



**OPTIMUM RE
MD MEETING
June 2009**

**HYPO
CHOLESTEROLEMIA
UNDER AGE 50 YEARS**

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Highlights

- ❖ Introduction
- ❖ Literature review (definition, variation etiology, primary and secondary)
- ❖ Analyzing the mortality risk
- ❖ Conclusions
- ❖ Questions ?

Introduction

- ❖ ORIC's last audit report 5 cases concerning a total cholesterol (TC) of < 140 mg/dl (3.6 mmol/l)
 - 4 / 5 TC less than 115 mg/dl (2.9 mmol/l)
- ❖ Climoa 2008 meeting: *Is Low Cholesterol dangerous?**
- ❖ Other studies linking hypocholesterolemia with many diseases.

* Bruce M.T Rowat – Climoa annual meeting – May 2008 - Montreal

Definition

- ❖ Hypocholesterolemia can be defined as plasma cholesterol concentrations less than **130 mg/dl (3.4 mmol/l)***
- ❖ Hypocholesterolemia is defined as total cholesterol less than **120 mg/dl (3.1 mmol/l)****
- ❖ Ultra low level is less than **110 mg/dl (2.86 mmol/l)**

* Williams Textbook of Endocrinology tenth edition 1167

** Merck Manual online edition-sec12/chap159

Variation

- ❖ Plasma lipid levels vary among individuals of different population owing to genetic and dietary factors
- ❖ Numerous studies* of total serum cholesterol in Asians (Japanese, Chinese, Indians, Korean) have demonstrated a lower level than for non-Asians.
- ❖ The mean plasma TC** for western men is 210 mg/dl, whereas for Japanese men it is 165 mg/dl

*Genetic disorders of the Indian subcontinent by Dhavendra kumar

*Miller et al (1984 & 1988)

*Beckeles et al (1986)

*Mckeigue et al (1985 & 1991)

**Williams Textbook of Endocrinology 10th edition 1167

Etiology

Possible causes of low cholesterol

1. Primary causes
2. Secondary causes (by far more common)

Primary hypocholesterolemia

- ❖ **Hypobetalipoproteinemia:**
 - Autosomal dominant
 - Mutation in the gene coding for apo B metabolism
 - Heterozygotes are usually asymptomatic / TC < 120 mg/dl (3.1 mmol/l)
 - Homozygotes: TC < 80 mg/dl (2.1 mmol/l), present with fat malabsorption; poor prognosis

Merck Manual online edition-sec12/chap159

Primary hypocholesterolemia, cont

- ❖ **Abetalipoproteinemia:** Autosomal recessive,
 - Deficiency of microsomal triglyceride transfer protein gene,
 - Detected in infancy, failure to thrive,
 - TC is typically < 45 mg/dl, Poor prognosis
- ❖ **Chylomicron retention disease:** very rare
 - Autosomal recessive
 - Deficient apo B secretion from enterocytes
 - Chylomicron synthesis absent
 - Failure to thrive, neurological disorders

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Secondary hypocholesterolemia

- ❖ Malignancy
- ❖ Depression
- ❖ Trauma and Violent death
- ❖ Liver diseases (*end stage cirrhosis, death within 2 years*)
- ❖ Digestive malnutrition
- ❖ Fever, Infection, AIDS, Tuberculosis
- ❖ Inflammatory disease and chronic anemia (SCD)
- ❖ Hypothyroidism

Revue de Medecine Interne 1998, 19(3):180-4

Low cholesterol and Cancer

Inverse association between TC & Cancer & All-cause mortality

- ❖ TC studied in relation to mortality from cancer
- ❖ Survey of 3091 (male 51%) healthy Dutch;
- ❖ Mean age: (male 53 y; female: 51 y)
- ❖ Follow-up: 28 years (0-15 y & 16-28 y)
- ❖ Participants divided into quintiles according to TC levels.
- ❖ Mortality rates calculated by categories of chol. level over 5-y periods

Albertine J et al. Am J Epidemiol 1993; 137: 966-76

Mean TC characteristics

TC (mg/dl)	Q1	Q2-Q4	Q5
Men	≤ 212	216-290	≥ 294
Women	≤ 224	228-321	≥ 325

Albertine J et al. Am J Epidemiol 1993; 137: 966-76

Baseline characteristics of total pop and subjects who died of cancer or CHD

Characteristics	Total population	Cancer deaths	CHD deaths
Men	N = 1452	N = 254	N = 219
Mean TC	259 mg/dl	250 mg/dl	267 mg/dl
Women	N = 1465	N = 144	N = 94
Mean TC	274 mg/dl	278 mg/dl	294 mg/dl

Albertine J et al. Am J Epidemiol 1993; 137: 966-76

RR for cancer mortality – short term

3-15 years of follow-up

Mortality	Adjusted RR for age, BMI & smoking				
	Q1	Q2	Q3	Q4	Q5
Cancer (men)	2.1	1.7	1.1	1.2	Ref
Cancer (women)	0.7	1.3	0.7	0.9	
Gastrointestinal ca (men)	4.2	3.0	1.9	1.3	Ref
Gastrointestinal ca (women)	0.7	2.5	1.6	0.9	
Lung cancer	1.5	1.8	1.2	1.5	Ref

Albertine J et al. Am J Epidemiol 1993; 137: 966-76

RR for cancer mortality – long term

16-28 years of follow-up

Mortality	Adjusted RR for age, BMI & smoking				
	Q1	Q2	Q3	Q4	Q5
Cancer (men)	0.8	0.8	0.9	1.0	Ref
Cancer (women)	0.7	0.5	1.2	1.4	
Gastrointestinal ca (men)	0.6	0.9	1.1	0.8	Ref
Gastrointestinal ca (women)	0.3	0.2	1.1	0.9	
Lung cancer	0.8	1.2	1.0	1.3	Ref

Albertine J et al. Am J Epidemiol 1993; 137: 966-76

RR for all-cause & CHD mortality short term

3-15 years of follow-up

Mortality	Adjusted RR for age, BMI & smoking				
	Q1	Q2	Q3	Q4	Q5
All-cause mortality (men)	Ref	1.2	0.9	1.0	1.1
All-cause mortality (women)		1.4	1.3	1.1	1.5
CHD mortality (men)	Ref	1.8	1.6	1.4	2.5
CHD mortality (women)		0.3	1.3	1.8	2.0

Albertine J et al. Am J Epidemiol 1993; 137: 966-76



RR for all-cause & CHD mortality long term

Mortality	16-28 years of follow-up				
	Adjusted RR for age, BMI & smoking				
	Q1	Q2	Q3	Q4	Q5
All-cause mortality (men)	Ref	1.0	1.1	1.3	1.4
All-cause mortality (women)		0.9	0.9	1.1	1.3
CHD mortality (men)	Ref	1.1	1.0	1.9	1.7
CHD mortality (women)		1.5	1.2	1.1	1.6

Albertine J et al. Am J Epidemiol 1993; 137: 966-76



All-cause Mortality Ratio

Follow-up	MR *		
	Men	Women	Combined
3 – 15 y	352%	416%	369%
16 – 28 y	213%	335%	246%

*Netherlands, life tables 1980

Adapted from Albertine J et al. Am J Epidemiol 1993; 137: 966-76

Conclusions

- ❖ An inverse association between TC and cancer mortality was observed in men during the first 15 years of follow-up; persistence when the first 5 y of FU are excluded
- ❖ Cancer: association mainly by gastrointestinal cancers; in women, no consistent association observed, may be explained by a hormonal or metabolic mechanism.
- ❖ All-cause mortality: an inverse association was observed with a variation between men & women

Albertine J et al. Am J Epidemiol 1993; 137: 966-76

Low serum cholesterol & mortality

- ❖ Prospective study of 5941 men,
- ❖ Age: 45 to 68 y; follow-up: 16 years
- ❖ No prior history of CHD, stroke, cancer or gastrointestinal disease
- ❖ To investigate the association of TC change with mortality
- ❖ TC examined at baseline and 6 y later

Iribarren C et al. Circulation 1995;92:2396-2403

Baseline characteristics for TC levels

	Low	Middle	High
TC level (mg/dl)	≤ 180	181-239	≥ 240

Groups by TC levels

Stable	High-high	Middle-middle	Low-low
Declining	High-middle	High-low	Middle-low
Rising	Low-middle	Low-high	Middle-high

Iribarren C et al. Circulation 1995;92:2396-2403

RR associated with a decline in TC

Cause of death	16-y	Excluding	TC change
	FU	first 5 y	
Age-adjusted RR			
Stomach ca	1.20	1.17	-7.1
Rectal ca	1.14	1.16	-10.5
Hematopoietic ca	1.40	1.28	-11.6
Prostate ca	1.38	1.48	-14.6
Esophageal ca	1.88	1.96	-22.3
Nonmalignant liver disease	1.56	1.59	-17.5
CHD	0.98	0.95	-4.7
Hemorrhagic stroke	1.02	1.12	-3.0
All-causes	1.07	1.07	-5.2

Iribarren C et al. Circulation 1995;92:2396-2403

RR of mortality by TC change

Pattern of cholesterol change	Cardiovascular (N = 385)	Cancer (N = 557)	Total (N = 1370)
RR adjusted for age, BMI, BP, alcohol, smoking			
Stable			
Low-low	0.79	1.18	1.07
Middle-middle	Ref	Ref	Ref
High-high	1.39	0.97	1.15
Declining			
High-middle	1.20	1.19	1.16
Middle-low	0.81	1.37	1.30
High-low	1.86	2.09	1.76
Rising			
Low-middle	1.02	1.14	1.16
Middle-high	1.03	0.80	0.92
Low-high	4.57	0.67	1.77

Iribarren C et al. Circulation 1995;92:2396-2403

Conclusions

- ❖ Falling TC level was accompanied by an increased risk of death by cancers, and all-cause mortality
- ❖ By contrast, no increase in all-cause mortality risk with a low stable TC

Iribarren C et al. Circulation 1995;92:2396-2403

Lowest TC level & mortality

- ❖ Study in Korea to evaluate the relation between lowest cholesterol level and mortality.
- ❖ 482,472 Korean followed for 7 years
- ❖ Age: 30-65 y (mean: 40 y)
- ❖ Age-adjusted mortality rates and relative risks for cancer, stroke, violent causes and all-cause mortality were calculated.

Yun-Mi Song et al. Am J Epidemiol 2000; 151: 739-47

Lowest TC level & mortality (Cont)

Multivariate adjusted* RR for mortality
 * age, BP, BMI, smoking, alcohol, exercise
 Total cholesterol level in mg/dl

	< 135	135-164	165-185
All-cause	1.30	1.11	Ref
Cancer	1.42	1.16	Ref
Stroke	1.42	1.07	Ref
CHD	1.44	0.98	Ref
Violent cause	1.04	1.07	Ref
Non cardiovascular			
Non cancer	1.40	1.21	Ref
Non violent causes			

Yun-Mi Song et al. Am J Epidemiol 2000; 151: 739-47

Conclusions

- ❖ Low cholesterol level was associated with increased risk of total mortality, even after excluding the first 5 years of FU
- ❖ Mortality from liver and colon cancer was significantly associated with a very low cholesterol level
- ❖ A weak relation was found with mortality due to violent causes and cholesterol level

Yun-Mi Song et al. Am J Epidemiol 2000; 151: 739-47

Association of low cholesterol & cancer mortality not for young

- ❖ Evaluating the association between low blood cholesterol and rare evaluated cancer sites
- ❖ 2974 men
- ❖ Study in Switzerland
- ❖ Follow-up: 17 years (1973-1990)

Monika Eichholzer et al. Am J Clin Nutr 2000; 71: 569-74

Low cholesterol & cancer mortality not for young (cont)

Cancer site	TC / Age	RR, all cases	RR, 2-y fu excluded
Lung	Low TC/age > 60	1.99	1.91
	Low TC/age ≤ 60	0.54	0.56
Prostate	Low TC/age > 60	7.71	6.41
	Low TC/age ≤ 60	0.28	0.28
Stomach	Low TC	1.70	1.51
Colon	Low TC/age > 60	4.07	3.49
	Low TC/age ≤ 60	0.90	0.91
All cancers	Low TC/age > 60	2.08	1.85
	Low TC/age ≤ 60	0.86	0.90

Monika Eichholzer et al. Am J Clin Nutr 2000; 71: 569-74

Conclusion

- ❖ An increase in total cancer mortality for ages > 60 y in lung, prostate, and colon.
- ❖ This increase was not observed in stomach cancer
- ❖ 2-y FU excluded, lung cancer mortality remain unchanged

Monika Eichholzer et al. Am J Clin Nutr 2000; 71: 569-74

What cause of mortality can we predict by cholesterol screening?

- ❖ Low TC has been reported to raise the mortality
- ❖ 9216 subjects (44% male)
- ❖ Study in Japan
- ❖ Male mean age: 51 y / female mean age : 45 y
- ❖ Follow-up (mean): 13 years

Okamura T et al. Journal of Internal Medicine 2003; 253: 169-180

RR for major causes of death according to TC level

TC level Mg/dl	Cancer mortality	Adjusted* Relative Risk	
		N CV, N cancer mortality, accidents, suicide	All-cause mortality (/ excl 5 y)
Male			
< 160	31 %	1.11	1.56
160-200	69 %	Ref	Ref
Female			
< 160	29 %	1.42	1.51
160-200	71 %	Ref	Ref
Combined			
< 160	28 %	1.22	1.49
160-200	72 %	Ref	Ref

Okamura T et al. Journal of Internal Medicine 2003; 253: 169-180

Low cholesterol and Psychiatric disorders



Plasma lipid levels and Psychologic characteristics in men

- ❖ Is low TC level predictive of violent deaths (suicides, homicides, and accidents)?
- ❖ Low level of TC observed among incarcerated men, prisoners with antisocial personality disorder, adolescents with aggressive conduct disorder and older men with depression
- ❖ 3490 veterans aged 31-45 years, who served the US army in Vietnam between 1965 and 1971 were examined

David Freedman et al. Am J Epidemiol 1995; 141: 507-17

Lipid levels according to various personality traits

	Total cholesterol mg/dl	
	Number	Mean
Overall	3490	213
Obsessive-compulsive disorder	42	206
Antisocial personality disorder	325	207
Schizophrenia	22	205

David Freedman et al. Am J Epidemiol 1995; 141: 507-17

Total serum cholesterol & Suicidality in Anorexia nervosa (AN)

- ❖ Serum cholesterol and nutritional status were evaluated in anorexia nervosa patients
- ❖ 74 Female, mean age: 24 y
- ❖ Mean cholesterol level: 170 mg/dl (range 69-312)
- ❖ Suicide and other psychiatric disorders were studied

Angela Favaro et al. Psychosomatic medicine 2004, 66: 548-552

Total serum cholesterol & Suicidality

Variable	# of cases	Mean TC (mg/dl)
All cases	74	170
Attempted suicide	8	150
Self-injurious behavior	18	146
Suicidal ideation	35	158

Angela Favaro et al. Psychosomatic medicine 2004, 66: 548-552

TC level & Suicidality in AN - Conclusions

- ❖ Results should be regarded with caution because of the limitations of the study:
 - Some of the variables considered were self-reported
 - The sample size was small

Angela Favaro et al. Psychosomatic medicine 2004, 66: 548-552

Low serum cholesterol and short term mortality

- ❖ Swedish study to determine whether total serum cholesterol concentration predicts mortality from injuries (motor vehicle accidents, accidental poisoning, accidental falls) and suicide
- ❖ 26693 men and 27692 women
- ❖ Age: 45-74 y; Follow-up: 20 years
- ❖ Quartiles for TC concentration were determined for each 5 years

Gunnar Lindberg et al. BMJ 1992; 305:277-279

Total Cholesterol distribution

Cholesterol distribution (Quarter)	Mean cholesterol concentration
Men	
First	205 mg/dl
Second	235 mg/dl
Third	260 mg/dl
Fourth	294 mg/dl
Women	
First	208 mg/dl
Second	243 mg/dl
Third	266 mg/dl
Fourth	305 mg/dl

Gunnar Lindberg et al. BMJ 1992; 305:277-279

RR for deaths from injuries by TC distribution and follow-up

Cholesterol distribution (Quarter)	RR / 0-6 y	RR / 7-13 y	RR / 14-20 y
Men			
First	2.75	1.10	0.83
Second	2.06	1.10	0.74
Third	1.79	1.11	0.82
Fourth	Ref	Ref	Ref
Women			
First	0.94	1.14	1.07
Second	0.70	2.02	0.57
Third	0.62	1.66	0.57
Fourth	Ref	Ref	Ref

Gunnar Lindberg et al. BMJ 1992; 305:277-279

RR for deaths from suicide by TC distribution and follow-up

Cholesterol distribution (Quarter)	RR / 0-6 y	RR / 7-13 y	RR / 14-20 y
Men on cancer register included			
First	4.22	1.65	0.66
Second	2.39	1.30	0.66
Third	1.99	1.20	0.78
Fourth	Ref	Ref	Ref
Men on cancer register excluded			
First	4.10	1.55	0.75
Second	2.21	0.97	0.75
Third	2.01	0.98	0.83
Fourth	Ref	Ref	Ref

Gunnar Lindberg et al. BMJ 1992; 305:277-279

Low cholesterol and Stroke



Intra cerebral hemorrhage in young and risk factors

- ❖ Study in Mexico of 200 patients (53% men), mean age 27 y
- ❖ Follow-up from 1986 to 1997
- ❖ Most frequent risk factors
 1. Tobacco use: 20%
 2. Hypo cholesterolemia \leq 160 mg/dl: 35%
 3. Hypertension (11%)
 4. Alcohol use (10%)

José Luis Ruíz-sandoval et al. Stroke 1999; 30: 537-541

ICH in young and risk factors - conclusions

- ❖ Two of the most common risk factors included hypo cholesterolemia and hypertension
- ❖ Increased incidence of ICH was associated with hypo cholesterol but the mechanism underlying this relationship is unclear
- ❖ In patients in whom cholesterol was measured, there were evidence of low TC level.
- ❖ This finding was common in patients aged < 20 y, in whom hypertension is uncommon

José Luís Ruiz-sandoval et al. Stroke 1999; 30: 537-541

Summary - Cancer

	RR, 15 y	RR, 28 y	RR Exc. 5 y
Cancer	2.1	0.8	
Gastrointestinal	4.2	0.6	
Lung	1.5	0.8	
Stomach	1.20		1.17
Rectal	1.14		1.16
Hematopoietic	1.40		1.28
Prostate	1.38		1.48
Esophagus	1.88		1.96

Summary – All other causes

	RR, 6 y	RR, 15 y	RR, 28 y	Excl. 5 y
All-cause		1.2	1.0	1.07
Liver disease		1.56		1.59
CHD (L/H)		1.8/2.5	1.1/1.7	0.95
Hemorrhagic stroke		1.02		1.12
Violent death	2.75	1.10	0.83	
Suicide + Cancer	4.22	1.65	0.66	
Suicide - Cancer	4.10	1.55	0.75	

Conclusions

- ❖ When rating a hypocholesterolemia: Remember that
 - Controversy still persists
 - Other ethnic group have naturally occurring low Cholesterol (Japanese, Indian, Korean, Chinese)
 - Take in consideration: an unexplained weight loss, fatigue, other blood chemistry abnormalities, i.e. low albumin
 - What about the non statin individual's low cholesterol?

Conclusions 2

- ❖ Pattern of low Chol. is important:
 - Is low TC stable, or not?
- ❖ A U-shaped relationship is seen with cholesterol concentrations: Coronary vs. cancers, liver diseases and all-cause mortality
- ❖ Any explanation about the difference between males and females?

Conclusions 3

- ❖ Cancer mortality is increased with low cholesterol (mostly for gastrointestinal, liver and lung cancer)
- ❖ Low TC and anorexia nervosa: results were not conclusive
- ❖ Low cholesterol increase death from injuries and suicide for men not for women?
- ❖ Low cholesterol is a risk factor for stroke in young; low TC and hypertension is specially a bad combination in young



Thank you!

Questions ?

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