PAPERS AND SHORT REPORTS

AIDS and haemophilia: morbidity and mortality in a well defined population

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Abstract

One hundred and forty three multitransfused patients with hereditary haemostatic disorders were examined for evidence of disease related to the acquired immune deficiency syndrome (AIDS). Ninety nine patients with severe haemophilia A were tested for anti-HTLV-III and 76 were found to be positive. All except one of these seropositive patients had received commercial factor VIII concentrates at some time. Eighteen patients with haemophilia B were tested and all were anti-HTLV-III negative. Three out of 36 sexual partners of patients with haemophilia A positive for anti-HTLV-III were also seropositive. One, who had recently received blood transfusions, had AIDS with *Pneumocystis carinii* pneumonia. Three patients with severe haemophilia A died from AIDS. A further 30 haemophiliacs had AIDS

related complex or lymphadenopathy that could be related to HTLV-III infection. There was a significant correlation between lymphadenopathy and anti-HTLV-III seropositivity. No evidence of casual spread of AIDS was found since all 68 health care staff tested were anti-HTLV-III negative, including three surgeons who regularly worked with patients positive for anti-HTLV-III.

The resources devoted to counselling and laboratory support in centres treating people at risk and their families need to be urgently reassessed.

Introduction

Most people with severe haemophilia depend on frequent intravenous injections of clotting factor prepared from human plasma. Both factor VIII for haemophilia A and factor IX for haemophilia B (Christmas disease) are available as lyophilised concentrates, which are convenient for the rapid delivery of treatment needed to arrest or prevent bleeds. These concentrates are made by fractionating plasma obtained from multiple donations. Concentrates became freely available in the early 1970s, when their many advantages over fresh frozen plasma and cryoprecipitate were recognised. Within the United Kingdom sufficient factor IX concentrate has always been available from volunteer donor sources for the treatment of haemophilia B. Patients with haemophilia A have fared less well, and in 1973 a scarcity of British products led to a decision to import factor VIII concentrates prepared from the plasma of paid donors.

Several thousand donations are required per batch of concentrate. Thus each patient using a concentrate is exposed to material from many donors every time he injects himself, and viral contamination of the source plasma through individual contaminated donations has become a well recognised hazard in the management of haemophilias. All patients using multi-donor material can be expected to have been repeatedly challenged by hepatitis B, hepatitis non-A non-B, and the human parvovirus. They have also been repeatedly challenged by proteins and other plasma constituents variously altered in the manufacturing process.

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In 1982 the first report of a link between the acquired immunodeficiency syndrome (AIDS) and transfusion of a blood product appeared,¹ and since 1983 it has become increasingly likely that immunological disturbances in haemophilia are caused by the aetiological agent for AIDS rather than by any alloantigenic response to denatured protein. The description of the AIDS virus, variously called lymphadenopathy associated virus (LAV)² and the human T cell lymphotropic virus type III (HTLV-III),³ and the development of tests for its antibody (anti-HTLV-III) have permitted identification of previous exposure to HTLV-III. The presence of viral contamination in biological materials from multidonor source plasma has been confirmed by the demonstration of virus infection in recipients, and the prevalence of anti-HTLV-III in severely affected haemophiliacs can be as high as 90%.⁴ By the end of June 1985 80 haemophiliacs in the United States and five in the United Kingdom had developed AIDS (data from the Communicable Diseases Surveillance Centre, Public Health Laboratory Service, London, and the AIDS Weekly Surveillance Report (1 July 1985) of the Centres for Disease Control, Atlanta). Intriguingly, none had developed Kaposi's sarcoma, one of the major features of AIDS in homosexual and some African patients.

We report here the prevalence of anti-HTLV-III and of overt AIDS and related disease in the population of haemophiliacs attending the haemophilia reference centre for the north of England.

Patients and methods

The Newcastle Haemophilia Reference Centre serves people with haemorrhagic disease and their families from a population of 3.1 million. With the support of four associate centres (in Carlisle, Sunderland, Middlesbrough, and Whitehaven) the staff of the centre supervise and follow up patients on a home therapy programme which was established in 1973-4 when the first freely available lyophilised concentrates became available. This report concerns the health of the 143 patients known to have been transfused with multidonor clotting factor concentrates. Ninety five had received factor VIII from both volunteer donor National Health Service and commercial sources. The remaining patients had received either NHS or commercial factor VIII alone or factor IX from NHS or commercial sources. Three patients had received commercial concentrates and treatment of unspecified origin at other centres (table I).

Since the start of the programme follow up in Newcastle has included repeated clinical examination and musculoskeletal assessment, monitoring of blood counts (including haemoglobin and white cell and platelet counts), liver function tests, urine analysis, and, when indicated, radiology and specialist referral. Children are examined at least once every six months and adults at least yearly.

SEROLOGY

HTLV-III antibody testing became available in 1984, initially through the services of the virology section, department of microbiology, Middlesex Hospital Medical School, using virus bearing cells (CEM, CBLI) generously provided by Professor R A Weiss, Institute of Cancer Research, Chester Beatty Laboratories, London, and latterly through the Public Health Laboratory Service at Newcastle General Hospital. Before February 1985 competitive radioimmunoassay was used in the London test; this has now been superseded by a competitive enzyme linked immunosorbent assay. In the fluorescent antibody test used in Newcastle 20 ml of chronically infected HTLV-III cell line (HT H9) was pelleted by light centrifugation and washed once in phosphate buffered saline. The cell pellet, containing about 2×10^6 cells, was resuspended in 1 ml of phosphate buffered saline and 2 μ l volumes applied to spots on eight holed teflon coated microscope slides. The slides were allowed to dry at room temperature and fixed in acetone for 10 minutes. Patients' serum samples were diluted 1/16 in phosphate buffered saline, applied to the spots, and left for 45 minutes at room temperature. After washing in the saline fluorescein isothiocyanate conjugated sheep antihuman IgG 1/30 in 20% normal sheep serum was applied to the spots and the slides left for 45 minutes at room temperature in a humidified base. The

slides were washed in phosphate buffered saline, mounted with coverslips in glycerol saline, and examined by fluorescent microscopy under epi-illumination. Positive samples showed the characteristic surface and cytoplasmic location of antigen within the cells. HT H9 cells were made available through the generosity of Dr R C Gallo, National Cancer Institute, Maryland, USA.

In 1984 voluntary HTLV-III antibody screening and counselling were offered to both members of staff and the relatives and close contacts of haemophilic patients. To date results are available from 68 members of staff and from 269 patients, relatives, or close contacts. A prerequisite of testing is that the results of tests are made known to those concerned, or when the person is aged under 16 years to parents, and that those tested are aware that confidential counselling and advice are available immediately within the local health authority. Given this assurance the service has already extended beyond the usual staff of the haemorrhagic service.

IMMUNOLOGY

Lymphocytes were separated from heparinised peripheral blood by centrifugation over Ficoll-hypaque (Flow Labs). Cells were washed and incubated for 30 minutes with monoclonal antibody against the human T4 (helper/inducer) lymphocyte subset using anti-leu 3a (Becton-Dickinson). After being washed cells were reincubated for 30 minutes with fluorescein isothiocyanate conjugated antimouse IgG (Miles Laboratories), which had previously been affinity purified with human IgG conjugated to Sepharose.

Serum immunoglobulins were measured using Nor-partigen plates (Behring) and serum β 2 microglobulin measured using a commercial radioimmunoassay (Pharmacia).

Intradermal challenge tests were performed as in vivo indices of cellular immunity using the following panel of agents: phytohaemagglutinin 20 μ g/ml (Wellcome), purified protein derivative 1/1000 (Evans), *Candida albicans* 1% (Bencard), and *Trichophyton* 0.5% (Bencard). Each agent (0.1 ml) was administered intradermally in the skin of the forearm and the phytohaemagglutinin response read at 24 and 48 hours for induration.

TABLE 1—Origin of blood products given to 143 patients together with their anti-HTLV-III status

	No of patients exposed	No tested for anti-HTLV-III	No positive	No negative
NHS and commercial factor VIII	95	88	73	15
NHS factor IX only	16	7	0	7
NHS and commercial factor IX (HT)	10	10	0	10
NHS factor VIII only	7	3	1	2
Commercial factor VIII only	7	4	3	1
NHS factor IX and commercial factor VIII*	3	3	1	2
Commercial factor VIII (HT) only	1	1	0	1
Commercial factor IX (HT) only	1	1	0	1
Commercial factor VIII and ? NHS factor VIII	3	3	3	0
Total	143	120	81	39

NHS = National Health Service. HT = heat treated.

*Patients with factor VIII antibodies.

Results

PREVALENCE OF ANTI-HTLV-III

By May 1985 the results on 337 people were known, 269 from the patient group (tables II and III) and 68 from staff. Sera from 76 out of 99 patients with severe haemophilia A tested for anti-HTLV-III were positive, five by solid-phase assay only. One of these patients had a repeat positive radioimmunoassay. Of the 23 severely affected patients negative for HTLV-III antibody, three had been tested by the immunofluorescence technique only; the latter results are being checked. All positive results obtained by immunofluorescence were confirmed by the solid phase assay.

Of the seven anti-HTLV-III positive patients who were not severely affected two had factor VIII coagulant (VIII:C) levels below 5% and two levels of 5-10%; all had clinical reasons for the use of concentrate rather than cryoprecipitate therapy. The remaining patients had factor VIII:C levels of 11% and 22%. The first had required concentrate while working offshore in 1984 and the second after a major bleed. No patient with haemophilia B was sero-

TABLE II—Anti-HTLV-III status by severity

	No (%) positive	No negative	Total tested
Haemophilia A:			
Severe (<1% factor VIIIIC)	76 (76)	23	99
>1% factor VIIIIC	7 (15)	38	45
Haemophilia B:			
Severe (<1% factor IXC)	0	14	14
>1% factor IXC	0	4	4
Sexual partners	3 (9)	33	36
Others (see table III)	0	71	71
Total	86	183	269

TABLE III—Numbers of other people tested (see table II). All were negative for HTLV-III

	No tested		No tested
Patients with other bleeding disorders:		Sons of haemophilia A patients	4
von Willebrand's disease	17	Carrier daughters of haemophilia A patients	2
Factor V deficiency	3	Carrier sisters of haemophilia A patients	3
Factor VII deficiency	1	Mothers of haemophilia B patients	1
Factor XII deficiency	1	Fathers of haemophilia B patients	1
Mothers of haemophilia A patients	22	Kidney recipient with von Willebrand's disease	1
Fathers of haemophilia A patients	14	Casual contact homosexual male	1
		Total	71

positive for anti-HTLV-III. Details of the results in family contacts and others tested are shown in table III. Thirty six sexual partners of patients with haemophilia A were tested: three were seropositive; their spouses were also seropositive.

None of the 68 members of staff tested was HTLV-III antibody positive. They comprised 24 medical laboratory scientific officers, 18 doctors, 15 nurses, 7 clerical staff, 2 physiotherapists, 1 social worker, and 1 domestic cleaner. Among the doctors were a dental, a general, and an orthopaedic surgeon who regularly worked with patients positive for HTLV-III antibody.

CLINICAL FINDINGS

All 143 multitransfused patients were examined within the past six months. Thirty three were found to have enlarged lymph nodes in one or more extrainguinal sites, persistent generalised lymphadenopathy, or overt immune disease. Three fulfilled the criteria for AIDS of the Centers For Disease Control and 19 the criteria for AIDS related complex (see Appendix). A further 11 patients had unexplained single site lymphadenopathy; in three cases node biopsy proved unhelpful, only non-specific changes being found on histological examination. There was a significant correlation between lymphadenopathy and anti-HTLV-III positivity (table IV) ($\chi^2 = 12.89$; $p < 0.01$).

Three patients with haemophilia A and AIDS died, one with cerebral toxoplasmosis and *Pneumocystis carinii* pneumonia and two with *Pneumocystis carinii* pneumonia. These findings are shown in table V, which includes a previously transfused spouse with AIDS (case 4). A further patient, who presented before anti-HTLV-III testing was available, died in 1984 after splenectomy for idiopathic thrombocytopenic purpura. This death was probably related to HTLV-III infection.

Two of the 33 patients with clinical abnormalities were anti-HTLV-III negative. One was a 56 year old man with haemophilia A and factor VIII antibodies who last received factor VIII concentrate in 1978. He has since been treated with NHS factor IX concentrate, and, apart from very severe arthropathy, was in good general health. He did, however, have persistently enlarged, bilateral axillary nodes.

TABLE IV—Lymphadenopathy and anti-HTLV-III status

	No tested for anti-HTLV-III (n = 120)	No positive	No negative
Without lymphadenopathy	87	50	37
With lymphadenopathy	33	31	2

TABLE V—Clinical abnormalities probably related to the acquired immunodeficiency syndrome in 33 of the 143 multitransfused patients together with one spouse (case 4)

Case No	Abnormalities
<i>Patients with AIDS</i>	
1	<i>Pneumocystis carinii</i> pneumonia cerebral toxoplasmosis; died 1984
2	<i>Pneumocystis carinii</i> pneumonia; died 1985
3	Oesophageal candidiasis; anorexia, weight loss; fatigue, malaise; infected prosthetic joint; died 1985
4	<i>Pneumocystis carinii</i> pneumonia
<i>Patients with AIDS related complex</i>	
5	Intermittent diarrhoea; night sweats; candidiasis; herpes simplex; ringworm
6	Intermittent diarrhoea; anorexia, weight loss; fatigue, malaise; marked seborrhoeic dermatitis
7	Persistent generalised lymphadenopathy; persistent anorexia, weight loss
8	Persistent generalised lymphadenopathy
9-17*	Lymphadenopathy in two or more extrainguinal sites of at least 3 months' duration; 2 patients with intermittent diarrhoea
18-22	Idiopathic thrombocytopenic purpura, including 3 patients with lymphadenopathy
23	Acquired haemolytic anaemia
<i>Patients with lymphadenopathy</i>	
24-34*	Single site persistent, extrainguinal lymphadenopathy

PGL = Persistent generalised lymphadenopathy.

ITP = Idiopathic thrombocytopenic purpura.

*In cases 17 and 34 the patients were negative for HTLV-III antibody.

The other patient was a 15 year old schoolboy with haemophilia B. He had received only NHS factor IX or commercial heat treated factor IX in the past, was in good health, but had left axillary lymphadenopathy.

The ages of the remaining three anti-HTLV-III positive patients ranged from 11 to 64, those dying with AIDS being 34, 61, and 64 years old. The youngest patient with idiopathic thrombocytopenic purpura and the patient with acquired haemolytic anaemia were 12 years old. Three of these patients (two with idiopathic thrombocytopenic purpura and one with acquired haemolytic anaemia) underwent splenectomy after failure of conservative management and at the time of writing were in good health, except for lymphadenopathy in those patients with idiopathic thrombocytopenic purpura.

All three anti-HTLV-III positive patients with physical abnormalities had haemophilia A and had received both NHS and commercial factor VIII concentrates or, in one case (case 23), commercial concentrate only from multiple batches in the past. The NHS material was supplied by the Lister Institute at Elstree, London. The commercial concentrates were bought from four companies—Alpha, Armour, Cutter, and Travenol. No links between specific batches of material and physical abnormality have yet been found. Of the concentrate sources shown in table I, however, seropositivity was associated with NHS factor VIII in only one patient and he had no physical signs. All other seropositive patients had received either both NHS and commercial concentrates or commercial concentrates alone.

The amounts of factor VIII used by those people with AIDS or severe AIDS related complex were not significantly different from those used by other patients treated at the Newcastle centre, and we could find no correlation with the timing or frequency of treatment. In the most recent five year period the two patients with AIDS treated exclusively in Newcastle had received 49 574 and 43 315 units of factor VIII on average each year. The third patient with AIDS had received treatment from other centres both in Britain and in other European countries. The two patients with multiple symptoms of AIDS related complex had received 48 985 and 36 652 factor VIII units and the two patients with persistent generalised lymphadenopathy 41 906 and 34 179 factor VIII units per year on average over the five years. All these patients had clinically severe haemophilia, and four (cases 2, 3, 6, and 7) had had major surgery in those years.

Newcastle patients with haemophilia A of all severities received on average 36 359 factor VIII units/patient/year from 1979 to 1984. The national average for the United Kingdom in 1982, the last year for which accurate figures are available, was 32 619 units/patient/year.

None of the 143 patients reviewed was known to be homosexual or to belong to other risk groups for AIDS, except for one man with a history of intravenous drug abuse. This patient had intermittent diarrhoea and supraclavicular lymphadenopathy and was anti-HTLV-III positive.

One of the seropositive women, aged 66 years (case 4), underwent a panproctocolectomy for ulcerative colitis in 1984 and developed AIDS with *Pneumocystis carinii* pneumonia. She received transfusions of blood after her operation; donors are being checked for anti-HTLV-III. Another woman was pregnant, with normal sonographic scan at 22 weeks' gestation.

IMMUNOLOGICAL RESULTS

Immunological studies were performed on all four patients with AIDS and five patients with the AIDS related complex who were seropositive for anti-HTLV-III (table VI). All patients showed major abnormalities, the most consistent and striking being a reduction in the absolute T4 count even in patients with normal total lymphocyte counts. Apart from the abnormalities of T cell function, these patients also showed other consistent immunological abnormalities that are features of HTLV-III infection, including hypergammaglobulinaemia and raised serum β 2 microglobulin concentrations.

Discussion

Our results show a high incidence of HTLV-III related disease in a multitransfused population of haemophiliacs exposed since the early 1970s to concentrates prepared from thousands of plasma donations. Nearly all patients with severe haemophilia A had at some time received factor VIII commercial concentrates and most of them were seropositive to HTLV-III. The few patients with haemophilia B within our population were all seronegative and had been exposed only to NHS factor IX concentrate from volunteer donors. However, seroconversion⁵ and, in one case, full blown AIDS have occurred in similar groups of patients with haemophilia B in the UK, indicating that the UK donor panel has included HTLV-III infected donors. All our patients now receive heat treated factor VIII or IX concentrates, except for some mildly affected patients, people with von Willebrand's disease, and young children. These patients are treated with either desmopressin, when this is likely to raise factor VIIC levels or shorten bleeding times, or, when available, with cryoprecipitate or fresh frozen plasma from a special donor panel of seronegative people. We are reluctant to use heat treated concentrates rather than cryoprecipitate or fresh frozen plasma, as advocated by Bloom and his colleagues,⁶ because of the high incidence of non-A non-B hepatitis which affects patients treated with multidonor products.

Our experience with florid AIDS is in keeping with that of Evatt and colleagues,⁷ which suggests that older patients are at increased risk of developing severe disease after HTLV-III infection; three of the four people with AIDS were aged over 60 when *Pneumocystis carinii* pneumonia was first diagnosed. Because of this we are now prescribing prophylactic therapy with pyrimethamine and sulfadoxine (Fansidar) for older patients with AIDS related complex.^{8,9}

Other workers have shown that seroconversion for anti-HTLV-III in haemophiliacs occurred as early as 1979-81.^{5,10} Although we have no direct evidence of the timing of seroconversion in our patient population, it probably did occur around this time, if not earlier. The widespread use of multidonor concentrates in Newcastle dates from 1973-4, and this may be the reason for both the high prevalence of seropositivity and the high incidence of virus related disease in our population when compared with other patient groups in the United

Kingdom. In our study patients with severe disease did not use significantly more factor VIII than those without AIDS or AIDS related disease, nor did they use significantly more blood products than similar patients treated elsewhere. It may be that cofactors in addition to HTLV-III infection are needed to produce severe disease. Further comparative studies will be needed to determine what, in addition to age, these might be. Given that seroconversion probably occurred as long ago as the late 1970s in many patients it is some comfort to presume that most of our patients have already lived through the median incubation period for AIDS¹¹ and remain in good general health. Further follow up will be needed to confirm this impression, which may simply reflect the slow development of AIDS related disease in some patients.¹²

A disturbing feature of this survey is the preliminary evidence for heterosexual transmission of HTLV-III in three regular sexual partners of patients with severe haemophilia A. Apart from an eight unit blood transfusion from volunteer donors in one woman, no other possible risk factors are known for these women. Our results are in keeping with those of others,¹³⁻¹⁵ and are of profound importance for haemophilic families. To counsel that vaginal intercourse should always be protected by condom and that couples should be advised not to start a family until we know more about the degree of risk of fetal transmission¹⁶ is bad enough. There is a most urgent need to put this advice in the context of real versus perceived risk.

Our immunological results confirm those of others¹⁷ in showing that the absolute reduction of T4 cells in AIDS is a more accurate predictor of overall immune function than the ratio of T4:T8 or skin testing for cell mediated immunity. Indeed, it is striking that one patient in this series with AIDS and another two with AIDS related complex still had intact antigen recall despite profound T4 lymphopenia, a situation which has been observed previously.¹⁸ Froebel and her colleagues have shown that HTLV-III seropositivity is associated with a significant reduction of T4 numbers in asymptomatic haemophiliacs when compared with seronegative individuals (personal communication), and therefore it is unlikely that the consistent reduction of the T4 population of our patients with HTLV-III related disease was the result of other factors. Indeed, the depression of T4 numbers seen in these patients is of a similar order to those associated with, or rapidly followed by, development of opportunistic infections in male homosexuals.¹⁷

Within the past two years AIDS and the problems it raises have transformed our relationships with haemophilic families and our pattern of working in Newcastle. As Evans *et al* have emphasised,¹⁹ AIDS consumes the time of staff concerned in the care of those at risk. Quite apart from having to learn to apply and work within the guidelines laid down by professional bodies and keep abreast of both medical and scientific developments (as well as what the lay media has to say) is the time needed to talk calmly with and to counsel patients and their families. This is especially difficult in the context of haemophilia because of the familial and social interactions of the disorder. Although an overall impression can be presented in open meetings and through newsletters, it is only in the privacy of

TABLE VI—Immunological investigation in 9 patients. Cases 1-4 had confirmed AIDS

Case No	Total lymphocyte count ($\times 10^9/l$)	Total T4 lymphocyte count ($\times 10^9/l$)	Immunoglobulins (g/l)			β 2 microglobulin (mg/l)	Skin test
			IgM	IgG	IgA		
1	1.0	0.10	3.0	18.3	6.8	4.6	PPD 2 cm
2	5.45	0.32	13.6	35.0	>25.0 g/l	6.8	All negative
3	0.7	0.10	2.4	15.6	11.4	4.5	All negative
4	1.1	0.07	2.6	19.0	18.9	4.8	All negative
5	1.18	0.20	2.4	15.0	9.2	5.2	All negative
6	1.7	0.22	1.5	22.6	3.2	4.4	PHA 1 cm
7	0.6	0.05	2.4	18.3	3.3	7.0	PHA PHD Trichophyton
8	1.7	0.13	2.2	24.9	1.9	2.7	No information
9	2.0	0.45	2.1	19.7	6.5	3.8	PHA 0.5 cm Candida 0.75 cm
Adult normal range	1.4-3.0	0.5-1.6	0.25-2.0	6-16	0.75-4.0	1-2.5	

PPD = purified protein derivative. PHA = phytohaemagglutinin.

the consulting room or the family home that many of those worried by AIDS can be helped. Consideration must also be given to the well being of staff, many of whom have known affected families for years and have watched the hitherto successful application of home therapy and prophylaxis.

To cope we think it imperative that the medical, nursing, social work, and laboratory support provided to every centre treating people in any group at risk, including haemophilia centres, should be assessed as a matter of urgency. Extra support is also needed by the voluntary societies concerned with the care of patients with AIDS in the community.

We thank the staffs of the Northern Regional Haemophilia Service and the Infectious Diseases Unit at Newcastle General Hospital for their help in the preparation of this paper. Dr John Craske of the regional virus laboratory, Withington Hospital, Manchester, gave us great help and advice.

Appendix: Centres for Disease Control Surveillance definitions

AIDS is (a) the presence of reliably diagnosed disease at least moderately predictive of cellular immune deficiency, and (b) the absence of an underlying cause for the immune deficiency or of any defined cause for reduced resistance to the disease. AIDS related complex is a condition in which a person must have two or more symptoms or signs of specific chronic unexplained conditions for three months or longer, together with two or more abnormal laboratory values. The symptoms and signs include non-inguinal lymphadenopathy, weight loss, fever, diarrhoea, fatigue-malaise, and night sweats and the laboratory studies include measurements of lymphocyte subsets and other blood cells, increased serum globulin concentrations, and measurements showing reduction in immune response. To fulfil the criteria of generalised lymphadenopathy at least two

extrainguinal sites must be affected for at least three months in the absence of any current illness or drug known to cause lymphadenopathy.

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Coffee, tea, and plasma cholesterol: the Jerusalem Lipid Research Clinic prevalence study

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Abstract

The association of intake of coffee and tea, assessed by 24 hour dietary recall, with plasma cholesterol and its lipoprotein fractions was studied in a sample of 1007 men and 589 women aged 35-64 resident in Jerusalem.

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These cross sectional data showed a significant linear association ($p < 0.001$) between consumption of coffee in men and plasma cholesterol and low density lipoprotein cholesterol concentrations. Men who drank five cups of coffee or more had plasma cholesterol concentrations about 0.5 mmol/l (20 mg/100 ml) higher than non-drinkers after controlling for age, ethnicity, body mass, education, season of year, smoking, tea drinking, and dietary intake of fat and carbohydrates. In women adjusted mean plasma cholesterol concentration was 0.34 mmol/l (13 mg/100 ml) higher in coffee drinkers grouped together ($p < 0.01$). The test for a linear trend was not significant. The association in both sexes was largely with the low density lipoprotein cholesterol fraction. High density lipoprotein cholesterol concentrations were somewhat increased in women who drank coffee ($p < 0.01$ for a linear trend) but not in men. Tea drinking was not associated with unadjusted plasma cholesterol concentrations in either sex. Male tea drinkers, but not female, had slightly higher adjusted plasma cholesterol concentrations than non-drinkers (0.15 mmol/l (6 mg/100 ml), $p = 0.04$). No dose response relation was evident.