58$  versus  $29.06 \pm 17.03$  mg/dL;  $p = 0.019$ ); and the presence of small, dense LDL ( $1.0314 \pm 0.0028$  versus  $1.0300 \pm 0.0003$  g/kg;  $p = 0.0099$ ). Total cholesterol ( $4.99 \pm 1.11$  versus  $4.75 \pm 1.11$  mmol/L;  $p = 0.099$ ), LPL ( $35.56 \pm 26.6$  versus  $27.89 \pm 11.96$  IU/L;  $p < 0.059$ ), and LDL cholesterol ( $3.06 \pm 1.12$  versus  $2.79 \pm 1.08$  mmol/L;  $p = 0.08$ ) were not found to be statistically significant coronary heart disease risk factors.

**Conclusions:** This study indicates that high TG, low HDL, high Lp(a) and the presence of small, dense LDL may contribute to the incidence of coronary heart disease and that TC was not significantly associated with incidence of coronary heart disease in the Saudi population.

**Keywords:** Coronary disease; triglycerides; cholesterol, HDL; LDL; lipoproteins.

### Resumo

**Contexto:** A população saudita é conhecida por apresentar dietas não saudáveis, além de inatividade física.

**Objetivo:** Investigar os lipídeos como fatores de risco que podem associar-se com o aumento da incidência de doença cardíaca coronariana na população saudita, uma vez que isso foi encontrado na população ocidental.

**Materiais e Métodos:** Duzentos e vinte indivíduos com suspeita de doença cardíaca coronariana submeteram-se a angiografia coronária e coleta de sangue, após jejum de 12 horas. Colesterol total e HDL, triglicerídeos, Lp(a) e lipase lipoproteica foram calculados por métodos padrão. LDL pequena e densa foi medida pelo método do iodixanol com ultracentrifugação por apenas 2,5 horas.

**Resultados:** Cento e quarenta indivíduos apresentaram resultado positivo para doença cardíaca coronariana, enquanto 80 pacientes mostraram resultado negativo. Os fatores de risco estatisticamente significantes para doença cardíaca coronariana na população saudita foram hipertrigliceridemia ( $1,93 \pm 0,95$  versus  $1,45 \pm 0,16$  mmol/L;  $p < 0,0001$ ); baixo colesterol HDL ( $1,09 \pm 0,55$  versus  $1,33 \pm 0,63$  mmol/L;  $p = 0,0001$ ); Lp(a) elevada ( $46,8 \pm 45,58$  versus  $29,06 \pm 17,03$  mg/dL;  $p = 0,019$ ) e a presença de LDL pequena e densa ( $1,0314 \pm 0,0028$  versus  $1,0300 \pm 0,0003$  g/kg;  $p = 0,0099$ ). Colesterol total ( $4,99 \pm 1,11$  versus  $4,75 \pm 1,11$  mmol/L;  $p = 0,099$ ), colesterol LPL ( $35,56 \pm 26,6$  versus  $27,89 \pm 11,96$  IU/L;  $p < 0,059$ ) e LDL ( $3,06 \pm 1,12$  versus  $2,79 \pm 1,08$  mmol/L;  $p = 0,08$ ) não foram fatores de risco estatisticamente significantes para doença cardíaca coronariana.

**Conclusões:** Este estudo indica que elevados triglicerídeos, baixo HDL, elevada Lp(a) e a presença de LDL pequena e densa podem contribuir para a incidência de doença cardíaca coronariana. O colesterol total não foi significativamente associado à incidência de doença cardíaca coronariana na população saudita.

**Palavras-chave:** Doença das coronárias; triglicerídeos; colesterol HDL; lipoproteínas LDL; lipoproteínas.

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## Introduction

Coronary heart disease (CHD) is the leading cause of morbidity and mortality in industrial and developing countries. The Framingham Heart Study commenced in 1948 to identify common risk factors contributing to CHD in over 5,000 men and women between the ages of 30 and 62<sup>1</sup>. As part of the Framingham Study, cholesterol was monitored in subjects who had not yet developed symptoms of CHD. The data showed that in subjects less than 50 years old, CHD was related to their total cholesterol (TC) level, but no relationship was found in subjects over 50 years old<sup>2</sup>. The Prospective Cardiovascular Münster (PROCAM), another epidemiological heart study that ran from 1979 to 1985, analyzed data from more than 26,000 subjects and is considered the first study to demonstrate an epidemiological link between plasma TG levels and CHD<sup>3</sup>.

The Helsinki Heart Study, which focused on CHD prevention in a group of dyslipidemic middle-aged men who were free from CHD or any other major illness, demonstrated an epidemiological link between plasma triglyceride level and CHD<sup>4,5</sup>. A meta-analysis of the PROCAM and Helsinki heart studies in which the patient's triglyceride levels were measured in a fasting state identified hypertriglyceridemia as a risk factor for CHD<sup>6,7</sup>. In a 15-year long population-based prospective study of 11,068 Japanese subjects aged between 40-69 years initially free of CHD or stroke, the incidence of CHD was positively correlated to high triglycerides in both genders<sup>8</sup>. Furthermore, a 17-year meta-analysis of population-based prospective studies of 46,413 men and 10,864 women confirmed that plasma triglyceride level is indeed a significant risk factor for cardiovascular disease independent of HDL-cholesterol levels for both men and women<sup>9</sup>. Though cholesterol efflux is considered to be one of the most important parts of reverse cholesterol transport (RCT), removing cholesterol from the macrophages in the subintima to the liver for excretion, mediated by both active and passive processes<sup>10,11</sup>.

There is now a wealth of evidence from cross-sectional and prospective studies to indicate that LDL particle size is significantly associated with CHD and predictive of increased coronary risk. The relationship between small, dense LDL and CHD risk has been described in a range of different situations<sup>12-21</sup>. One underlying mechanism to explain the production of small, dense LDL, involves the overproduction and increased residence time of large, triacylglycerol-rich VLDL in the postprandial phase, a situation thought to involve the pathways of insulin resistance<sup>22,23</sup>. Hence, an increase in the number of small, dense LDL particles may originate

from a defect in the metabolism of triglyceride-rich lipoproteins as described by Berneis and Krauss<sup>22</sup>. There are a number of possible mechanisms to explain the link between small, dense LDL and CHD. Firstly, the passage of serum lipoproteins into the arterial wall is known to be a function of particle size, so that small, dense LDL more readily penetrate the artery wall than larger LDL<sup>13</sup>. Arterial proteoglycans may selectively bind small, dense LDL with higher affinity, possibly through a specific apolipoprotein B (apoB) binding site<sup>23</sup>.

The hypothesis of this study is that the predominance of small dense LDL and the elevated level of traditional coronary risk factors influenced by diet and physical inactivity might play a role as major risk factors for CHD in an angiographically defined unique group in the Saudi Arabian population. This under-studied Saudi population has been targeted for multiple lipid-mediated risk factors measurement, particularly the small, dense LDL. The objective of this study was to evaluate this hypothesis on the strength of the available evidence that the Saudi population has a diet and lifestyle that is inappropriate for cardiovascular health<sup>24</sup>. We hypothesize that the Saudi population will demonstrate increased cardiovascular risks as determined by traditional and emerging biomarkers of CHD risk, particularly small, dense LDL.

## Materials and methods

### Subjects

The ethical approval from the local medical ethical committee at Prince Sultan Cardiac Centre in Riyadh, Saudi Arabia, was obtained before the study was started. Informed written consent was obtained from all subjects before blood draw. Two-hundred and twenty subjects were randomly selected and recruited from the Cardiology Department at Prince Sultan Cardiac Center if they were suspected of having CHD (not previously diagnosed as CHD patient) and were not on lipids lowering medicine or any prescribed medicine except insulin or oral diabetes control medicines. The subjects were selected for coronary angiography based on one or more of the following criteria: chest pain, shortness of breath, resting or exercise stress ECG changes (such as abnormal Q-waves, ST depression or ST elevation), or hypertension. The subjects were then divided into two groups depending on the findings of the coronary angiogram:

1. positive for CHD (CHD+), if an occlusion of  $\geq 50\%$  in any coronary artery vessel was detected; all subjects had at least one or more vessel of 90 to 100% occlusion;
2. negative for CHD (CHD-), if no occlusion was detected by coronary angiography.

Subjects with long hospitalization, severe or chronic illness such as cancer or renal disease were excluded from the study.

### **Heparin**

All subjects in this study received a heparin dose calculated according to their body mass index (data not shown) for the angiography procedure and release of capillary-bound lipoproteins lipase (LPL) before the sample was drawn.

### **Blood collection**

All subjects fasted for 12 hours, and then venous blood was obtained by venesection using a 21-gauge Venflon needle just before the angiogram procedure started. Blood was collected into plain SST tubes for lipids (TC, TG, HDL, LPL, Lp(a) and LDL). Small, dense LDL was measured from serum samples stored at  $-70^{\circ}\text{C}$ . All subjects then underwent a standard coronary angiography carried out by a cardiologist at Prince Sultan Cardiac Center.

### **Plasma lipid and lipoprotein analysis**

TC, TG and HDL cholesterol were determined by an automated enzymatic technique using a Hitachi 917 auto-analyzer from Roche Diagnostics (Riyadh, Saudi Arabia). LDL cholesterol was calculated using the Friedewald equation:  $\text{LDL cholesterol (mmol/L)} = \text{TC} - (\text{TG}/2.2) - \text{HDL cholesterol}$ . Friedewald equation is inaccurate at higher triglycerides levels, therefore subjects with triglycerides of  $\geq 4.52 \text{ mmol/L}$  were excluded from the LDL analysis. Lp(a) was quantified using an immunoturbidimetric assay on the Hitachi 911 auto-analyzer. All measured assays were established on Hitachi analyzers 911 or 917 with tested accuracy and precision in addition to the two levels of controls materials (low and high) all of which were meeting the acceptable criteria (data not shown).

### **Iodixanol gradient separation for small dense LDL**

Iodixanol is a contrast media commercially available as Optiprep (Cambridgeshire, UK). Iodixanol is a non-ionic iso-osmotic medium and has been validated for use in this technique due to its ability to form self-generating gradients. This enables the separation of the LDL subfractions to form not discrete bands but rather banding patterns, which can then be analyzed using computer software. As previously described<sup>25</sup>, and in this procedure, the iodixanol gradient was prepared in a 4.9 mL tube as follows: first, 1.52 mL plasma

was mixed with Optiprep (60% (w/v) iodixanol) and pre-stained with Coomassie blue R-250 (50 mg/mL in PBS; from Sigma, (Milwaukee, WI, USA)). In this plasma sample, 0.4 mL of the Optiprep solution and 80  $\mu\text{L}$  of the Coomassie blue solution was added to provide a working sample of 2 mL with the desired concentrations. The upper layer thus consisted of a 9% solution of iodixanol prepared using phosphate buffered saline (PBS) as the diluent, so that the final density is 1.050 kg/L. Then, 3.4 mL aliquots of this solution were transferred to 4.9 mL Beckman Optiseal centrifuge tubes. A syringe and cannula was used to carefully under-layer 1.5 mL of the working solution. The tubes were housed in a Beckman NVT65.2 near vertical rotor (Beckman Coulter, Inc. Fullerton, CA, USA). Separation was performed in a Beckman Optima L-100 ultracentrifuge at 370,000g for 2.5 h. Post-centrifugation, the tubes were carefully removed from the rotor and photographed with a Nikon D1X digital camera. Digital images were downloaded directly to a PC in which they were analyzed using Total-lab 1D gel-scan software (Pharmacia UK, Milton Keynes, UK). This software converted the photographs of the stained LDL into LDL profiles comprised of an x-axis of distance (mm) versus a y-axis of pixel intensity. The package then automatically assigned relative electrophoretic migration distance values (Rf values) to the principal peak and any other peaks present.

The main drawbacks with this method are the partial overlap between LDL and HDL boundaries and the challenge in scaling up for testing larger numbers of patient's samples in hospital or reference laboratories. Furthermore, the minimum sample required for this method is 1.52 mL plasma compared to  $\leq 5 \mu\text{L}$  for some methods for measuring/detecting small, dense LDL such as non-denaturing polyacrylamide gradient gel electrophoresis.

### **Statistical analysis**

The data were analyzed using the following software: (1) JMP from SAS Institute Inc. (Cary, NC, USA); (2) InStat statistical package from InStat Corporation (InStat, San Diego, USA). The following statistical tests were used: nonparametric analysis of variance (ANOVA), unpaired t test, and the chi-square test. All data are presented as mean  $\pm$  the standard deviation (SD).

### **Results**

Two hundred and twenty subjects suspected of having CHD underwent coronary angiography and blood draw following a 12-hour fast. Based on coronary angiography data, one hundred and forty subjects were found to be positive for CHD

**Table 1:** Summary of subjects' demographic data and test results

	CAD+ (n=140)	CAD- (n=80)	p value
Age group(years)±SD	51±11.6	41±10.8	<0.0001
Male/female	110/19	44/35	<0.0001
Hypertension	31	27	0.34
Diabetes (type I + type II)	63	12	<0.0001
Smokers	49	13	<0.04
TC mmol/L ± SD	5.0±1.11	4.75±1.10	0.099
TG mmol/L ± SD	1.93±0.95	1.45±0.85	<0.0001
HDL-C mmol/L ± SD	1.09±0.55	1.33±0.63	0.0001
TC/HDL-C ± SD	5.16±1.69	4.07±1.44	<0.0001
LDL-C mmol/L ± SD	3.06±0.12	2.79±1.09	0.08
LPL U/L ± SD	35.56±26.63	27.9±11.96	0.059
Lp (a) mg/dL ± SD	46.87±45.58	29.06±17.03	0.019
s,denseLDL g/kg ±SD	1.031±0.0028	1.030±0.0003	0.0099
% s,denseLDL:large LDL	28.55±13.62	23.38±90.82	0.01

SD: standard deviation; TC: total cholesterol; TG: triglycerides; HDL-C: high density lipoproteins cholesterol; LDL-C: low density lipoproteins cholesterol; LPL: lipoproteins lipase; Lp(a): lipoprotein(a); s,dense: small dense.

(mean age: 51 years, 79% men) while 80 subjects were shown to be negative for CHD (mean age: 41 years, 55% men). None of subjects had renal disease, previous CHD, myocardial infarction or cerebrovascular disease, and 45% in the CHD positive group (mean HbA1C=9.0%) and 15% in the CHD negative group (mean HbA1C=5.9%) had diabetes mellitus (type I or II). Metabolic syndrome was found in 63% of the CHD positive compared to only 8% in the CHD negative group. Hypertension was found in 22% of the positive and in 34% of the CHD negative group. History of Kawasaki disease was reported in one subject in CHD positive group. Table 1 shows the main characteristics of the study population including the information's on lipids, lipoproteins and small dense LDL.

Coronary angiography was used to distinguish between normal and diseased coronary arteries, and for determining the severity of disease. A total of 128 subjects (one subject was excluded due to incomplete data) had between one to five diseased vessels, with disease severity ranging from 50 to 100% occlusion. Of those subjects, 25% had single vessel disease, 31% had double vessel disease, 34% had triple vessel disease, 9% had four diseased vessels, and 2% had five diseased vessels. Of these subjects, 85% had left anterior descending artery (LAD) disease, 64% had left circumflex (LCX) disease, 12% had obtuse marginal artery (OMA) disease, 58% had right coronary artery (RCA) disease, 6% had left main artery (LM) disease, 6% had diagonal artery (DI) disease, 4% had posterior descending artery (PDA) disease, and 1% had posterior lateral artery (PLA) disease (subjects with multiple vessel disease may overlap in percentage calculations). LAD disease contributed to 84% of the instances of single vessel disease, 79% of the instances of

double vessel disease, 91% of the instances of triple vessel disease, and all of the instances of four and five vessel disease.

## Discussion

The Saudi population is renowned for its high incidence of coronary artery disease (CHD) in comparison to other Middle Eastern countries. While the origin of increased CHD risk in this relatively understudied group is unknown this makes the observations in this study somewhat unique.

The hypothesis of this project stated that the predominance of small dense LDL and the elevated levels of traditional coronary risk factors influenced by diet and physical inactivity may be major risk factors for the development of CHD in angiographically defined subjects in the Saudi population.

The aim of the current research was to undertake a case-controlled study of CHD risk factors from a randomly selected sample of the Saudi population such as cigarette smoking and hypertension, with a focus on lipid mediated risk factors such as TC, TG, Lp(a), lipoprotein lipase, HDL-cholesterol, LDL cholesterol, and small, dense LDL.

In this study, CHD+ group was on average older than the CHD- group, which may add some influence of the age contribution as a risk to CHD, even after adjustment for age difference this group remained to have higher incidence of CHD risk factors. The number of females within the CHD+ group were small due to the lesser number of women qualified for the study; in addition this may provide some evidence that females under the age of 50 years old may be at lower risk of CHD compared to males in the Saudi population similar to what was found in western populations.

Cigarette smoking is known to increase the risk of CHD. Our data show that smokers were more prevalent in the CHD+ group, these subjects demonstrated multiple sites of atherosclerosis ranging from two to four vessel disease, except in eight subjects, in which single vessel disease was detected. The degree of atherosclerosis was mostly 100% occlusion with several between 50 to 90%. Of these smokers, 37 had slightly increased TG (>1.5 mmol/L), slightly increased TC (5.2 to 6.99 mmol/L) and all had Lp(a) levels of >30 mg/dL, which suggests that cigarette smoking may play some role as a risk factor by acting synergistically with other risk factors leading to an increased incidence of CHD in the Saudi population, as has been seen in other populations.

Diabetes is well-known to have strong relationship with CHD. In this study, diabetes was found to be dominant in CHD positive group. Diabetes may influence the metabolic syndrome, lipid abnormalities and atherosclerosis, all of

which may lead to CHD as this was previously reported in Western population.

Hypertension was equally distributed in both CHD+ and CHD- groups, but in lesser proportion compared to the non-hypertensive subjects within each group. This finding does not provide strong evidence to support the role of hypertension in the etiology of CHD in this population, which differs from what was found in other populations. In addition, hypertension may or may not play a major role in development of CHD in the Saudi population and could possibly be secondarily or non-causally present within the subjects with heart disease.

TC and LDL-cholesterol were not significantly different between the CHD+ and CHD- groups ( $p < 0.1$ ), suggesting that total and LDL cholesterol measurement may have less predictive power on the incidence of CHD in the Saudi population (compared to the other risk factors) which is different than what was found in the past in other populations<sup>1</sup>. For both groups mean TC remained below the desired limit ( $< 200$  mg/dL or  $< 5.2$  mmol/L) assigned by the guidelines of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATPIII); the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. This research finding suggests that the measurements of TC and LDL-cholesterol are insufficient to discriminate between individuals at risk of CHD and those who are not at risk. In favor of this finding, some recent research has provided more evidence suggesting that smaller LDL particles are more atherogenic and hence more closely associated with CHD, regardless of total or LDL cholesterol levels. Furthermore, TC and LDL-cholesterol measurements will not indicate the presence or absence of small, dense LDL and other TG enriched atherogenic particles. Therefore measurement of the latter parameters may add considerable discriminatory power for diagnosing and predicting cardiovascular risk. In conclusion, CHD is highly related to other risk factors and the TC itself may not be a significant predictor of CHD risk in the Saudi population.

As a major component of an atherogenic lipoprotein phenotype (ALP), a predominance of small, dense LDL has been shown to be present in patients with CHD+ compared to the CHD- group ( $p < 0.01$ ), with all patients with predominance of the small, dense LDL subclass i.e. Pattern B falling into this disease group. This finding might suggest that small, dense LDL plays some major role as an atherogenic risk factor for CHD in the Saudi population, thus confirming the original hypothesis.

Serum concentrations of TG were significantly higher in the CHD+ compared to the CHD- group ( $p < 0.0001$ ); thus triglycerides were one of the major risk factors for CHD in the Saudi population. This relationship may have

a multifactorial origin and could arise from metabolic defects associated with obesity, as found in metabolic syndrome and diabetes, or in response to a high fat and/or carbohydrate diet or to physical inactivity, all of which may contribute to the production of small, dense LDL and increase risk of CHD in the Saudi Arabian population. These current findings would support recommendations to modify lifestyle through diet changes in addition to exercise as a first line of prevention against CHD. This may require medication to lower serum TG, all of which may improve health and reduce the incidence of CHD in this population.

RCT is known to be a function of HDL. In this study, serum HDL was found to be significantly lower in the CHD+ group compared to the CHD- group ( $p = 0.0001$ ), which may indicate either decreased synthesis or increased catabolism of HDL, and that as a result, cholesterol efflux may be compromised in this population. The transforming of HDL into smaller and denser particles by increased serum TG may underlie the rapid clearance of HDL from the circulation, thus increasing the demand on HDL in RCT.

The TC/HDL-cholesterol was significantly higher in the CHD+ group compared to the CHD- group ( $p < 0.0001$ ). This is due to significantly lower HDL-cholesterol in the CHD+ group, the HDL-cholesterol concentration alone was very nearly as statistically significant ( $p = 0.0001$ ) as the TC/HDL ratio, and not due to elevated TC. In this study, TC/HDL ratio of  $> 4.1$  may discriminate between individuals at CHD risk from those who are not at risk in Saudi population.

The activity of total LPL in post-heparin plasma was found to be higher in the CHD+ group compared to the CHD- group, but not significantly so ( $p < 0.059$ ). LPL is known to be the key enzyme in hydrolyzing the triglycerides carried by lipoproteins to provide the tissue with fatty acids<sup>26</sup>. Low levels of plasma LPL have been associated with increased TG levels which may promote and increase incidence of CHD<sup>27,28</sup>. The result of this research finding differs from that previously reported in regards to the low level of LPL activity and its relation to CHD.

Lp(a) was significantly higher in the CHD+ group compared to the CHD- control group ( $p = 0.019$ ) as previous studies had shown that high plasma Lp(a) is associated with premature coronary atherosclerosis<sup>29</sup>. The findings from the present study suggest that Lp(a) may play a role in identifying and predicting individuals at risk for CHD in the Saudi population.

In conclusion, the findings of this study would suggest that the assessment of CHD risk by measurement of a traditional serum lipid profile (TC, LDL-cholesterol, HDL-cholesterol, TG) may be inadequate in this particular population. The addition of small, dense LDL measurement,



may further improve the ability to discriminate individuals at CHD risk in the Saudipopulation.

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