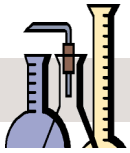

Serum Total Cholesterol and Cardiovascular Mortality in Israeli Males: The CORDIS Study

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Abstract

Background: The degree to which serum total cholesterol predicts cariovascular disease is uncertain. While most authors have placed TC among the most powerful risk indicators of CVD, some have claimed that it predicted CVD in women only, or even not at all.

Objective: To determine the predictive value of serum total cholesterol relative to diabetes, smoking, systolic blood pressure and body mass index (kg/m^2), for cardiovascular disease mortality in 3,461 occupationally active Israeli males.

Methods: A prospective follow-up was carried out for the years 1987–1998 to determine the effect of age, smoking habits, a history of diabetes, SBP, BMI and TC, at entry, on CVD mortality.

Results: There were 84 CVD deaths during a total of 37,174 person-years follow up. The hazard ratios (95% confidence intervals) for CVD mortality with respect to variables at entry were: diabetes 5.2 (2.1–13.2), age 2.2 (1.7–2.9), smoking 1.3 (1.0–1.8), SBP 1.4 (1.1–2.0), TC 1.5 (1.0–2.1) and BMI 1.2 (0.7–2.2). Among non-obese, non-diabetic, normotensive subjects the hazard ratio of TC adjusted for age and smoking was 1.16 (1.09–1.22) per 10 mg/dl. In the remaining subjects it was 1.04 (0.98–1.12) only. There was a significant interaction between TC and diabetes, hypertension or obesity (P=0.003).

Conclusions: In this population of Israeli males we found an interaction between TC and other risk indicators for CVD. Confirmation is required for the unexpected finding that the predictive value of TC for CVD mortality among non-diabetic, non-obese and normotensive subjects exceeded that among subjects with either of these risk factors.

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TC = total cholesterol
CVD = cardiovascular disease
SBP = systolic blood pressure
BMI = body mass index

Advancing age, diabetes, cigarette smoking, systolic blood pressure, body mass index and serum total cholesterol increase the risk of cardiovascular disease [1–10]. Since these risk indicators tend to cluster in the same individuals [7,11], the degree to which TC is an independent predictor of CVD is uncertain. Some researchers place TC among the three most powerful predictors of CVD [2–4,6,8]. Others found that it predicted CVD in women but not in men [1], that CVD mortality was associated with SBP and smoking but not with TC [5], that CVD mortality ratios for the highest compared with the lowest TC quartiles in eight nations ranged from 1.1 to 2.3 [9], and that prediction of CVD within a country using risk computations from other countries might lead to errors of from -19% to +51% [8].

The Israeli population ingests less fat [12,13] and in 1986 had lower TC values [14] than the U.S. population. A 23 year follow-up of the 10,059 participants in the Israeli Ischemic Heart Disease Study revealed that between 1960 and 1983 lipids were less effective in predicting CVD mortality than hypertension and smoking. The authors suggested that the association between TC and mortality is affected by co-existing CVD risk factors [15]. The objective of the present study was to re-examine the independent predictive value of TC relative to that of diabetes, smoking, SBP and BMI for CVD mortality in a more recently studied population of occupationally active Israeli adults who were followed between 1987 and 1998.

Materials and Methods

Study population

In 1985 a total of 5,547 Jewish male employees of 21 furniture, electronic, textile, food, tire and metal manufacturing plants throughout Israel were located and offered free screening examinations for selected risk factors for CVD. Almost 70% were blue-collar workers. A total of 3,816 (68.8%) of all eligible employees responded and were entered between 1985 and 1987 into the Cardiovascular Occupational Risk Factor Determination in Israeli Industry (CORDIS) study. The median age was 43 years for the entire

cohort, 44 years for the participants, and 39 years for the non-participants. We excluded 255 men whose recorded identity numbers did not match those from the Ministry of Interior Affairs – 121 men aged 25 or less, 117 men with a history of cerebral vascular events or myocardial infarction, and 96 men with missing data on serum cholesterol, blood pressure, smoking history and body mass index. Complete data were available for the remaining 3,461 subjects.

Data collection

Between 1985 and 1987 trained technicians visited the plants and conducted interviews and physical examinations in a quiet air-conditioned room allocated by the management. The interviews and the examinations were carried out between 7 a.m. and 4 p.m. in a non-fasting state on the same day; blood samples were taken on a different day within several weeks of the interviews.

Independent variables

At entry into the study the following variables were noted:

- Age (<30, 30–39, 40–49, and >50 years)
- History of diabetes (yes or no)
- Blood pressure measured with a standard mercury sphygmomanometer, once with the subject supine and twice with the subject seated (1 minute apart). SBP corresponded to the first Korotkoff sound. The average of the second and third measurements was included in the analysis. A person was defined as hypertensive if he reported being under treatment for hypertension or if his SBP equaled or exceeded 140/90.
- Weight was measured in kilograms using a Seca electronic scale, accurate to 0.1 kg, with the subject wearing light clothing and without shoes.
- Height was determined in centimeters. A person was defined as obese if his body mass index was 27.8 kg/m^{-2} or higher [16].
- Total cholesterol level was determined with the enzymatic color method (CEH Mas Cholesterol reagent, Lancer, USA) [17], and recorded both as a continuous variable and as low (<180 mg/dl), intermediate (180–239 mg/dl) and high (≥240 mg/dl).
- High density lipoprotein cholesterol was measured after precipitation with magnesium phosphotungstate (Sigma, USA).
- Triglycerides were determined by the enzymatic color method (Biotrol). TC and HDL-C measurements were standardized through the lipid reference laboratory of the MONICA project of the World Health Organization and average coefficients of variation of 3% and 4% respectively were obtained.
- Low density lipoprotein cholesterol level was derived from the equation: LDL-C = TC – HDL – TG/5 [18].
- Smoking habits were classified into two mutually exclusive groups: never smokers, or current/past smokers. We defined past smokers as persons who did not smoke at the time of the examination but who reported a past history of smoking.

Outcome measure

The outcome measure was mortality. Data were obtained from the National Death Registry of the Israel Ministry of the Interior, and verified by contacting the households of 2,690 of the participants during 2 years after the first 8 years of the follow-up period. There were no deaths other than those recorded in the National Death Registry. Data on the causes of death were derived from the death certificates and from the reports of cancer deaths from the National Cancer Registry. Causes of death were classified into CVD (ICD-9-CM: 401-459.9) and other causes.

Analysis

Data were analyzed with the SAS software (SAS Institute, Cary, NC, USA). We used the two-sample *t*-test for differences between groups of continuous variables, and Pearson's, Chi-square and Fisher's exact tests for differences in categorical parameters. Multivariate analyses of independent variables affecting total and CVD mortality were performed using Cox proportional hazard regression models (SAS PHREG procedure).

Results

• ***Correlates of total serum cholesterol:*** Average TC levels, prevalence of self-reported diabetes and proportion of overweight (BMI 27.8 kg/m^2 or more) increased significantly with age (data not shown). Bivariate analysis revealed that TC levels were significantly related to systolic blood pressure, BMI, HDL-C, LDL-C and triglyceride levels. Participants with higher TC levels were more likely to be past or current smokers and to have diabetes and hypertension [Table 1].

• ***Predictors of all cause mortality:*** A total of 230 participants died during the 11 year follow-up. The observed total mortality was less than expected in the total Israeli population, with a standardized mortality ratio of 73% (95% confidence intervals 64–84) [Table 1]. Participants who died were older. They were more likely to have hypertension, diabetes and to be current or past cigarette smokers. Cox's proportional hazards analysis showed that diabetes, age and smoking were independent predictors of all cause mortality [Table 2].

• ***Predictors of cardiovascular mortality:*** There were 84 CVD deaths. The standardized CVD mortality ratio was 69% (95% CI 53–82), and it increased with increasing age-corrected TC levels at entry into the study [Table 1]. Those who died of CVD were significantly older. They were more likely to be current or past cigarette smokers, and to have diabetes, hypertension and higher TC and LDL-C levels. Cox's proportional hazards analysis identified age, diabetes,

HDL-C = high density lipoprotein cholesterol
LDL-C = low density lipoprotein cholesterol

Table 1. Distribution of age-adjusted health-related characteristics of 3,461 male employees at entry into the CORDIS study by total serum cholesterol level

Variable	All	Serum total cholesterol levels (mg/dl)			*P*
		<180	180–239	≥ 240	
Age (yr)	44.3±11	39.4±11	44.8±11	49.3±10	0.001
Sample size (n)	3,461	943	1,752	766	
Person/yr follow up	37,174	10,216	18,865	8,093	
Past/current smokers (%)	58	55	57	67	0.001
Treated diabetes (%)	1.5	1.0	1.6	2.1	0.050
Hypertension (%)	21	12	22	33	0.001
SBP (mm Hg) (mean±SE)	126.3±0.4	124.7±0.4	125.4±0.4	128.3±0.5	0.001
BMI (kg/m^2) (mean±SE)	25.8±0.004	25.1±0.01	26.1±0.008	26.4±0.01	0.001
HDL-C (mg/dl) (mean±SE)	43.5±0.3	42.6±0.4	44.2±0.3	44.9±0.5	0.001
LDL-C (mg/dl) (mean±SE)	132.8±0.7	92.0±0.75	134.0±0.54	184.0±0.86	0.001
Triglycerides (mg/dl) (mean±SE)	155±3.5	117±3.2	155±2.3	215±3.5	0.001
Glucose (mg/dl) (mean±SE)	96.60.4	91.20.6	96.60.5	103.21.2	0.001
All cause mortality (per 10,000 person/yr)	61.9	39.1	58.3	98.8	
Standardized all cause mortality ratio (%) (95% CI)	73 (64–84)	68 (49–93)	69 (57–83)	83 (66–103)	
CVD mortality, (incidence/10,000 person/yr)	22.6	9.8	19.0	49.4	
Standardized CVD mortality ratio (%) (95% CI)	69 (53–82)	44 (21–82)	64 (36–84)	99 (71–134)	

Table 2. Proportional hazard model of the various risk indicators in predicting total mortality during 11 years follow-up in the Israeli CORDIS study in the entire study population (n=3,461)

Variable	Entered as	Parameter estimate	Hazard ratio	95% confidence intervals	*P*
Diabetes	Yes/no	1.40	4.06	6.91–2.38	0.0001
Age	10 year increments	0.94	2.57	3.13–2.11	0.0001
Cholesterol	Low/medium/high	0.06	1.06	1.37–0.82	0.656
SBP (mm Hg)	10 mm Hg increments	0.08	1.09	1.19–0.99	0.062
Smoking, past or present	None/past or current	0.38	1.46	1.81–1.19	0.0003
BMI (kg/m^2)	10 unit increments	0.01	1.01	1.67–0.61	0.956

Table 3. Proportional hazard model of the various risk indicators in predicting cardiovascular deaths during 11 years follow-up in the Israeli CORDIS study in the entire study population (n=3,461)

Variable	Entered as	Parameter estimate	Hazard ratio	95% confidence intervals	*P*
Diabetes	Yes/no	1.65	5.24	2.07–13.2	0.0001
Age	10 year increments	0.81	2.24	1.70–2.91	0.0001
Cholesterol	Low/medium/high	0.37	1.45	0.99–2.07	0.070
SBP (mm Hg)	10 mm Hg increments	0.13	1.43	1.05–1.96	0.011
Smoking, past or present	None/past/current	0.29	1.34	1.02–1.76	0.030
BMI (kg/m^2)	10 unit increments	0.17	1.19	0.65–2.17	0.563

smoking and systolic blood pressure as significant and independent predictors of CVD mortality. TC had a borderline significance in predicting CVD mortality [Table 3].

We subdivided the study population into "low risk" subjects (non-diabetics, with blood pressure <140/90 mm Hg *and* BMI ≤ 27.8), and "high risk" subjects with either of these risk indicators. The risk of dying from CVD was calculated separately for these two sub-populations [Table 4] using a proportional hazard model that included TC, LDL-C, HDL-C and triglycerides after adjustment for age and cigarette smoking. TC, LDL-C and triglycerides independently predicted the risk of CVD mortality in low risk subjects only, with a 16% increase in risk for every 10 mg/dl TC. None of the components of the model significantly predicted CVD mortality in high risk subjects.

Discussion

Our cohort differs from those in other studies in several aspects. First, Israelis have different dietary habits [12–14]. Second, the secular trends in TC [19], SBP [20] and CVD mortality during the last decades in the western world [20] and in Israel [21] may have affected the predictive power of the various risk indicators. Third, our study was restricted to gainfully employed persons, who are healthier than the general population [22]. Although the prevalence of diabetes by age in the study cohort was similar to that reported in Israeli [23] and U.S. [24] populations, the prevalence of obesity was lower than that in a representative sample of a U.S. population in 1996 [25], and mortality, both all cause and CVD, was lower than that expected in the Israeli population [Table 1].

In this highly selected cohort, we confirmed the inter-relationship between age, TC, diabetes, SBP, smoking and LDL-C, and their association with all cause and CVD mortality. Similarly to the Israeli Ischemic Heart Disease Study [15], we found that TC was less powerful in predicting CVD mortality than diabetes, age, smoking and SBP. Unexpectedly, however, TC, LDL-C and triglycerides were found to be more powerful predictors of CVD mortality in low risk non-obese, normotensive non-diabetics than in subjects with either of these risk indicators.

This latter finding is inconsistent with existing evidence, and should be considered preliminary and warranting confirmation. The absence of a significant relationship between TC and CVD mortality in the high risk group

Table 4. Proportional hazard models of blood lipids adjusted for age, and smoking in predicting cardiovascular deaths in those with and without other risk factors

Variable	Entered as	"Low risk subjects"		"High risk subjects"		*P* for
		Hazard ratio	95% CI	Hazard ratio	95% CI	interaction
TC	Low/medium/high	2.49	1.48–4.17	1.05	0.67–1.66	0.014
TC	10 mg/dl increments	1.16	1.09–1.22	1.04	0.98–1.12	0.003
HDL-C	10 mg/dl increments	1.03	0.80–1.33	1.00	0.80–1.26	0.168
LDL-C	10 mg/dl increments	1.20	1.11–1.23	1.05	0.98–1.34	0.041
Triglycerides	10 mg/dl increments	1.03	1.00–1.05	0.99	0.97–1.07	0.266
TC/HDL-C	Units	0.99	0.95–1.04	1.10	0.91–1.34	0.169

"Low risk" refers to normotensive, non-obese, non-diabetic subjects, and "High risk" to persons with either of these risk indicators.

might have been restricted to this specific cohort, or is due to artifacts of uncontrolled confounding or the limited power of our study. Indeed, the wide confidence intervals indicate that even in the high risk sub-population, an increase of 10 mg/dl in TC may increase the risk of CVD mortality by as much as 12%. However, if confirmed, this finding indicates that decisions for treatment of blood lipids need not be affected by the presence of additional risk indicators for CVD, as suggested by the Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults [26]. Indeed, Downs et al. [27] recently reported similar treatment benefits of lovastatin in participants with and without hypertension, or in smokers and non-smokers.

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