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Short Communication

Cholesterol profile in people with newly diagnosed coeliac disease: a comparison with the general population and changes following treatment

Nina R. Lewis[1]*, David S. Sanders[2], Richard F. A. Logan[1], Kate M. Fleming[1], Richard B. Hubbard[3] and Joe West[1]

[1]*Division of Epidemiology and Public Health, Medical School, Queen's Medical Centre, University of Nottingham, Nottingham NG7 2UH, UK*
[2]*Department of Gastroenterology and Liver Unit, Royal Hallamshire Hospital, Sheffield S10 2JF, UK*
[3]*Division of Epidemiology and Public Health, Nottingham City Hospital, University of Nottingham, Clinical Sciences Building, Nottingham NG5 1PB, UK*

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Recent studies have suggested that untreated coeliac disease is associated with lower total cholesterol than in the general population while the effect of treatment with a gluten-free diet on the cholesterol profile of clinically apparent coeliac disease is not known. We measured the cholesterol profile at diagnosis, and compared this with Health Survey for England figures, and again following 12 months treatment with a gluten-free diet in 100 consecutive adults with coeliac disease attending the Royal Hallamshire Hospital, Sheffield, UK. The mean total cholesterol was 4·84 (SD 1·2) mmol/l in adults (mean age 51 (SD 16) years) newly diagnosed with coeliac disease. At diagnosis of coeliac disease, men had 21 % lower and women had 9 % lower mean total cholesterol in comparison to the general population (difference in age-adjusted mean total cholesterol −1·09 mmol/l (95 % CI −0·97, −1·21); −0·46 mmol/l (95 % CI −0·24, −0·68), respectively). There was no change in mean total cholesterol following treatment. However, there was a small but statistically significant increase of 0·12 mmol/l (95 % CI 0·05, 0·18) in the mean HDL-cholesterol. Total cholesterol was lower at diagnosis in coeliac patients than in the general population and did not increase with 1 year of a gluten-free diet while HDL-cholesterol increased following treatment. Any increase in risk of IHD or stroke in people with coeliac disease is unlikely due to an adverse cholesterol profile either before diagnosis or after treatment with a gluten-free diet.

Cholesterol: Coeliac disease: Gluten-free diet

Recent studies have suggested that untreated coeliac disease is associated with a low serum cholesterol. Ciacci *et al.* [1] observed 0·7 mmol/l lower total cholesterol in ten adults with coeliac disease presenting with hypochromic anaemia in comparison to those with hypochromic anaemia due to other causes, while West *et al.* [2] found that total cholesterol in people with undetected coeliac disease as assessed by endomysial antibody positivity was 0·5 mmol/l lower in comparison to endomysial antibody-negative general population controls. While these reductions might seem modest it has been calculated that a reduction in total cholesterol of 0·6 mmol/l will result in 25–30 % reduction in the risk of mortality from IHD in people aged 55–64 years[3].

Nevertheless, patients with coeliac disease do not appear to have a decreased risk of IHD or stroke, despite an apparently favourable vascular risk profile such as the low cholesterol, lower levels of hypertension[4] and lower prevalence of smoking[5] observed in people with coeliac disease. Indeed, the evidence on vascular outcomes appears to be conflicting with some studies[6,7] suggesting an increased risk of ischaemic stroke and heart disease while others show no increase in risk[4]. Ludvigsson *et al.* [6] observed a 27 % (hazard ratio 1·27; 95 % CI 1·09, 1·48) increased risk of myocardial infarction and 35 % increased risk of ischaemic stroke (hazard ratio 1·35; 95 % CI 1·14, 1·60) in coeliacs using the Swedish in-patient registry. In contrast, the hazard ratio for myocardial infarction was 0·85 (95 % CI 0·63, 1·13) and for stroke 1·29 (95 % CI 0·98, 1·70) in the study by West *et al.* [4]. Concern has been raised as to whether treatment of coeliac disease may have an adverse effect on serum cholesterol. We have therefore prospectively examined cholesterol profiles at diagnosis and after 1 year of a gluten-free diet in a contemporary cohort of newly diagnosed coeliac disease patients.

Abbreviation: tTG, tissue transglutaminase.

* **Corresponding author:** Dr Nina R. Lewis, fax +44 115 8230464, email nina.lewis@nottingham.ac.uk

Methods

Serum total cholesterol (mmol/l), HDL-cholesterol (mmol/l), total cholesterol:HDL-cholesterol ratio, TAG (mmol/l), ferritin (μg/l), folate (μg/l), erythrocyte sedimentation rate (mm/h), C-reactive protein (mg/l), glucose (mmol/l), leucocyte count (10^9/l), albumin (g/l), platelet count (10^9/l) and Hb (g/l) were measured on consecutive incident cases of coeliac disease between 2004 and 2006 at both diagnosis of coeliac disease and following approximately 12 months of treatment with a gluten-free diet. A patient was said to be newly diagnosed (incident) if they were seen within 1 month of being diagnosed with coeliac disease and had not commenced treatment with a gluten-free diet. A diagnosis of coeliac disease has been substantiated by histological features consistent with coeliac disease on duodenal biopsy with the degree of intestinal inflammation graded according to the modified Marsh criteria[8].

Dietary compliance was subjectively assessed by the gastroenterologist and dietitian. In addition, changes in the titre levels of tissue transglutaminase titre and endomysial antibody positivity were noted as a quantitative surrogate for compliance at the time of diagnosis and thereafter whilst following a gluten-free diet. IgA antibodies to tissue transglutaminase (tTG) were measured using a commercially available ELISA (Aesku Diagnostics) where titres greater than 15 U/ml were taken as positive as recommended by the manufacturer. Endomysial antibody was detected by standardised indirect immunofluorescence techniques using human umbilical cord as the substrate. Total and HDL-cholesterol concentrations were measured by a timed end-point method using the Beckman Coulter LX20 Pro[9]. TAG were measured by a timed end-point method using SYNCHRON LX® system[10].

Statistical analysis

We examined the association between baseline HDL-cholesterol and other continuous baseline variables using Spearman's rank correlation coefficients. We examined the association between baseline HDL-cholesterol with each of sex, age group and symptoms using Student's unpaired *t* tests. Paired *t* tests were used to examine changes in blood variables from baseline to 12 months following a gluten-free diet. We explored univariate associations between baseline characteristics and change in HDL-cholesterol using correlation coefficients for continuous variables and Student's *t* tests for categorical variables. Finally, in order to examine the potential effect of a change in the severity of coeliac disease we modelled the change in tTG against change in HDL-cholesterol using multiple linear regression. We included any factors that were found to be associated in the univariate model as well as adjusting for *a priori* confounders of age and sex, and to account for potential regression to the mean, for baseline HDL-cholesterol measurements.

Finally, we carried out a comparison of baseline cholesterol with the findings from the Health Survey for England 2006[11], which is representative of the whole population at both national and regional level. In this survey, non-fasting blood samples were collected from a representative sample of the general population (70 % of sampled population provided valid blood samples) with total cholesterol measurements obtained on 3618 men and 3850 women. For our comparisons we firstly age-adjusted the mean cholesterol values in our coeliac cohort compared with those in the Survey with men standardised to the male population and women to the female population. We also calculated the ratio of observed number of people with total cholesterol greater than 5·0 mmol/l *v.* expected, standardised for age and sex. The standardisations were performed to adjust for the confounding effects of differences in the age and sex population structure between the coeliac and Health Survey for England cohorts, allowing the two populations with different demographic characteristics to be compared directly with each other.

We considered a *P* value of 0·05 to represent statistical significance in all tests. All analyses were performed using Stata SE 9.2 (TexCorp).

Results

Demography and presenting features of cohort

We identified 100 people with incident coeliac disease between 2004 and 2006. Iron deficiency anaemia and diarrhoea were the most common presenting features, affecting 30 % of the cohort; 28 % had partial villous atrophy, 36 % had subtotal villous atrophy and 23 % had total villous atrophy. At diagnosis, the median tTG was 194 (range 2–300) and 86 % (*n* 86) were endomysial antibody-positive. Forty-nine (49 %) of the study cohort had ferritin values below 22 μg/l, the lowest limit of the normal range, whereas fourteen (14 %) had vitamin B_{12} values below 211 ng/l. Seventeen (17 %) of the study cohort had folate values below 3·4 μg/l, the lowest limit of the normal range of values.

Lipid profile at diagnosis of coeliac disease

The mean total cholesterol at diagnosis of coeliac disease was 4·84 (SD 1·2) mmol/l (Table 1). HDL-cholesterol at diagnosis of coeliac disease was associated with weight and sex but no other variables.

Both men and women with incident coeliac disease had lower age-adjusted mean total cholesterol in comparison to the general population (difference in mean age-adjusted total cholesterol −1·09 mmol/l (95 % CI −0·97, −1·21) and −0·46 mmol/l (95 % CI −0·24, −0·68), respectively). The observed reduction in total cholesterol was greater in male incident coeliacs (21 %) than female (9 %). Furthermore, men with incident coeliac disease were 60 % less likely (ratio of observed *v.* expected 0·40 (95 % CI 0·12, 0·68)) to have a total cholesterol of ≥5·0 mmol/l when compared with the general population. In women the effect was smaller and not statistically significant (ratio of observed *v.* expected 0·91 (95 % CI 0·61, 1·20)).

Change in inflammatory markers and weight with gluten-free diet

Follow-up serum values were obtained after a mean of 12·6 (SD 1·9) months on a gluten-free diet (Table 1). All of these patients were considered by the gastroenterologist and dietitian to adhere strictly to a gluten-free diet. The mean value of Hb significantly increased with exposure to a gluten-free

Table 1. Change in vascular profile with gluten-free diet (GFD)*
(Mean values and standard deviations)

		At diagnosis of coeliac disease		After 12 months of GFD		Difference		
	n	Mean	SD	Mean	SD	Mean	95 % CI	*P* value†
Total cholesterol (mmol/l)	100	4·84	1·18	4·82	1·23	−0·013	−0·16, 0·14	0·87
HDL-cholesterol (mmol/l)	92	1·36	0·48	1·48	0·58	0·12	0·05, 0·18	0·0005
Total cholesterol:HDL-cholesterol ratio	92	4·00	2·36	3·71	1·82	−0·28	−0·09, −0·47	0·0035
TAG (mmol/l)	95	1·24	0·78	1·20	0·70	−0·04	−0·15, 0·07	0·48
Ferritin (μg/l)	89	71·55	13·80	84·21	18·08	12·66	−7·60, 32·92	0·22
Folate (μg/l)	93	8·99	0·68	15·12	3·98	6·14	−1·57, 13·85	0·12
ESR (mm/h)	89	13·40	1·3	11·92	1·14	−1·48	−3·23, 0·27	0·10
C-reactive protein (mg/l)	94	4·35	0·41	4·17	0·55	−0·18	−1·21, 0·86	0·73
Glucose (mmol/l)	89	5·85	0·27	5·69	0·21	−0·15	−0·61, 0·31	0·51
Leucocyte count (10^9/l)	96	7·20	0·25	7·18	0·23	−0·02	−0·37, 0·42	0·90
Albumin (g/l)	98	39·51	0·40	40·12	0·38	0·61	−1·36, 0·14	0·11
Platelet count (10^9/l)	96	307·78	8·91	303·15	9·23	4·64	−19·91, 10·64	0·55
Hb (g/l)	96	12·99	0·21	13·64	0·15	0·65	0·29, 1·02	0·0006
tTG (IU)	83	172·2	123·0	71·4	104·7	−100·84	−72·63, −129·06	0·00001

ESR, erythrocyte sedimentation rate; tTG, tissue transglutaminase.
* For details of subjects and procedures, see Methods.
† Paired *t* test.

diet (Table 1) though there were no substantial changes in folate, ferritin, albumin, erythrocyte sedimentation rate, C-reactive protein, leucocyte count or platelet counts. There was a 4·2 kg increase in mean weight (95 % CI 2·9, 5·5) from the baseline mean weight of 66·5 (SD 4·0) kg.

Change in lipid profile following treatment with gluten-free diet

There was no change in mean cholesterol or TAG level with treatment of incident cases of coeliac disease. However, there was a small and statistically significant increase of 0·12 mmol/l (95 % CI 0·05, 0·18) in the mean value of HDL-cholesterol with exposure to a gluten-free diet. Furthermore the total cholesterol:HDL-cholesterol ratio was reduced by 0·28 (95 % CI −0·09, −0·47).

On univariate analyses the changes in HDL-cholesterol observed did not vary with demographic variables such as age at diagnosis nor sex. Features suggestive of malabsorption (such as by stratifying the cohort into those having diarrhoea and or weight loss; height, weight, albumin, Hb), systemic inflammation (such as ferritin, erythrocyte sedimentation rate, leucocyte count, platelet count) or more severe coeliac disease (such as by stratifying the cohort into those with subtotal or total villous atrophy, those with higher tTG) were not associated with change in HDL-cholesterol.

However, when we examined change in tTG, a proxy marker often used in clinical practice to reflect response to treatment in coeliac disease, this was weakly associated with change in HDL-cholesterol on univariate analysis ($P=0·06$). After adjusting for age at diagnosis, sex, baseline HDL-cholesterol and baseline tTG, change in tTG was independently associated with change in HDL-cholesterol ($P=0·03$) on treatment of incident coeliac disease with a gluten-free diet on multivariate analyses. Thus for each 50 unit decrease in tTG that occurred on treatment of coeliac disease there was a 0·03 mmol/l increase in HDL-cholesterol.

Discussion

Principal findings

The present study shows that at diagnosis coeliacs have much lower total cholesterol levels than the general population with the observed reduction greater in men (21 %) than in women (9 %). In addition to the changes in weight and Hb profile expected when diagnosing and treating people with coeliac disease, the present study reassuringly observed no increase in total cholesterol on treatment with a gluten-free diet. Furthermore, HDL-cholesterol showed a small but statistically significant increase following treatment. Any increase in risk of vascular events such as IHD or stroke in people with coeliac disease is unlikely due to an adverse cholesterol profile either before diagnosis or after treatment with a gluten-free diet. On the contrary, the lower total cholesterol levels and increases in HDL-cholesterol on treatment should afford people with coeliac disease relative protection against vascular events.

Merits and limitations

This is the first prospective cohort study where there has been systematic collection of lipid profile in a large and unselected sample of cases of incident coeliac disease. Since serum total cholesterol and HDL-cholesterol can both be measured accurately on a random non-fasting sample[12,13], fasting status or timing of blood collection is unlikely to have had an effect on the values obtained. In the absence of malabsorptive processes and systemic inflammation one would not expect HDL-cholesterol to increase as substantially as we have observed simply during a 12-month period. For example, exposure to 4 years of the Mediterranean dietary pattern did not cause any change in serum levels of total cholesterol nor HDL-cholesterol, suggesting that change in dietary patterns alone was not responsible for the change in HDL-cholesterol observed in the present study[14]. Clearly though, if the

gluten-free diet is markedly different with respect to its effect on cholesterol profile then this could be a potential explanation for our observations but there is no evidence that this is true. Though we did not collect dietary data such as the macronutrient content of the gluten-free diet consumed by the cohort, dietary intake such as fat by coeliacs on a gluten-free diet is comparable to the general population[15]. Neither the effects of BMI nor exercise have been shown to alter cholesterol profile substantially over such a short time period[16].

Comparison with other studies

The present observation that people with newly diagnosed coeliac disease have a lower total cholesterol compared with the general population is new though it was suggested in the only comparable study of ten patients presenting with hypochromic anaemia where no general population comparison was made[1]. The reductions in total cholesterol we have found in diagnosed coeliacs were somewhat greater than those reported by West *et al.* [2], who found total cholesterol levels were 10 % lower in endomysial antibody-positive people in comparison to endomysial antibody-negative general population controls.

The finding of no increase in total cholesterol following treatment with a gluten-free diet is in contrast to the only other study to have examined cholesterol profile before and after treatment. Brar *et al.* [17] observed a 0·5 mmol/l (11 %) increase in total cholesterol despite similar proportions of men and women in the cohort, and similar proportions of partial to total villous atrophy present on duodenal biospy at diagnosis. This is probably a reflection of differences in the study populations. As only a small proportion of their study population (132 out of 700) had a cholesterol measurement there are likely to have been specific reasons for doing so. Conversely, the present study was based on all newly diagnosed patients over a 2-year period and is likely to be more representative of coeliac disease in general.

Possible explanations for altered cholesterol profile in coeliac disease

Intestinal malabsorption, reduced cholesterogenesis, increased biliary secretion and/or high faecal elimination of cholesterol have all been proposed as mechanisms which might lower total cholesterol in people newly diagnosed with coeliac disease in comparison to the general population[18–20]. However, the lack of increase in total cholesterol with treatment of coeliac disease suggests that any mechanism based on intestinal malabsorption is less likely. Conversely, there has been no reported increase in risk of cholesterol gallstones or cholecystectomy in people with coeliac disease to support increased biliary secretion as the mechanism involved.

An inverse association has been reported between proxy markers of vascular inflammation (such as C-reactive protein, erythrocyte sedimentation rate) and HDL-cholesterol[21]. HDL-cholesterol is regarded as a potent anti-atherogenic mediator[22] having a wide range of anti-oxidative, anti-thrombotic and anti-inflammatory effects[23]. Indeed HDL-cholesterol-increasing compounds have been shown to attenuate systemic inflammation[24], vessel wall inflammation[25] as well as reducing risk of IHD events[26,27]. Anti-inflammatory treatment of active rheumatoid arthritis, an autoimmune and chronic inflammatory disorder like coeliac disease, has been observed with a reduction in median erythrocyte sedimentation rate levels by 36 % (23 mm/h) and an increase in median HDL-cholesterol by 9 % (0·10 mmol/l) over a 12-month period[21]. With this in mind, perhaps the increase in HDL-cholesterol we have observed on treatment of active coeliac disease is a proxy marker for reduction in intestinal and or systemic inflammation. We did not, however, observe any particularly strong associations between the inflammatory markers we measured and cholesterol profile.

Summary

People with coeliac disease have lower total cholesterol levels than the general population, with the reduction greater in men (21 %) than in women (9 %). While we observed no increase in total cholesterol following treatment with a gluten-free diet, there was a small but significant increase in HDL-cholesterol. Any increase in risk of vascular events such as IHD or stroke in people with coeliac disease is unlikely due to an adverse cholesterol profile either before diagnosis or after treatment with a gluten-free diet.

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