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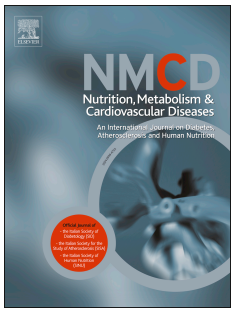

Associations of Tissue Transglutaminase Antibody Seropositivity with Coronary Heart Disease: Findings from a Prospective Cohort Study

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Associations of Tissue Transglutaminase Antibody Seropositivity with Coronary Heart Disease: Findings from a Prospective Cohort Study

Katriina Heikkila[1,2], Harri Rissanen [2], Markku Heliövaara [2], Paul Knekt [2], Markku Mäki [3], Katri Kaukinen [3,4]

[1] Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine, London, UK

[2] National Institute for Health and Welfare, Helsinki, Finland

[3] Tampere Centre for Child Health Research, University of Tampere and Tampere University Hospital, Finland

[4] Department of Internal Medicine, Tampere University Hospital, Tampere, Finland

Corresponding author:

Dr Katriina Heikkila

Department of Health Services Research and Policy, Faculty of Public Health and Policy, London School of Hygiene and Tropical Medicine

15-17 Tavistock Place, London WC1H 9SH, United Kingdom

E: katriina.heikkila@lshtm.ac.uk, T: +44 (0)20 7958 8299, F: +44 (0)20 7927 2701

Abstract

Background and aims Clinical experience and observational studies suggest that individuals with coeliac disease are at increased risk of coronary heart disease (CHD), but the precise mechanism for this is unclear. Laboratory studies suggest that it may relate to tissue transglutaminase antibodies (tTGAs). Our aim was to examine whether seropositivity for tTGA and endomysial antibodies (EMAs) are associated with incident CHD in humans.

Methods We used data from Mini-Finland Health Survey, a prospective cohort study of Finnish men and women aged 35-80 at study baseline 1978-80. TTGA and EMA seropositivities were ascertained from baseline blood samples and incident CHD events were identified from national hospitalisation and death registers. Poisson regression was used to examine the associations between antibody seropositivity and incident CHD.

Results Of 6,887 men and women 562 were seropositive for tTGAs and 72 for EMAs. During a median follow-up of 26 years 2,367 individuals experienced a CHD event. We found no clear evidence for an association between tTGA positivity (hazard ratio, HR: 1.04, 95% confidence interval, CI: 0.83, 1.30) or EMA positivity (HR: 1.16, 95% CI: 0.77, 1.74) and incident CHD, once pre-existing CVD and known CHD risk factors had been adjusted for.

Conclusion We found no clear evidence for an association of tTGA or EMA seropositivity with incident CHD outcomes, suggesting that tTG autoimmunity is unlikely to be the biological link between coeliac disease and CHD.

Keywords: coronary heart disease, CHD, tissue transglutaminase antibody, tTGA, endomysial antibody, EMA, cohort study

Introduction

Coeliac disease is an autoimmune-mediated condition triggered by the ingestion of gluten, a storage protein in wheat, rye and barley[1] Prolamine peptides from these cereals are deamidated by tissue transglutaminase (tTG) in the small intestine and in genetically susceptible individuals the deamidated peptides activate a T-cell driven immune response and production of immunoglobulin A class autoantibodies against tTG [2]. When this autoimmune reaction become chronic, it leads to small intestinal mucosal villous atrophy and crypt hyperplasia, which are currently the diagnostic gold standard for coeliac disease [3].

Coeliac disease can be effectively managed by excluding gluten from the patients' diet, thus stopping the autoimmune response and reversing the mucosal damage [4]. Individuals with coeliac disease who consume gluten, either because they have not been diagnosed or because their adherence to a gluten-free diet is poor, have gluten-induced elevated circulating concentrations of tissue transglutaminase antibodies (tTGAs) and endomysial antibodies (EMAs) [5, 6]. These autoantibodies have been used as serological markers for unrecognised coeliac disease in general population-based screening studies, the findings of which suggest that clinically unrecognised coeliac disease is more common than was previously thought [7-10]: it has been estimated that in addition to the 0.1-0.6% of the population with diagnosed coeliac disease, unrecognised coeliac disease may be present in up to 2% of the population in high income countries [11-13] .

Clinically diagnosed coeliac disease co-occurs with various comorbidities, including neurological and liver abnormalities [14], certain cancers [15] and bone fractures [16], and appears to be associated with an increased risk of cardiovascular outcomes, including coronary heart disease (CHD) [17]. However, the exact mechanism for these associations is

unclear. Laboratory studies have pointed to tissue transglutaminase autoimmunity as one potential link between coeliac and cardiovascular diseases. Findings from *in-vivo* and *in-vitro* studies suggest that tTG has the ability to enhance angiogenesis and that, by contrast, tTGAs can inhibit blood vessel formation. [18-20]. It is not known, however, whether these findings translate into humans. To explore this, we have examined the associations of tTGA and EMA seropositivity with incident coronary heart disease (CHD) using data from Mini-Finland Health Survey, a prospective population-based cohort study of over 6,000 Finnish men and women.

Materials and methods

Participants

Details of the design and data collection in Mini-Finland Health Survey have been reported previously and are provided in the Online Supplement [21]. Briefly, 7,217 men and women (90% of those recruited) aged 35-80 attended a baseline examination in 1978-80. The analyses presented here are based on 6,887 participants with complete data on serology, CHD outcomes and covariates (Online Supplement, Figure S1. Participant flow chart).

Exposures and outcomes

Seropositivity for tTGAs and EMAs were determined from baseline serum samples. Details of the assays have been reported previously and are provided in the Online Supplement [22]. All serum samples were tested for tTGA (Eu-tTG umana IGA, Eurospital S.p.A., Trieste, Italy; abbreviated as Eu-tTG). Positive samples were re-tested using another tTGA test (Celikey Tissue Transglutaminase IgA Antibody Assay, Phadia, Freiburg, Germany; abbreviated as Celikey-tTG) and an EMA test (indirect immunofluorescence, in-house test,

Coeliac Disease Study Group, Tampere University and Tampere University Hospital; abbreviated as EMA).

Incident CHD events were ascertained from national hospitalisation and death registers; baseline cardiovascular disease (CVD) was ascertained from hospitalisation records and baseline health examination. Two outcome measures were used: any CHD (CHD death, non-fatal MI or angina) and hard endpoint CHD (coronary death or non-fatal MI, excluding angina). Full details of the assessment of outcomes and covariates are provided in the Online Supplement.

Statistical analyses

We estimated the incidence of CHD outcomes per 1000 person years, and used Cox proportional hazards regression to model the associations between seropositivity and incident CHD. Full details of the statistical methods are provided in the Online Supplement. Multivariable-adjusted Cox models were adjusted for age (as the timescale in the model), sex (binary), alcohol intake (grams of ethanol per week: 0, 1-49, 50-249, >=250), years of education (0–8, 9–12, >=12), BMI ($kg/m^{2:}$ < 18.5, 18.5-24.9, 25-29.9, 30-34.9, >=35), smoking (never, quit, pipe or cigars or 1-19 cigarettes per day, >=20 cigarettes per day), systolic and diastolic blood pressure (mmHg), total and HDL cholesterol, baseline diabetes and homoeostasis model assessment-estimated insulin resistance (HOMA-IR). Blood pressure, cholesterol and HOMA-IR were natural log-transformed for the analyses. All analyses were conducted using Stata SE 14 (Stata Corporation, College Station, Texas, United States).

Results

Our analyses were based on 6,887 men and women, of whom 562 were seropositive for Eu-tTGA, 197 for Celikey-tTGA and 72 for EMA. In all, 937 participants had CVD at baseline. CVD was more common among seropositive than seronegative participants, but after adjustment for age, the odds of baseline CVD did not significantly differ between these groups (Table 1).

During a median follow-up of 26 years (range: <1 to 32 years), 2,367 individuals experienced a CHD event. Age-adjusted Cox models provided no evidence for an association between antibody seropositivity and any CHD or hard endpoint CHD, and additional adjustment for pre-existing CVD or known CHD risk factors did not markedly alter the results (Table 2 and Online Supplement, Tables S1 and S1).

To investigate whether tTGA positivity is related to CHD incidence independently of EMA, we post-hoc investigated CHD risk in participants who were positive for Eu-tTGA and Celikey-tTGA but negative for EMA (n=130). Again, multivariable-adjusted analyses provided no clear evidence for an association independently of age, sex, pre-existing CVD and other covariates (Table 2).

Discussion

Summary of main findings

Our prospective investigation of over 6,800 Finnish men and women, who were followed up for up to three decades, provided no clear evidence for an association of tTGA or EMA seropositivity with incident CHD. Our findings support those of a previous register-based study conducted in Sweden, in which seropositivity was not associated with the risk of myocardial infarction or angina pectoris (HR: 1.14, 95% confidence interval, CI: 0.87, 1.50).

[23] In the latter investigation, however, the seropositive group included individuals who were positive for gliadin antibodies [23], which can be detected not only in coeliac disease patients but also in healthy people as well as those with other autoimmune diseases [24-26]. It is thus possible that the seropositive group in this study represented a population heterogeneous in terms of the origins of their serological status. In the present study similar may be true of Eu-tTGA positive participants. In Mini-Finland Health Survey the seropositivity for Eu-tTGA (8.2%) was higher than the estimated prevalence of coeliac disease in the Finnish population overall (2.4%) [27]. This suggests that this group includes individuals with a mix of tTGA-associated conditions, such as ulcerative colitis or various forms of arthritis [28]. However, EMAs are pathognomonic for coeliac disease and the prevalence for seropositivity for the other two tests, Celikey-tTGA (2.9% of our study population) and EMA (1.0% of our participants) are closer to the estimated prevalence of coeliac disease, suggesting that the individuals positive for these tests are more likely to have elevated antibody levels related to gluten-induced autoimmunity.

Taken together, our observations and the findings reported before suggest that seropositivity for tTGAs or EMAs is unlikely to explain the previously observed elevated CHD risk in individuals with coeliac disease. One possible explanation for the apparent discrepancy between laboratory-based investigations and human studies is that the angiogenesis-regulating properties of tTGAs reported in cells and animal models [18-20] do not translate to humans. It is also possible that the association is weak and that considerably larger studies than ours (with 235 incident CHD cases in the seropositive group) or Ludvigsson and colleagues' (with 62 incident CHD cases) would be needed to ascertain sufficient power to detect it. However, the clinical significance of such a weak association is uncertain. Either way, although early diagnosis and initiation of gluten-free diet will undoubtedly improve the

prognosis and well-being of individuals with coeliac disease, they are unlikely to have a significant impact on CHD burden in this patient population.

An important strength of our investigation is that we used prospectively collected data and register-based CHD outcomes, which are generally not prone to recall or other biases. Indeed, validation studies suggest that the Finnish hospitalisation and death registers have good coverage and reasonable diagnostic accuracy for CHD outcomes [29]. As Mini-Finland Health Survey had a 90% participation rate, with negligible amounts of missing data or attrition, it is unlikely that the latter have unduly biased our findings. Antibody measurements were missing from 3.1% of participants due to serum samples having been used up in other assays, and such data, likely to be missing completely at random, may have slightly biased our estimates towards the null. We examined the possibility of exposure misclassification in our data by testing a randomly selected sub-sample of 128 Eu-tTGA negative individuals for Celikey-tTG and EMA. No-one tested positive, suggesting that such exposure misclassification is unlikely. A further strength of our investigation is that we were able to adjust our estimates for a large number of covariates, which tend not to be available in studies based on electronic hospitalisation records only. We cannot, of course, exclude the possibility that our observations occurred due to chance.

Implications for future research

The mechanisms for the apparent association between coeliac disease and cardiovascular disease are not fully understood, but currently available evidence suggests several possibilities. Coeliac disease patients often suffer from chronic low level inflammation, which can drive atherosclerosis and vascular damage. [30] A further possibility is that the malabsorption of nutrients, often observed in untreated disease or patients whose adherence

to gluten-free diet is poor, can lead to low circulating concentrations of folate or elevated concentrations of homocysteine, [31] which are implicated in the cardiovascular disease pathology. [32, 33] It is also possible that coeliac disease patients are more likely to receive diagnoses of other diseases and conditions due to their regular contact with healthcare professionals. These mechanisms would merit further research.

Conclusion

In a prospective study of over 6,800 Finnish men and women we found no clear evidence for an association of tTGA or EMA seropositivity with incident CHD outcomes, suggesting that tTG autoimmunity is unlikely to be the biological link between coeliac disease and CHD. Thus, although early diagnosis and initiation of gluten-free diet will undoubtedly improve the prognosis and well-being of individuals with coeliac disease, they are unlikely to have a significant impact on CHD burden in this patient population.

Table 1. Participant characteristics

Baseline characteristic	Eu-tTGA negative (n=6 325)	Eu-tTGA positive (n=562)	p vs. Eu-tTGA negative	Celikey tTGA positive (n=197)	p vs. Eu-tTGA negative	EMA positive (n=72)	p vs. Eu-tTGA negative
CVD (N, %)	812 (12.8)	125 (22.2)	<0.0001	44 (22.3)	<0.0001	6 (8.3)	0.3
Female (N, %)	3 439 (54.4)	280 (49.8)	0.038	125 (63.5)	0.012	51 (70.8)	0.005
Age (years) (mean, SD)	50.4 (13.9)	57.9 (14.2)	<0.0001	59.6 (14.0)	<0.0001	50.2 (11.4)	0.9
Years of education (N, %)							
0-8	4 241 (67.1)	427 (76.0)	<0.0001	151 (76.7)	0.013	45 (62.5)	0.6
9-12	1 349 (21.3)	98 (17.4)		33 (16.8)		19 (26.4)	
>=12	735 (11.6)	37 (6.6)		13 (6.6)		8 (11.1)	
Alcohol intake (N, %)							
None	2 826 (44.7)	292 (52.0)	0.008	119 (60.4)	<0.0001	40 (55.6)	0.07
1-49 gr ethanol/week	2 749 (43.5)	215 (38.3)		61 (31.0)		30 (41.7)	
50-249 gr ethanol/week	257 (4.10	16 (2.9)		5 (2.5)		1 (1.4)	
250+ gr ethanol/week	493 (7.8)	39 (6.9)		12 (6.1)		1 (1.4)	
BMI (kg/m^2) (N, %)							
<18.5	308 (4.9)	31 (5.5)	0.3	15 (7.6)	0.1	6 (8.3)	0.3
18.5-24.9	2 611 (41.3)	206 (36.7)		65 (33.0)		30 (41.7)	
25-29.9	2 461 (38.9)	236 (42.0)		87 (44.2)		30 (41.7)	
30-34.9	779 (12.3)	73 (13.0)		24 (12.2)		4 (5.6)	
>=35	166 (2.6)	16 (2.9)		6 (3.1)		2 (2.8)	
Smoking (N, %)							
Never smoked	3 499 (55.3)	333 (59.3)	0.048	134 (68.0)	0.003	51 (70.8)	0.06
Ex-smoker	1 302 (20.6)	123 (21.9)		35 (17.8)		8 (11.1)	
Pipe/cigars/1-19 cigarettes/day	952 (15.1)	68 (12.1)		18 (9.1)		8 (11.1)	
20+ cigarettes/day	572 (9.0)	38 (6.8)		10 (5.1)		5 (6.9)	
Diabetes (N, %)	329 (5.2)	52 (9.3)	<0.0001	28 (14.2)	<0.0001	2 (2.8)	0.4
Systolic blood pressure (mmHg) (mean, SD)	145.5 (23.6)	152.1 (26.0)	<0.0001	153.8 (26.7)	<0.0001	143.9 (25.7)	0.6
Diastolic blood pressure (mmHg) (mean, SD)	87.1 (11.7)	88.4 (13.1)	0.0109	87.1 (12.8)	0.9	85.4 (10.9)	0.2
Total cholesterol (mmol/L) (mean, SD)	6.9 (1.4)	6.9 (1.4)	0.6	6.6 (1.4)	0.0002	6.3 (1.2)	0.0002
HDL cholesterol (mm/L) (mean, SD)	1.7 (0.4)	1.6 (0.4)	<0.0001	1.6 (0.4)	<0.0001	1.5 (0.3)	0.0008
HOMA-IR[3] (mean, SD)	2.5 (7.5)	2.8 (4.1)	0.4	3.6 (6.2)	0.0471	2.1 (1.5)	0.7

[1] CVD: cardiovascular disease.
[2] HDL: high-density lipoprotein cholesterol
[3] HOMA-IR: homeostasis model assessment; insulin resistance

Table 2. Associations of antibody seropositivity with incident CHD

Antibody test status	**Person-years at risk**	**N CHD[1] (incidence per 1000 person-years)**	**HR[2] (95% CI) Adjusted for age**	**HR[2] (95% CI) Adjusted for age, sex and baseline CVD[3]**	**HR[2] (95% CI) Adjusted for age, sex, baseline CHD and covariates[3]**
Eu-tTGA negative (n=6 325)	141 907	2 132 (15.0)	1 (ref.cat.)	1 (ref.cat.)	1 (ref.cat.)
Eu-tTGA positive (n=562)	10 094	235 (23.3)	1.16 (1.05, 1.33)	1.06 (0.93, 1.22)	1.05 (0.92, 1.21)
Celikey-tTGA positive (n=197)	3 470	80 (23.5)	1.04 (0.83, 1.30)	1.04 (0.82, 1.30)	1.04 (0.83, 1.30)
EMA positive (n=72)	1 789	24 (13.4)	0.80 (0.54, 1.21)	1.00 (0.67, 1.51	1.16 (0.77, 1.74)
Eu-tTGA and Celikey-tTGA positive, EMA negative (n=130)	1 815	57 (31.4)	1.18 (0.90, 1.54)	1.06 (0.81, 1.38)	1.01 (0.77, 1.31)

[1] CHD: coronary heart disease
[2] HR: hazard ratio
[3] Covariates: level of education, BMI, smoking, alcohol intake, blood pressure, total cholesterol, HDL cholesterol, diabetes and HOMA-IR.

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Supporting Information

Online Supplement 1.

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Ethics statement

Mini-Finland Health Survey precedes the current legislation on ethics in medical research, so no formal ethics committee approval was required at the time of the study baseline. All study participants received written information about the aims and purpose of the study, about the use and storage of the data collected, and that participation was voluntary. Agreeing to participate in the baseline examination was taken to indicate informed consent.

Author contributions

KH and KK designed the study, with input from MH and MM. KH and MH planned the statistical analyses, with input from HR and PK. KH conducted the statistical analyses and wrote the first draft of the paper. KH, MH, HR, PK, MM and KK critically reviewed the manuscript and participated in writing the final version.

Disclosure/ Conflict of interest

The authors declare no conflict of interest.

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Study Highlights

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Clinical experience and observational studies suggest that individuals with coeliac disease are at increased risk of coronary heart disease (CHD), but the mechanism for this is unclear.

Laboratory studies suggest that it may relate to tissue transglutaminase antibodies (tTGAs).

In our prospective, population-based study of over 6,800 Finnish men and women, we fould no clear evidence for an association of seropositivity for tTGA and endomysial antibodies (EMAs) with incident CHD in humans.

These findings suggest that though early diagnosis and initiation of gluten-free diet will undoubtedly improve the well-being of individuals with coeliac disease, they are unlikely to have a significant impact on CHD burden in this patient population.