Lower total cholesterol and triglyceride levels in ankylosing spondylitis than non-inflammatory rheumatic disease controls in a 1978-98 study: a potential effect of increased physical energetics in manual occupations in the pre-2000 chronologic era

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Abstract

Objective

No article on serum lipids in ankylosing spondylitis (AS) and control subjects has been reported from USA. The primary aim of this study was to determine if any difference occurred in serum lipid levels in AS and control rheumatic disorders in two time periods, 1978-98 and 2000-10. The secondary aim was to investigate variables associated with lipid levels and if a difference was found between AS and control disorders.

Methods

The AS patients were compared to non-inflammatory rheumatic disorders (NIRDs) in 1978-98 and 2000-10 surveys and to rheumatoid arthritis (RA) in the 2000-10 survey. Patients were matched within 5 years of age, sex, and clinic or hospital source.

Results

In the 1978–98 survey, entry mean (SEM) serum cholesterol level [mg/dL] was highly ($p<0.001$) significantly lower in 69 AS [179.0 (4.8)] than 69 matched NIRD controls [208.0 (5.6)]. In 29 pairs of AS and NIRD subjects having manual labour occupations, mean (SEM) cholesterol level was additionally lower in AS [156.7 (5.9)] and higher in 29 NIRD controls [213.3 (8.6)] ($p<0.001$). In manual labour workers, mean (SEM) serum triglyceride was significantly lower ($p=0.004$) in 15 AS [110.3 (14.1)] than 14 NIRD controls [185.2 (19.3)]. In the 2000-10 survey, no lipid difference was found between AS vs. NIRD control patients.

Conclusion

In the 1978-98 survey, AS had significantly lower mean serum cholesterol and triglyceride levels than NIRD control patients. Associated manual labour occupations may have significantly contributed to results, possibly related to increased energy expenditures from physical activity in the pre-2000 era.

Key words

ankylosing spondylitis, cholesterol, triglycerides, musculoskeletal disorders, non-inflammatory, chronology of events

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Received on December 31, 2023; accepted in revised form on March 11, 2024.

Abstracts of the 1978-98 survey were published in 1999 (20), 2000 (21), and 2001 (22).

Funding: partial support for this study was obtained from a UICOMP Resident Research Grant, approved by the research committee.

Competing interests: none declared.

Introduction

The rheumatology clinic at the University of Illinois College of Medicine at Peoria (UICOMP) was initiated in 1978 by the senior author. Several male ankylosing spondylitis (AS) patients had consistently low serum cholesterol levels <150 mg/dL with normal body mass index (BMI). The primary aim of this study was to determine if any difference occurred in serum lipid levels in AS and control rheumatic disorders. In the initial 1978-98 population survey, the AS patients were compared to non-inflammatory rheumatic disorder (NIRD) controls. A second survey using the same study design was conducted during 2000-10 to confirm results of the initial 1978-98 study and included a second control cohort of rheumatoid arthritis (RA) patients.

If a significant difference is found between the AS and control cohorts, the secondary aim was to identify variables associated with lipid levels. Manual labour occupation was unexpectedly associated with lower AS lipid levels in the initial survey. The total aims are to investigate AS *versus* control lipid differences in two time periods, 1978-98 and 2000-10, and to analyse association of manual labour category with lipid levels.

In 1978, only three articles were identified of cholesterol levels in AS, each reporting significantly lower levels than community comparison subjects (1-4).

In the 1963 report (1), 49 English AS patients were studied at two medical centers during 1959-62, excluding patents known to have disease affecting serum cholesterol. The AS patients had 44 percent lower cholesterol than a control population in the town of Leigh and the rural area of Wensleydale (1). Westergren sedimentation rates were performed on 47 of the 49 AS patents at the time of the cholesterol determinations. In 29 AS patients having ESR <40 mm/hr, cholesterol was 32 percent lower than controls. In the remaining 18 AS patients having ESR 40+ mm/hr, cholesterol was 62 percent lower than population controls, suggesting that serum cholesterol is correlated with the degree of AS activity or inflammation present.

The 1978 report (2) was based upon cholesterol level in 8 male AS patients of ages 28-46 years having mean (SEM) of 183.1 (7.0) mg/dL. This level compared to 247.7 (12.0) mg/dL for 47 healthy non-overweight male community controls, of ages 30-59 years, (p=0.033) (3). The 8 AS patients had highly (p<0.001) significantly lower mean (SEM) serum triglyceride level of 83.3 (11.5) mg/dL (2) *vs*. 150.0 (13.3) mg/dL for 47 non-overweight, healthy normal male controls (3). The 1997 report (4) was an abstract of fasting cholesterol in an Asian population, which revealed significantly (p=0.007) lower level in 50 male AS patients than age-matched control males.

During our 1978-98 study, the senior author critically reviewed the epidemiology of AS (5). The male predominance and impressive increase in AS incidence during puberty and early adulthood was identified. The younger male AS predominance suggested greater androgenicity, targeting lower lumbar myofascial hypertonicity, possibly contributing to enthesopathy (5).

In earlier generations, AS was believed by some to be a variant of rheumatoid arthritis, previously termed "rheumatoid spondylitis" (6). It was clinically described as mainly affecting thin, young men (7). In a 1966 report (8), bodyweight in 78 AS patients was compared to 105 normal persons, revealing an underweight status in 35 (45%) *versus* 15 (14%), respectively (p<0.001). More recent studies of biomechanical and metabolic factors in AS suggest evidence of lumbar spinal myofascial hypertonicity (9).

The traditional lipoprotein profile includes cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides (10, 11). In this cross-sectional study, sources of variation in serum lipids between AS and control patients was decreased by matching on age, sex, and service provider (10, 11).

In a literature review primarily encompassing the two decades preceding year 2000, serum lipids decreased after 12 weeks of aerobic exercise training (AET) in adult men and women (12). From 1960–2005, age-adjusted prevalence of obesity (BMI 30+) increased consistently from 13.4 (1960-62) to 35.1 percent (2005-06) according to the

National Health and Nutrition Examination Surveys (NHANES) (13). The prevalence of central obesity in eight cross-sectional NHANES survey cycles of USA adults significantly increased from 45.2 percent in 1999-2000 to 56.7 percent in 2013–2014 (p=0.003) (14).
Longitudinal multi-decade trends in serum lipid levels may be influenced by body weight changes and their determinants, like physical activity (15). A five-decade analysis from 1960-62 to 2003–06 of energy expenditures in USA private industry occupations and mean body weight were reported for 40- to 50-year-old males and females (15). Occupational caloric expenditures decreased by 140 kilocalories in males and 124 kilocalories for females from the 1960 baseline to 2008 (15). The decreased occupational energy expenditure of more than 100 kilocalories can account for the increase in mean USA body weights for males and females (15). The degree to which body weight metabolism *versus* occupational energy expenditures affect serum lipid levels requires further study (15). Higher HDL cholesterol was observed in 2492 randomly selected Finnish males aged 42–60 years during 1984-1989 who had greater occupational and leisure time activity (16).
A recently published meta-analysis of 68 articles on serum lipids in AS and healthy control subjects (17) included only the 1978 serum lipid article (2) contemporaneous with our earlier 1978-98 study. The remaining meta-analysis articles were subsequently published between 2005 and 2021, with the median publication date of 2014. In this meta-analysis (17), which was mainly in the post-2000s era, no difference was found in lipid levels between AS and healthy control subjects. The marked increased prevalence of obesity (14) and decreased occupational caloric expenditures from 1978-98 to post-2000s may have contributed to serum lipid differences found in this early 1978–98 study, but not in the later meta-analysis (17).

Materials and methods

Design

In this observational retrospective case-control study, case subjects were accepted under 60 years of age who had a diagnosis of definite or probable AS by either the Rome or alternative New York criteria (18). The diagnostic code for AS, *i.e.* 720.0 in the 9th revision of the International Classification of Diseases Clinical Modification (ICD-9-CM) diagnostic classification system, was used for case identification. Comparison subjects in both the 1978-98 and 2000-10 studies had non-inflammatory rheumatic disorders (NIRDs) (19). In addition, RA subjects were added as a second control cohort in the second survey. All control subjects were matched to AS cases on age (±5 years), sex, race, and source of medical service. Subjects were excluded if they had evidence of associated disease, including obesity (BMI 35+), or drug therapy that might meaningfully affect lipid levels.
Hospitalised AS and control subjects were also matched on lengths of stay (±3 days) to select study subjects with equivalent extent of evaluation and similar amounts of available data relevant to this study.
The study design attempted to increase the number of AS subjects by searching for those who did not attend the 3 rheumatology clinics, but had that diagnosis coded in hospital records. In the initial 1978-98 study of 69 AS and 69 NIRD subjects, 20 pairs were identified as having those diagnoses in hospital records. Their inclusion was intended to increase the number of closely matched study pairs. In the second study (2000-10), 11 inpatients were identified for RA and 9 for NIRD and their AS paired subjects. The AS, RA, and NIRD subjects were closely matched on age, sex, and duration of hospital stay. Each analysis of AS, RA, and NIRD demographic or lipid variables in the second study (2000-10) included a stratification of results obtained between the 11 inpatients and 29 outpatients for AS and RA *versus* 9 inpatients and 31 outpatients for NIRD. As stated, all subjects were excluded if they had any condition or used drugs affecting lipid levels.
A structured abstract form was composed prior to data collection and coding. Five research assistants who gathered data in this study were instructed in preliminary training sessions to abstract each questionnaire item. When complete accuracy was achieved in coding 5 AS and 5 NIRD subjects from the medical school clinic, the physician abstractors (PCM and TSR) were assigned to abstract study subjects at other medical services. The two non-physician undergraduate research assistants were only assigned at the medical school clinic and performed duplicate coding under supervision of the senior author. All coding was scrutinised for consistency (PCM and TSR) prior to database entry.
Data were collected on subjects' principal job at study entry and were abstracted in pre-defined, 10-point ordinal scale of occupational categories. Degrees of manual labour (light, moderate, and heavy) were combined as "labour occupations." The distribution of individual occupational scales of AS and NIRD subjects were closely similar (p=0.945).
The earlier 1978-98 referral medical center study included 69 matched pairs of AS and control subjects derived from the medical school rheumatology clinic (n=27), two other hospital rheumatology clinics (n=22) and hospital admissions (n=20). Determination of a least one cholesterol level was required in the medical records for inclusion in study. No bias or selection was attributed to the cholesterol value in AS or control subjects. Entry and last cholesterol were recorded as well as accompanying values for triglycerides, HDL cholesterol, and LDL cholesterol. A detailed abstract form (114 items) was composed prior to data collection. Items included functional class, manual and non-manual labour work categories, BMI, smoking status (non-smokers *vs.* smokers), and multiple laboratory tests, *e.g.* serum chemistry, Westergren erythrocyte sedimentation rate (ESR), and other markers of inflammation. In the 1978-98 study, serum triglyceride levels were available in the records of 37 AS and 37 control subjects having cholesterol testing. Data on HDL and LDL cholesterol were available from 27 AS and 25 control subjects.
The later 2000-10 matched AS case-control study began in 2000 with continued collection of study subject data

Table I. Mean (SEM) Age, Body Mass Index (BMI) and serum total cholesterol level (TCL) in 69 ankylosing spondylitis and 69 non-inflammatory rheumatic disorders (NIRD). Comparison of subjects by occupational subgroups.

	Ankylosing spondylitis			Non-inflammatory rheumatic disorders		
Matched Subgroups	Age	BMI	TCL	Age	BMI	TCL
Manual (n=29)	37.3 (2.2)	25.7 (0.9)	156.7 (5.9)[†]	36.4 (1.8)	27.4 (1.0)	213.3 (8.6)[†]
Non-manual (n=40)	39.6 (1.5)	26.8 (0.9)	194.4 (5.9)[†]	41.5 (1.7)	26.6 (0.8)	204.4 (7.3)
Total (n=69)	38.7 (1.3)	26.3 (0.6)	179.0 (4.8)[‡]	39.4 (1.3)	26.9 (0.6)	208.0 (5.6)[‡]

[†]In manual workers (n=29), mean (SEM) total cholesterol level was highly ($p<0.001$) significantly lower in AS than NIRD and lower than in non-manual AS (n=40). [‡]In total subjects (n=69), mean (SEM) total cholesterol level was highly ($p<0.001$) significantly lower in AS than NIRD subjects.

for 10 years on AS subjects and two sets of control subjects, NIRD and rheumatoid arthritis (RA). The same study methodology for data collection in the 1978-98 study was used in the 2000-10 study. The shorter interval in the second study yielded 40 AS subjects with data on cholesterol and the same number in matched patients with NIRD and RA. Data on triglycerides, HDL cholesterol, and LDL cholesterol were available in 40, 39 and 36 AS subjects respectively and almost identical numbers in NIRD and RA controls.

Preliminary reports of our 1978-98 study were published in abstracts of the 1999, 2000, and 2001 American College of Rheumatology Annual Meetings (20-22). A formal manuscript on the initial 1978-98 findings (20-22) was not previously submitted by the senior author due to competing demands, including initiation of the subsequent 2000-10 study and detailed literature review, leading to the recent meta-analysis (17). The present 1978-98 study results include data from the 3 published abstracts (20-22), their presentation posters, and subsequent analyses, as summarised in Tables I and II.

Objectives and statistical analysis

The primary objective of both 1978-98 and 2000-10 studies was to determine the frequency distribution of serum cholesterol, triglyceride, HDL cholesterol and LDL cholesterol levels in the AS compared to matched control subjects. The secondary objectives were to search for correlates of lipid levels and to determine differences between the two studies. Statistical probability of differences in binomial frequencies of serum lipids in AS *versus* control subjects was determined by Fisher's exact test. The mean standard error [mean (SEM)] of continuous variables in case and control cohorts was used as an inferential statistic to test the hypothesis of difference in serum lipids. Other statistical and multivariate analyses were performed using SPSS for Windows 11.0.1 release (Chicago, IL 2001 software), and $p<0.05$ was considered significant for a two-tailed test. No correction for multiple comparisons was performed in statistical testing of the primary variable of interest since this study was designed to specifically analyse the entry serum lipids of cases *versus* controls (23). Neither was correction made for multiple comparisons of the secondary variables since they were investigated as modifiers for the primary relationship (23). The study was approved by UICOMP community-wide Intuitional Review Board (IRB) prior to initiation (Serum Cholesterol Levels in Ankylosing Spondylitis [85286]). All data were collected from medical records and no patient involvement occurred in this study.

Table II. Mean (SEM) serum lipids (mg/dL) in 1978-98 Community Survey of 69 ankylosing spondylitis cases and 69 matched non-inflammatory rheumatic disorders.

Serum lipid type	Ankylosing spondylitis	Non-inflammatory rheumatic disorders	*p*-value
Total cholesterol	179.0 (4.8) (n=69)	208.0 (5.6) (n=69)	<0.001
Manual workers' total cholesterol	156.7 (5.9) (n=29)	213.3 (8.6) (n=29)	<0.001
Total triglycerides	126.2 (10.1) (n=37)	162.8 (11.4) (n=37)	0.019
Manual workers' triglycerides	110.3 (14.1) (n=15)	185.2 (19.3) (n=14)	0.004
HDL cholesterol	42.6 (2.5) (n=27)	37.3 (2.1) (n=25)	NS
Manual workers' HDL cholesterol	39.7 (4.3) (n=13)	33.0 (2.7) (n=11)	NS
LDL cholesterol	107.7 (5.9) (n=27)	120.7 (6.8) (n=25)	NS
Manual workers' LDL cholesterol	97.5 (7.7) (n=13)	108.9 (9.2) (n=11)	NS
Lower BMI cholesterol	164.7 (6.3) (n=36)	196.9 (8.2) (n=31)	0.002
Higher BMI cholesterol	193.8 (6.3) (n=35)	216.7 (7.3) (n=40)	0.022
Lower BMI triglycerides	109.3 (9.9) (N=23)	174.7 (17.1) (n=18)	<0.001
Higher BMI triglycerides	150.0 (19.4) (N=14)	151.6 (15.3) (n=19)	NS

Manual job categories were predefined; lower body mass index (BMI) of <25 for females, <27 for males; High-density lipoprotein (HDL); Low-density lipoprotein (LDL).

Results

In the initial 1978-98 study of 69 matched pairs of AS and NIRD control subjects, mean (SEM) entry serum cholesterol level was 179.0 (4.8) in AS, which was highly ($p<0.001$) significantly lower than 208.0 (5.6) in NIRD subjects (Tables I, II), (Poster in 20). No significant difference was found in age and BMI between AS and NIRD subjects in total or any occupational subgroup (Table I). In the 29 pairs of subjects having manual occupations, the mean (SEM) total cholesterol level in AS was 156.7 (5.9), which was 27 percent lower ($p<0.001$) than the matched NIRD control level of 213.3 (8.6). In the 40 matched pairs of non-manual AS *versus* NIRD controls, no significant mean SEM difference was found in total cholesterol [194.4 (5.9) *vs.* 204.4 (7.3)] (Tables I, II). Markers of inflammation and functional class level of AS and NIRD did not correlate with cholesterol levels in the 1978-98 study (Poster in 20).

Also, in the initial 1978-98 study, mean (SEM) triglyceride level in a subsample

Table III. Mean (SEM) serum lipids (mg/dL) in 2000-10 Community Study of 40 ankylosing spondylitis (AS) cases *vs*. matched 40 non-inflammatory rheumatic disorder (NIRD) and 40 rheumatoid arthritis (RA) controls.

Serum lipid type	2000-10 AS	2000-10 NIRD	2000-10 RA	*p*-value AS/NIRD	*p*-value AS/RA
Total cholesterol	187.1 (6.2) (n=40)	198.8 (7.3) (n=40)	194.8 (7.5) (n=40)	0.225	0.431
Manual workers' total cholesterol	182.5 (12.5) (n=8)	207.8 (11.8) (n=14)	201.3 (9.1) (n=10)	0.182	0.231
Total triglycerides	152.1 (11.1) (n=40)	173.1 (11.8) (n=40)	136.9 (10.5) (n=40)	0.199	0.323
Manual workers' triglycerides	190.9 (31.3) (n=8)	177.4 (9.4) (n=14)	175.8 (9.14) (n=10)	0.614	0.617
HDL cholesterol	49.7 (4.2) (n=39)	43.3 (3.7) (n=39)	43.1 (3.8) (n=37)	0.256	0.249
Manual workers' HDL cholesterol	52.5 (6.6) (n=8)	40.4 (2.9) (n=14)	35.3 (1.7) (n=10)	0.068	0.013
LDL cholesterol	111.3 (6.3) (n=36)	121.2 (7.4) (n=39)	124.5 (7.6) (n=37)	0.316	0.187
Manual workers' LDL cholesterol	95.3 (14.2) (n=8)	115.8 (10.3) (n=14)	139.5 (12.7) (n=10)	0.251	0.034
Lower BMI cholesterol	187.9 (6.9) (n=9)	198.3 (13.2) (n=3)	181.4 (13.7) (n=8)	0.477	0.667
Higher BMI cholesterol	185.2 (6.8) (n=25)	197.8 (8.9) (n=28)	201.1 (7.4) (n=28)	0.275	0.123
Lower BMI triglycerides	92.9 (13.9) (n=9)	158.0 (47.4) (n=3)	108.9 (17.7) (n=8)	0.092	0.483
Higher BMI triglycerides	187.6 (31.1) (n=25)	180.2 (24.0) (n=28)	149.2 (15.3) (n=28)	0.850	0.258

Manual job categories were predefined; lower body mass index (BMI) of <25 for females, <27 for males; High-density lipoprotein (HDL); Low-density lipoprotein (LDL).

of 37 AS *versus* 37 NIRD pairs revealed a lower (*p*=0.019) mean (SEM) of 126.2 (10.1) in AS *versus* 162.8 (11.4) in NIRD subjects. The results were not altered by available clinical markers of inflammation, BMI, functional class, or occupational category (Poster in 21). After controlling for BMI, functional and occupational class, lower triglycerides (<130 mg/dL) was more frequently found (OR 4.3, 1.61-12.19) in 37 AS than 37 matched NIRD subjects (*p*=0.004) (Poster in 21). Markers of inflammation of AS did not significantly affect triglyceride levels (Poster in 21). Mean (SEM) HDL cholesterol was non-significantly higher in 27 AS [42.6 (2.5)] than 25 NIRD control subjects [37.3 (2.1)] (Table II), (Poster in 22). Mean (SEM) LDL cholesterol was non-significantly lower in 27 AS [107.7 (5.9)] than 25 NIRD control subjects [120.7 (6.8)] (Table II, Poster in 22). In non-smoking subjects, HDL cholesterol level of 35+ mg/dL occurred in 14 of 15 AS (93.3 percent) than 5 of 10 (50.0 percent) non-smoker NIRD controls (*p*=0.023) (22). Also, in 15 AS non-smokers, higher HDL cholesterol was negatively correlated with triglyceride level (r= -0.883) (Poster in 22). In AS subjects, HDL cholesterol level on study entry correlated positively with limitations of neck and back hyperextension (*p*<0.01) (Poster in 22).

In the later 2000–10 study, 40 AS cases were compared to 40 matched NIRD and 40 RA control cohorts (Table III). No difference was found in mean (SEM) of any serum lipid between 40 AS and 40 matched NIRD controls, as well as between subgroups categorised by manual labour occupation (Table III). Also, no difference was found in mean (SEM) of any serum lipid between 40 AS and 40 matched RA controls (Table III). However, comparison of manual workers revealed higher (*p*=0.013) mean (SEM) HDL cholesterol level in 8 AS [52.5 (6.6) mg/dL] than in 10 RA [35.3 (1.7) mg/dL] (Table III). Also, in manual workers, 8 AS had a lower (*p*=0.034) mean (SEM) LDL cholesterol [95.3 (14.2) mg/dL] than 10 RA manual workers [139.5 (12.7) mg/dL] (Table III). To exclude confounding factors contributing to the preceding HDL cholesterol and LDL cholesterol differences, results of inflammatory markers were analysed in AS and RA subjects in the 2000-10 population survey (Table IV). No significant difference between AS and RA was found in the available serum inflammatory markers of albu-

Table IV. Results of inflammatory markers in ankylosing spondylitis and rheumatoid arthritis subjects in the 2000-10 Population Study.

Inflammatory markers*	Ankylosing spondylitis	Rheumatoid arthritis
Albumin	4.0 ± 0.08 (n=38)	3.9 ± 0.08 (n=40)
Globulin	3.5 ± 0.12 (n=25)	3.2 ± 0.10 (n=30)
Alb/Glob ratio	1.2 ± 0.06 (n=32)	1.2 ± 0.00 (n=35)
CRP	2.3 ± 0.70 (n=19)	2.7 ± 0.78 (n=22)
ESR†	28.3 ± 3.11 (n=31)	28.6 ± 4.41 (n=34)

*No significant difference in above inflammatory markers between AS and RA.
†Mean ESR in NIRD of 16.6 was non-significantly (*p*=0.093) lower than AS and RA.

Table V. Functional class categories in ankylosing spondylitis, rheumatoid arthritis, and non-inflammatory rheumatic disorder subjects in the 2000-10 Population Study.

Functional class	Ankylosing spondylitis	Rheumatoid arthritis	Non-inflammatory rheumatic disorders
I* (no limitations)	16	6	14
II† (hobbies limited)	19	31	18
III (vocation limited)	3	2	6
IV (full limitations, including self-care)	0	0	0

*Lower frequency (*p*=0.038) of Functional Class I (no limitations) in RA than AS and NIRD.
†Greater frequency (*p*=0.018) of Functional Class II (hobbies limited) in RA than AS and NIRD.
[Similar (*p*=0.436) Functional Class frequency distributions between AS and NIRD subjects, by published categories (PMID: 1575785).]

min, globulin, C-reactive protein, and erythrocyte sedimentation rate (Table IV). Since activity of disease might influence serum lipid levels, functional class categories were compared in AS, RA, and NIRD subjects in the 2000-10 population survey (Table V). The 39 RA had a lower frequency (p=0.038) of Functional Class I (no limitations) of only 6 subjects than 16 of 38 AS and 14 of 38 NIRD subjects (Table V). Accordingly, the RA had a higher frequency (p=0.018) of 31 Functional Class II (hobbies limited) than 19 AS and 18 NIRD subjects (Table V). Similar (p=0.436) functional class frequency distributions were found between AS and NIRD subjects (Table V).

Discussion

The mean (SEM) serum cholesterol of NIRD control subjects in the initial 1978-98 study (Tables I, II) is comparable to 20–74 aged populations of males and females, having means of 211 and 215 mg/dL, respectively, in a published 1976-80 survey (24). Those values are highly (p<0.001) significantly greater than those in 69 AS cases from the 1978-98 study (Tables I, II). The AS cases and NIRD controls were closely balanced on age, sex, source of medical service, manual *versus* non-manual occupations, and history of cigarette smoking, implying that significantly lower cholesterol in AS cases did not likely result from sampling biases. The 1978-98 study data are cross-sectional and cannot be deduced as causal differences. Carefully controlled longitudinal and prospective studies are needed to further investigate serum lipids in AS and NIRD subjects. The later 2000-10 survey in the same community population was designed to determine confirmability of the previously observed significant lipid differences (Tables I, II), and to include comparison of RA control subjects (Table III). Importantly, the 2000-10 repeat study did not reveal a significant difference in cholesterol level of AS and NIRD subjects (Table III).

The lower cholesterol and triglyceride levels observed in AS than matched NIRD subjects in the 1978-98 study may have resulted from their increased energy expenditures during physical activities in those earlier decades, particularly noted in the AS group who performed manual labour occupations (Tables I, II). Lower lumbar axial skeletal muscle hypertonicity of some AS patients is suspected to increase their energy expenditures, resulting in lower cholesterol and triglyceride levels, rather than being due to inflammatory processes (9, 25, 26). In 2015, greater resting lower lumbar extensor myofascial stiffness by quantified myotonometry was noted by our team in younger ankylosing spondylitis patients than age-comparable healthy volunteers (27). In recent years, biomechanical stresses and microtrauma are being recognised as contributory mechanisms to spondyloarthritis (28). In the 1978-98 study, non-smoking AS subjects had higher HDL cholesterol level than NIRD controls. Nicotine is a psychoactive drug which produces arousal, relaxation, and skeletal muscle relaxation (29). Non-smoking AS patients may have greater intrinsic lower lumbar myofascial hypertonicity than smokers (9, 25, 26-28).

Limitations of the 1978-98 and 2000-10 studies are retrospective data collection on AS patients compared to matched NIRD control subjects as well as RA controls in the later survey. Matching was successful on pre-defined demographic and medical service variables, but did not include behavioral, dietary, socioeconomic, or lower lumbar myofascial hypertonicity (27). Such behavioral, dietary, socioeconomic, and lower lumbar myofascial tonicity characteristics may have differed between the AS and NIRD subjects which were not ascertained or controlled in the analyses. The study design limits current interpretations of the data as preliminary and tentative, especially since manual labour occupation was the only variable associated with lipid level differences in the 1978-98 study.

The only difference in serum lipids found in the 2000-10 study was the lower HDL cholesterol and higher LDL cholesterol of manual workers in 10 RA than 8 AS (Table III). A nickname for HDL cholesterol is "good cholesterol," and for LDL cholesterol is "bad cholesterol" (30). A diet with low fat and regular exercise may help achieve a favourable lipoprotein balance (30), which were not investigated as contributors to the difference found between 10 RA and 8 AS manual workers.

Strengths of the 1978-98 and 2000-10 studies are the same pre-defined data collection methodology in the same population for medical referral of patients with AS, NIRD, and RA. This original research adds to the body of knowledge in rheumatic diseases, particularly its documentation of sequential lipid levels in AS over separated decades. Research on temporal sequence of events and rheumatic diseases are extremely rare, yielding only five articles in PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%22Chronology+as+Topic%22%5BMesh%5D+AND+rheumatic&sort=pubdate). A potential asset of our two studies is the novel hypothesis of chronologic differentiation of results between 1978–98 and 2000-10, possibly resulting from population trends of obesity and particularly occupational energy expenditures (9, 25-27).

Conclusions

The initial 1978-98 study of serum lipids indicated significantly lower cholesterol and triglyceride levels in AS *versus* matched NIRD controls, which supported three previously published articles on AS from 1963 (1), 1978 (2), and 1997 (4). Labour occupation was the main factor associated with lower serum cholesterol and triglyceride levels in AS than NIRD controls in the 1978-98 study. Importantly, the later 2000-10 study in the same medical service referral population did not indicate any significant lipid difference between AS and matched NIRD control subjects. A recently published meta-analysis of serum lipids in AS and healthy control subjects, almost exclusively post-2000, did not indicate any significant difference in random-effects models of 58 cholesterol (p=0.069) and 61 triglyceride (p=0.825) articles (17). The difference in results of controlled serum lipid level studies conducted pre- and post-2000 may suggest an influence of chronologic population changes in obesity (13) and particularly occupational energy expenditures (15).

Resolving the pre- *versus* post-2000 chronologic difference in cholesterol and triglyceride serum levels between AS and matched NIRD control subjects may also provide new mechanistic insights of factors influencing AS and its serum lipid levels, like lower lumbar myofascial hypertonicity (9, 25-27).

Acknowledgements

Gerald R. Cooper, MD, PhD, expertly collaborated in review and revision of an earlier manuscript draft of the 1978-98 study, particularly during 2007-08. His 1992 (10) and 1994 (11) published articles contributed to interpretation of the differences in serum lipids between AS and NIRD control subjects in the 1978-98 study. He collaborated until his death (05/25/2009).

Our initial reports were vitally assisted by medical resident co-authors, Drs PC Mohan and Tsr Murugan, available as research coordinators. Our later report was based upon the James Scholar research of Drs Chadrick R. Evans and Michael J. Ryan during their medical school tenure. Partial support for this study was obtained from a UICOMP Resident Research Grant, approved by the research committee.

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