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Association of anti-thyroid antibodies with radiographic knee osteoarthritis and chondrocalcinosis: a NHANES III study

Clement E Tagoe, Wanyi Wang, Shudan Wang and Kamil E Barbour

Abstract

Objectives: To examine the relationships between radiographic knee osteoarthritis (RKOA), symptomatic radiographic knee osteoarthritis (sRKOA), and chondrocalcinosis, as outcome variables, and the autoimmune thyroid disease (AITD) autoantibodies, anti-thyroid peroxidase antibody (TPOAb) and anti-thyroglobulin antibody (TgAb), in the Third National Health and Nutrition Examination Survey (NHANES III) data source.

Methods: NHANES III provided data on 2291 persons over the age of 60 years that included the osteoarthritis variables of interest RKOA, sRKOA and chondrocalcinosis, and the thyroid autoantibodies TPOAb and TgAb. A log-binomial regression model was fit to examine the relationships between anti-thyroid autoantibodies and RKOA. Modified Poisson regression models were employed for the thyroid autoantibodies compared to sRKOA and chondrocalcinosis.

Results: Patients with higher levels of TPOAb were more likely to have chondrocalcinosis [prevalence ratio (PR) 1.247, 95% confidence interval (CI) 1.051, 1.479, $p = 0.012$]. A piecewise regression analysis indicated that this relationship between TPOAb and chondrocalcinosis was only observed when TPOAb was above 35 IU/ml (PR 1.482, 95% CI 1.233, 1.781, $p < 0.001$). Levels equal to or below 35 IU/ml were not associated with chondrocalcinosis. TPOAb was not associated with RKOA or sRKOA, and TgAb was not significantly related to any of the outcomes.

Conclusion: There was no association of AITD autoantibodies TPOAb and TgAb with RKOA or sRKOA. However, there may be an association of TPOAb with the presence of chondrocalcinosis.

Keywords: autoimmune thyroid disease, chondrocalcinosis, Hashimoto's thyroiditis, osteoarthritis

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Correspondence to:
Clement E Tagoe
Division of Rheumatology, Montefiore Medical Center, 111 East 210th Street, Bronx, NY 10467-2490, USA

Division of Rheumatology, Department of Medicine, Albert Einstein College of Medicine, Bronx, NY, USA
ctagoe@aol.com; ctagoe@montefiore.org

Wanyi Wang
Elite Research, LLC, Irving, TX, USA

Shudan Wang
Division of Rheumatology, Department of Medicine, Albert Einstein College of Medicine, Bronx, NY, USA

Kamil E. Barbour
Centers for Disease Control and Prevention, Atlanta, GA, USA

Introduction

Autoimmune thyroid disease (AITD) is an inflammatory thyroiditis characterized by varying degrees of thyroid lymphocytic infiltration. It encompasses a spectrum of disorders, from asymptomatic autoimmune thyroiditis to conditions associated with thyroid enlargement or atrophy, with or without functional derangement.[1,2] The form associated with glandular hypofunction, chronic lymphocytic thyroiditis (CLT), commonly referred to as Hashimoto's thyroiditis, results in hypothyroidism in a significant proportion of affected individuals.[3] In iodine replete populations Hashimoto's thyroiditis is the commonest cause of hypothyroidism.[4] In epidemiological studies AITD is identified by the presence of thyroid autoantibodies expressed by the vast majority of affected individuals with a female predominance, estimated between 10% and 13% of the population.[5] The anti-thyroglobulin antibody

(TgAb) occurred in about 11.5% of the United States (US) population aged ⩾12 years as assessed in the Third National Health and Nutrition Examination Survey (NHANES III), while the anti-microsomal antibody, also referred to as the anti-thyroid peroxidase antibody (TPOAb), was found in about 13%.[5]

Although described as a prototype of single-organ autoimmunity AITD, particularly as CLT, has been associated with several musculoskeletal (MSK) syndromes including osteoarthritis (OA) and inflammatory arthritis.[6,7] The prevalence of well-defined connective tissue disease (CTD) is also increased with AITD, which shares genetics with CTD.[8–10] The arthritis, although generally non-erosive, can be aggressively degenerative and sometimes associated with erosive OA.[11] Recently, chronic widespread pain and fibromyalgia syndrome (FMS) have also been linked to AITD, in particular CLT, with a prevalence rate approaching 30–40%.[12] Most reports of the association of AITD with MSK conditions have been from small studies and were assumed to be hormonally derived.[13] However, many subjects with MSK signs and symptoms have no evidence of hormonal imbalance.[14] In thyroid disease the ability of TPOAb to fix complement has been suggested as contributing to the mechanism of injury of AITD.[15,16] Similar to the finding of TPOAb being more closely associated with thyroid destruction and hypothyroidism than TgAb, some studies have suggested a closer association of TPOAb with some MSK manifestations including FMS in rheumatoid arthritis.[17] In a recent study, total thyroidectomy with subsequent reductions in the levels of TPOAb improved symptoms in subjects with TPOAb levels in excess of 1000 IU/mL, suggesting immunological pathophysiological mechanisms over hormonal mechanisms of injury in AITD-related disease.[18]

Previous large studies investigating thyroid hypofunction and knee OA or chondrocalcinosis could not find a significant relationship.[19,20] Furthermore, a recent prospective cohort study did not find an association between the incidence of knee or hip replacement due to OA and the levels of thyroid-stimulating hormone (TSH).[21] However, a clear association was demonstrable between chondrocalcinosis and knee OA in the Framingham cohort, and chondrocalcinosis has been associated with the presence and severity of knee OA.[22,23] Our study aimed to re-examine the complex relationships between thyroid disease, knee OA and chondrocalcinosis, looking more closely at the relationships with the thyroid autoantibodies, and by inference with AITD. We used NHANES III, because data were acquired for radiographic knee osteoarthritis (RKOA), the presence of chondrocalcinosis on radiographs and the thyroid autoantibodies. We hypothesized that a closer examination of the question of OA of the knee using AITD instead of thyroid dysfunction as an outcome would provide a more pathophysiological understanding of the relationship between AITD as an immunological disease, and knee OA.

Materials and methods

Data source

The NHANES III, conducted in two phases, phase I (1988–1991) and phase II (1991–1994) used complex, multi-stage, stratified, clustered national probability samples of civilian, non-institutionalized persons in the US population, oversampling for children aged 2 months to 5 years, persons aged ⩾60 years, Black non-Hispanics and Mexican Americans. NHANES III included a home examination option to obtain data for very young children and for elderly persons who were unable to visit the mobile examination centers (MECs). The operation and procedures for NHANES III have been described in detail.[24] The consent process is described in detail in the same document. The local conduct of our secondary data analysis was approved by the institutional review board of the Albert Einstein College of Medicine [institutional review board (IRB) no. 11-04-142E]. This study was conducted following the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement checklist from the Equator network guideline.[25]

Study population

Of the NHANES III participants interviewed, 2589 aged ⩾60 years were in phase II (1991–1994) of the study in which data for OA were collected as part of the MEC examination, including physician-performed physical examinations and knee and hand radiographs. Knee radiographs were available for 2415 persons who were able to self-transfer to the X-ray table or could be assisted in doing so and excluded homebound subjects who could not make it to the MECs (Figure 1).

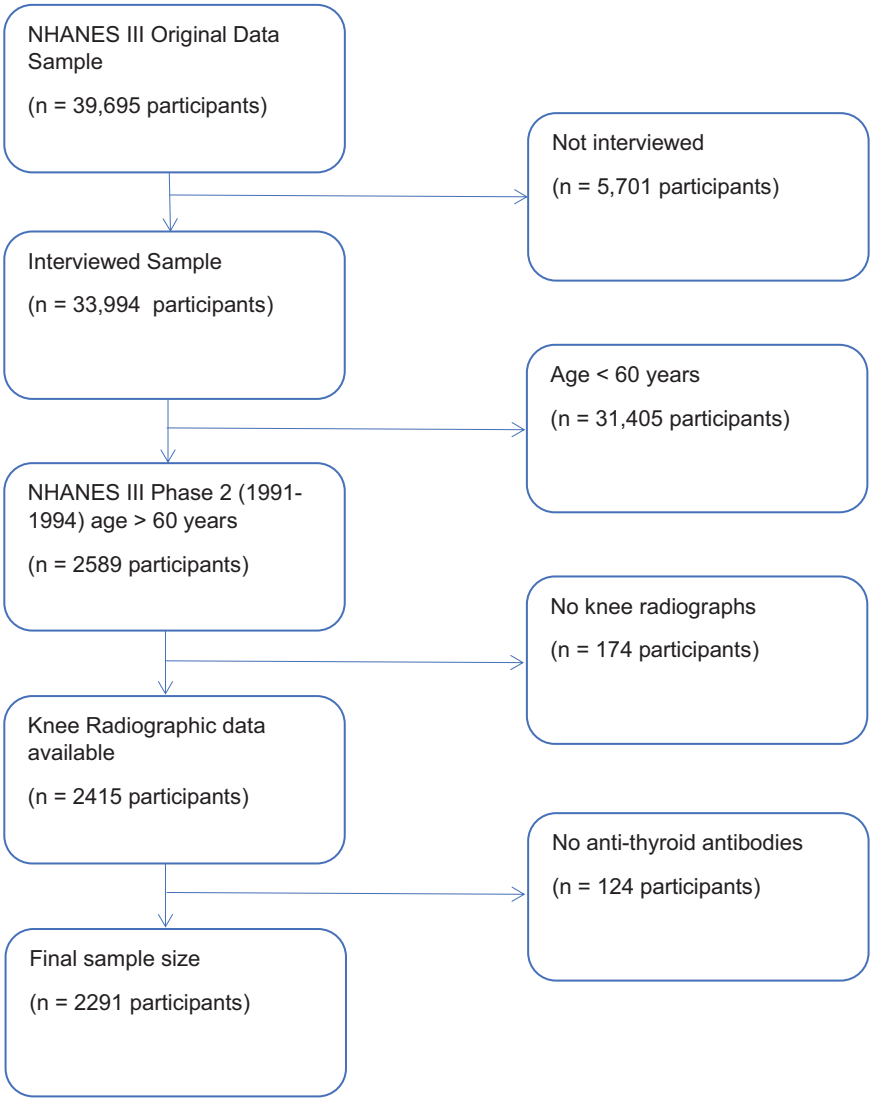

Figure 1. Flow diagram of study participant selection process.

Outcome measures

RKOA and symptomatic radiographic knee osteoarthritis (sRKOA). Radiographs obtained in NHANES III were non-weight-bearing, single view, anterior-posterior (AP) films. Participants with Kellgren and Lawrence (KL) grades ⩾2 (definite osteophytes with possible joint space narrowing) in either knee were determined to have RKOA.[26] All diseased knee films were flagged and read by a second trained radiologist after an initial reading of all radiographs by the first trained radiologist. Consensus readings were thus performed for 35.6% of the radiographs. The intra-reader and inter-reader reliability were assessed as very high for KL scores and were reported in detail elsewhere.[27,28] As current estimates suggested that over 95% of knee replacements were for the indication of OA and only 1.56% of the study population had had knee replacements, we included participants with knee replacements into the study cohort, classified as having RKOA.[27,29] sRKOA was defined as the presence of RKOA in subjects who also answered yes to the survey question, 'Have you ever had pain in your knees on most days for at least 6 weeks? This also includes aching and stiffness'.

Chondrocalcinosis. Chondrocalcinosis was defined by the radiographic appearance of calcifications due to the deposition of calcium pyrophosphate dihydrate crystals in articular cartilage. Chondrocalcinosis was identified using the NHANES

variable names XRPCHOR and XRPCHOL for right and left knee chondrocalcinosis, respectively.

Covariates

Covariates were established as age, gender, race, ethnicity, education, occupation, smoking, body mass index (BMI), and other medical conditions. Data were obtained by patient interview and examination at the home interview or MEC portions of the study.

Demographic information. Participants aged ⩾60 years were included in this study. Race/ethnicity was identified as non-Hispanic White, non-Hispanic Black, Mexican American, and other. Education was dichotomized into ⩽12 years and >12 years. BMI was calculated based on body weight and height. Occupation was classified as manual workers and non-manual workers following the same methods as Dillon *et al.*[27]

Clinical covariates. The details of NHANES III laboratory methods on clinical variables are published online.[30] Thyroid autoantibodies and thyroid function assays were measured in NHANES III as detailed in the manual of medical procedures.[30] TPOAb (anti-microsomal antibody in NHANES III) and TgAb were measured by a highly sensitive, direct radio immunoassay system. Abnormal values of TPOAb and/or TgAb, in which the normal range was <0.5 IU/ml and <1.0 IU/ml, respectively, indicated the presence of AITD.[30] Serum TSH was measured with a chemiluminescence immunometric assay. The working range for this method was 0.01 mIU/L to 50 mIU/L. The reference (normal) range for the test was 0.39–4.6 mIU/L. Euthyroidism, hyperthyroidism and hypothyroidism were defined serologically as corresponding to TSH levels of 0.39–4.6 μIU/mL, <0.39 μIU/mL and >4.6 μIU/mL, respectively. Thyroxine (T4) was measured using an immunoassay which had a reference (normal) range of 57.9 nmol/L to 169.9 nmol/L (4.5–13.2 μg/dl).[30] Self-reported conditions included thyroid disease, lupus, gout, goiter, and diabetes. In the specific case of diabetes participants answered yes to the question 'Have you ever been told by a doctor that you have diabetes or sugar diabetes?'.

Statistical methods

Of the 2589 participants who were 60 years old and above with non-missing KL scores, a total of 2291 cases had non-missing dependent (RKOA, sRKOA, and chondrocalcinosis) and independent variables (TPOAb and TgAb). For the remaining sample, approximately 2.09% were missing information in the dataset. Multiple imputation with fully conditional specification (FCS) in the chained equation approach was used to replace the missing data, and five pseudo-complete datasets were generated. The results from multiple datasets were combined using Rubin's rules.[31] Bivariate relationships were assessed between dependent variables and the categorical demographic/clinical variables using Rao–Scott chi-squared tests. Correlation analyses were performed pairing the continuous variables, and no significant relationship was identified between TPOAb and TgAb. Independent *t*-tests and one-way analyses of variance (ANOVA) were used between continuous variables and categorical demographic/clinical variables. Sample demographic and clinical characteristics were summarized with means and standard deviation (SD) for continuous variables, and frequencies, weighted percentages and standard errors (SEs) of weighted percentages for categorical variables. In the primary analyses, a log-binomial regression model was fit to predict RKOA from TPOAb and TgAb while controlling for some covariates. Due to the low percentages of sRKOA and chondrocalcinosis, modified Poisson regression models with robust error variance were performed to predict these two dependent variables from TPOAb and TgAb while controlling for various covariates. The adjusted prevalence ratio (PR) and 95% confidence interval (CI) were reported to compare each category to the reference group for the categorical predictors. The 95% CI for PR was obtained using the antilog of upper and lower limits of the CI for Ln(PR) (natural log). All continuous variables were normalized before being added into the models due to the various scales between the variables, so the PRs for the continuous variables were interpreted as every SD change of the demographics and disease incidence. Covariates for regression models were selected based on the bivariate analyses results and previous findings.[27,32] Finally, a piecewise regression model with the non-linear logistic procedure was used to identify a threshold of TPOAb, above which a positively stronger relationship between TPOAb and chondrocalcinosis was found using modified Poisson regressions. All analyses were conducted using SAS, version 9.4 (SAS Institute) survey procedures, taking into account the cluster, strata, and MEC-examined final sampling weights adjusted for interview non-response, MEC examinations non-response, non-coverage, and differential selection probabilities on

the population by age, race, household size, and self-reported health status, etc. A two-sided $p < 0.05$ was considered statistically significant.

Results

Sample characteristics

Over half the population were women (57.5%) and 60–69 years old (50.2%) with average age of 70.64 years (SD 7.55). Most were non-Hispanic White (83.1%) with education ⩽12 years (71.2%). The average BMI was 27.08 kg/m^2 (SD 5.03). Approximately 40.3% were overweight and 24.8% had obesity. Fifty-three per cent were non-manual workers. Most participants had no diabetes (88.4%), did not smoke (80.2%), were euthyroid (85.9%), without thyroid disease (92.0%), and did not have gout (93.9%) (Table 1). Approximately 37.8% had RKOA, 13.2% had sRKOA, and 7.3% had chondrocalcinosis. The TPOAb ranged from 0.30 IU/ml to 850.00 IU/ml (mean 10.09 IU/ml), and TgAb ranged from 0.70 IU/ml to 3000.00 IU/ml (mean 8.83 IU/ml).

Associations of anti-thyroid antibodies with demographic/clinical characteristics and RKOA

When adjusted for gender, race/ethnicity, age, education, BMI, TSH, diabetes, and gout, neither TPOAb nor TgAb was significantly associated with the presence of RKOA, $p > 0.05$ (TABLE2Table 2). The log-binomial regression model showed women were 1.242 times more likely than men to have RKOA, PR 1.242 (95% CI 1.063, 1.451), $p = 0.006$. Non-Hispanic Black participants were 1.302 times more likely to have RKOA than non-Hispanic White participants, PR 1.302 (95% CI 1.131, 1.498), $p < 0.001$. Older participants were more likely to have RKOA, PR 1.353 (95% CI 1.259, 1.455), $p < 0.001$. Specifically, participants with 1 SD increase in age were 1.353 more likely to have RKOA. Also, participants with 1 SD increase in BMI were 1.424 times more likely to have RKOA, PR 1.424 (95% CI 1.341, 1.513), $p < 0.001$.

Associations of anti-thyroid antibodies with demographic/clinical characteristics and sRKOA

Due to the small percentage of participants with sRKOA (13.2%, SE 0.8%), a modified Poisson model was performed to examine the relationships between sRKOA and anti-thyroid autoantibodies

Table 1. Descriptive statistics for sample characteristics.

Categorical variables	*n*	Weighted %	SE of weighted %
Outcomes			
RKOA			
Yes	986	37.8	1.4
No	1305	62.2	1.4
sRKOA			
Yes	371	13.2	0.8
No	1920	86.8	0.8
Chondrocalcinosis			
Yes	201	7.3	0.7
No	2090	92.7	0.7
Demographics			
Age (years)			
60–69	1042	50.2	2.1
70–79	754	34.6	1.5
80 and above	495	15.2	1.7
Gender			
Male	1075	42.5	1.2
Female	1216	57.5	1.2
Race/ethnicity			
Non-Hispanic White	1303	83.1	2.0
Non-Hispanic Black	417	7.5	1.0
Mexican American	471	2.4	0.3
Others	100	7.1	1.5
Education (years)			
Less than or equal to 12	1806	71.2	2.7
Greater than 12	472	28.8	2.7
BMI			
Underweight/normal	754	34.9	2.2
Overweight	949	40.3	1.5
Obese	584	24.8	1.1
Occupation			
Manual	1297	47.0	2.5
Non-manual	994	53.0	2.5

(Continued)

Table 1. (Continued)

Categorical variables	*n*	Weighted %	SE of weighted %
Smoking			
Yes	492	19.8	2.2
No	1798	80.2	2.2
Clinical			
TSH levels			
Hyperthyroidism	97	4.1	0.5
Euthyroidism	1969	85.9	0.9
Hypothyroidism	225	10.0	0.8
Thyroid disease			
Yes	145	8.0	0.8
No	2144	92.0	0.8
Diabetes			
Yes	355	11.6	1.0
No	1934	88.4	1.0
Gout			
Yes	129	6.1	1.0
No	2162	93.9	1.0
Lupus			
Yes	6	0.6	0.3
No	2284	99.4	0.3
Goiter			
Yes	55	2.7	0.4
No	2235	97.3	0.4
Continuous variables	***n***	**Mean**	**SD**
TPOAb	2291	10.09	42.45
TgAb	2291	8.83	82.42
T4	2288	8.57	2.26
RFP	2278	44.72	346.69
CRP	2287	0.55	0.91
Age	2291	70.64	7.55
BMI	2287	27.08	5.03

BMI, body mass index; CRP, C-reactive protein; *n*, sample size; RFP, rheumatoid factor; RKOA, radiographic knee osteoarthritis; SD, standard deviation; SE, standard error; sRKOA, symptomatic radiographic knee osteoarthritis; T4, thyroxine; TgAb, anti-thyroglobulin antibody; TSH, thyroid-stimulating hormone; TPOAb, anti-thyroid peroxidase antibody.

while controlling for demographic/clinical characteristics. TPOAb and TgAb were not significant predictors of sRKOA while controlling for gender, ethnicity, age, BMI, occupation, TSH levels, diabetes, gout, T4, and C-reactive protein (CRP), $p > 0.05$. Older participants were more likely to have sRKOA, PR 1.408 (95% CI 1.209, 1.641), $p < 0.001$. Participants with higher BMI had a higher prevalence of sRKOA, PR 1.651 (95% CI 1.480, 1.842), $p < 0.001$. Of note, manual workers demonstrated a higher prevalence of sRKOA than non-manual workers, PR 1.347 (95% CI : 1.013, 1.791), $p = 0.040$ (Table 3). Occupation was not associated with RKOA, TPOAb, and TgAb in preliminary analyses, so it was not included in the RKOA model.

Associations of anti-thyroid antibodies with demographic/clinical characteristics and chondrocalcinosis

A modified Poisson regression was also conducted as the zero-inflated model due to the low percentage of chondrocalcinosis cases around 7.3% (SE 0.7%). Controlling for other demographic/clinical variables (Table 4), participants with higher levels of TPOAb demonstrated a higher prevalence of chondrocalcinosis, PR 1.247 (95% CI 1.051, 1.479), $p = 0.012$. Older participants were more likely to have chondrocalcinosis, PR 1.875 (95% CI 1.494, 2.353), $p < 0.001$. Participants reporting diabetes had a higher prevalence of chondrocalcinosis than those who did not, PR 1.805 (95% CI 1.088, 2.995), $p = 0.022$ (Table 5).

Because the positive relationship between TPOAb and chondrocalcinosis may not occur throughout all value ranges of TPOAb, a piecewise regression model was used to identify a breakpoint above which TPOAb was positively related to the incidence of chondrocalcinosis, and below which no significant relationship or an inverse relationship was found. A potential range of breakpoints was initially identified by plotting the data with a smooth graph. Piecewise regressions with nonlinear NLIN procedure in SAS were then used to determine that the estimated breakpoint of the TPOAb was 35 IU/ml. The modified Poisson regressions were performed again on the two sub-samples (TPOAb $\leq$35 IU/ml and TPOAb $>$35 IU/ml, respectively). The models included TPOAb, gender, BMI, and the significant factors that were found in Table 4 (age and diabetes). The results, in the sub-sample with TPOAb $>$35 IU/ml, revealed that participants

Table 2. The associations of RKOA with anti-thyroid antibodies and other covariates.

Predictor	β	SE	PR	*p*-value	95% CI of PR	
					LL	UL
TPOAb	−0.003	0.06	0.997	0.959	0.887	1.120
TgAb	0.026	0.03	1.026	0.362	0.971	1.085
Female[a]	0.217	0.08	1.242	**0.006**	1.063	1.451
Race/ethnicity[b]						
Mexican American	0.108	0.08	1.114	0.201	0.944	1.314
Non-Hispanic Black	0.264	0.07	1.302	<**0.001**	1.131	1.498
Others	0.063	0.17	1.065	0.715	0.759	1.495
Education[c]						
Greater than 12	−0.097	0.09	0.908	0.288	0.759	1.085
Age	0.303	0.04	1.353	<**0.001**	1.259	1.455
BMI	0.354	0.03	1.424	<**0.001**	1.341	1.513
TSH levels[d]						
Hyperthyroidism	0.075	0.18	1.078	0.670	0.763	1.523
Hypothyroidism	−0.064	0.11	0.938	0.566	0.754	1.167
Gout (yes)	−0.008	0.13	0.992	0.948	0.775	1.270
Diabetes (yes)	0.006	0.10	1.006	0.954	0.821	1.232

The analyses were run on five imputed datasets ($N = 2291$ in each dataset) and pooled estimates were reported.
[a]Compared with male.
[b]Compared with Non-Hispanic White.
[c]Compared with 12 years and below of educational level.
[d]Compared to euthyroidism.
Boldfaced text indicates statistically significant values.
BMI, body mass index; CI, confidence interval; LL, lower limit; PR, prevalence ratio; RKOA, radiographic knee osteoarthritis; SE, standard error; TgAb, anti-thyroglobulin antibody; TPOAb, anti-thyroid peroxidase antibody; TSH, thyroid-stimulating hormone; UL, upper limit.

with a 1 SD increase in TPOAb were 1.482 times more likely to have chondrocalcinosis, PR 1.482 (95% CI 1.233, 1.781), $p < 0.001$. There was no significant relationship between TPOAb and chondrocalcinosis ($p = 0.728$) in the sub-sample with TPOAb ⩽35 IU/ml (Table 5). The sample description was reported by TPOAb sub-sample group, and they are displayed in Table 6.

A preliminary analysis of the relationship between TPOAb and CRP was done looking for evidence of inflammation and acute phase reactant elevation with increasing concentrations of thyroid antibodies. Although the CRP was significantly positively correlated with the TPOAb ($p < 0.001$) this was with an $R^2 = 0.0129$ which showed a relatively weak relationship.

Discussion

In this study we analyzed the complex relationships between the thyroid autoantibodies as evidence for AITD and RKOA, sRKOA, as well as chondrocalcinosis. Our premise was that it could provide a closer association with thyroid disease than examining thyroid hormone function alone as has been done in the past. Our analysis suggests a significant association between TPOAb and

Table 3. The associations of sRKOA with anti-thyroid antibodies and other covariates.

Predictor	β	SE	PR	*p*-value	95% CI of PR	
					LL	UL
TPOAb	−0.090	0.15	0.913	0.543	0.682	1.223
TgAb	−0.050	0.08	0.952	0.553	0.808	1.121
Female[a]	0.306	0.17	1.357	0.065	0.982	1.877
Race/ethnicity[b]						
Mexican American	0.179	0.16	1.196	0.261	0.875	1.634
Non-Hispanic Black	0.161	0.15	1.174	0.296	0.869	1.587
Others	−0.408	0.32	0.665	0.198	0.357	1.238
Manual workers[c]	0.298	0.15	1.347	**0.040**	1.013	1.791
Age	0.342	0.08	1.408	<**0.001**	1.209	1.641
BMI	0.502	0.06	1.651	<**0.001**	1.480	1.842
TSH levels[d]						
Hyperthyroidism	−0.087	0.29	0.917	0.766	0.517	1.625
Hypothyroidism	0.097	0.22	1.101	0.664	0.713	1.702
Gout (yes)	0.244	0.21	1.276	0.252	0.841	1.938
Diabetes (yes)	−0.077	0.20	0.926	0.702	0.626	1.370
T4	−0.013	0.07	0.987	0.855	0.859	1.134
CRP	−0.043	0.08	0.958	0.609	0.812	1.130

The analyses were run on five imputed datasets ($N = 2291$ in each dataset) and pooled estimates were reported.
[a]Compared to male.
[b]Compared to Non-Hispanic White.
[c]Compared to non-manual workers.
[d]Compared to euthyroidism.
Boldfaced text indicates statistically significant values.
BMI, body mass index; CRP, C-reactive protein; CI, confidence interval; LL, lower limit; PR, prevalence ratio; SE, standard error; sRKOA, symptomatic radiographic knee osteoarthritis; T4, thyroxine; TgAb, anti-thyroglobulin antibody; TPOAb, anti-thyroid peroxidase antibody; TSH, thyroid-stimulating hormone; UL, upper limit.

chondrocalcinosis but not with RKOA or sRKOA as determined by NHANES III criteria. The data suggest a similar association between diabetes and chondrocalcinosis but not with NHANES III RKOA or sRKOA. Using the analogy of a significant threshold for anti-nuclear antibodies (ANAs) in certain rheumatic diseases, we looked for a threshold effect with TPOAb in chondrocalcinosis and found that the prevalence increased significantly above 35 IU/ml and was not significant below that value. Although the Framingham cohort showed clearly that chondrocalcinosis is associated with RKOA, NHANES III does not.[22] This may be due to differences in methodology because the former study acquired weight-bearing radiographs and NHANES III did not. Furthermore, lateral views of the knees, not performed in this study, might have added to the sensitivity for detecting the secondary OA generally attributed to chondrocalcinosis, and their absence may have reduced the ability of the current study to detect OA. Foreman *et al.*[33] using data from the OA initiative and magnetic resonance imaging have shown the mainly cartilaginous involvement of chondrocalcinosis in causing knee degeneration, including in the anterior compartment not

Table 4. The associations of chondrocalcinosis with anti-thyroid antibodies and other covariates.

Predictor	β	SE	PR	*p*-value	95% CI of PR	
					LL	UL
TPOAb	0.221	0.09	1.247	**0.012**	1.051	1.479
TgAb	−0.106	0.14	0.899	0.431	0.690	1.172
Female[a]	0.046	0.21	1.047	0.826	0.692	1.584
Race/ethnicity[b]						
Mexican American	0.030	0.23	1.031	0.897	0.653	1.625
Non-Hispanic Black	−0.119	0.24	0.888	0.624	0.551	1.430
Others	−0.595	0.47	0.552	0.207	0.219	1.389
Age	0.628	0.12	1.875	<**0.001**	1.494	2.353
BMI	−0.018	0.10	0.982	0.852	0.810	1.191
TSH levels[c]						
Hyperthyroidism	−0.433	0.45	0.649	0.332	0.271	1.554
Hypothyroidism	0.188	0.25	1.207	0.446	0.744	1.957
Gout (yes)	0.057	0.38	1.059	0.879	0.506	2.218
Smoking (yes)	−0.568	0.33	0.567	0.083	0.298	1.077
Diabetes (yes)	0.591	0.26	1.805	**0.022**	1.088	2.995
T4	0.071	0.08	1.073	0.399	0.911	1.265
RFP	−0.327	0.24	0.721	0.178	0.448	1.161
CRP	0.045	0.08	1.046	0.598	0.886	1.233

The analyses were run on five imputed datasets ($N = 2291$ in each dataset) and pooled estimates were reported.
[a]Compared to male.
[b]Compared to Non-Hispanic White.
[c]Compared to euthyroidism.
Boldfaced text indicates statistically significant values.
BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; LL, lower limit; PR, prevalence ratio; SE, standard error; T4, thyroxine; TgAb, anti-thyroglobulin antibody; TPOAb, anti-thyroid peroxidase antibody; TSH, thyroid-stimulating hormone; UL, upper limit.

visualized on AP radiographic views. The association of chondrocalcinosis with TPOAb but not TgAb is in line with other observations that show similar relationships with a severe symptom complex (including fatigue, increased need for sleep with reduced sleep quality, joint and muscle tenderness, and dry mouth and eyes), hypothyroidism, spinal degenerative disc disease, and with FMS in rheumatoid arthritis.[15,17,18,34] The validity of our data is supported by similar findings to the study of Dillon *et al.*[27] on RKOA. They demonstrated that both RKOA and sRKOA are highly dependent on greater BMI (BMI ⩾30), and are also significantly associated with greater age, non-Hispanic Black race/ethnicity, and men with manual labor occupations. Their study also examined functional limitations and analgesic use but did not study an OA association with diabetes. Our finding of an association between subject-reported diabetes and chondrocalcinosis is novel in a population-based cohort and warrants corroboration using firm classification criteria. Of the metabolic syndromes there is good evidence for an association of chondrocalcinosis with hereditary

Table 5. The associations between chondrocalcinosis and TPOAb in sub-sample.

Predictor	TPO >35						TPO ⩽35					
	β	SE	PR	*p*-value	95% CI of PR		β	SE	PR	*p*-value	95% CI of PR	
					LL	UL					LL	UL
TPOAb	0.393	0.09	1.482	**<0.001**	1.233	1.781	0.454	1.30	1.574	0.728	0.122	20.234
Female[a]	−1.630	0.88	0.196	0.065	0.035	1.108	0.182	0.20	1.200	0.365	0.805	1.789
Age	0.328	0.57	1.388	0.566	0.453	4.254	0.677	0.11	1.969	**<0.001**	1.580	2.453
BMI	−0.186	0.46	0.831	0.689	0.335	2.060	0.017	0.10	1.017	0.871	0.831	1.244
Diabetes (yes)	1.722	1.18	5.594	0.145	0.551	56.780	0.511	0.26	1.667	0.052	0.997	2.790

The analyses were run on five imputed datasets (N = 143 for TPO >35 and N = 2148 for TPO ⩽35 in each dataset) and pooled estimates were reported.
[a]Compared to male.
[b]Compared to 60–69 years old.
[c]Compared to underweight/normal weight.
Boldfaced text indicates statistically significant values.
BMI, body mass index; CI, confidence interval; LL, lower limit; PR, prevalence ratio; SE, standard error; TPOAb, anti-thyroid peroxidase antibody; UL, upper limit.

hemochromatosis, hyperparathyroidism, and hypomagnesaemia.[35] Although diabetes and hypothyroidism have been linked to chondrocalcinosis in observational trials, more controlled studies until now have failed to show an association.[35]

Autopsy data from thyroid tissue suggest the prevalence of microscopic foci of thyroiditis may be 30% or higher.[36] Proposed mechanisms for the causation of AITD include immunological changes that cause tissue destruction through molecular mimicry, direct immune complex deposition and complement activation, and a bystander effect through cytokine release and other inflammatory processes.[37,38] Whether or not similar mechanisms can be inferred to play a role in the MSK associations of AITD remains to be determined. The intricate relationship between the immunological destruction of the thyroid and the loss of thyroid function further complicates any analysis. In another NHANES III study, 31% of men and 11% of women with TSH over 10 mIU/L had no thyroid autoantibodies detected, suggesting perhaps that in the natural history of the disease antibodies may be lost with time or perhaps as the gland fails.[39] Thus, an understanding of the duration of exposure to elevated levels of the anti-thyroid antibodies may be important in following the evolution of the MSK associations of AITD if there is a causal relationship.

Because of the close association genetically and epidemiologically with other well-defined CTD, it has been difficult to separate the phenomena seen in patients with AITD from the effects of such diseases. There were very few patients with CTD in our data set and our outcome measures did not appear to be related to these conditions including lupus and rheumatoid arthritis, or to gout. Therefore, we do not think our conclusions were affected by the presence of those conditions.

Our study had some limitations. The cross-sectional nature of the data source limits interpretation beyond association alone and can only generate questions regarding causation for future inquiry with well-designed prospective cohort studies. The examinations, blood draws and radiographs were completed in the MEC and thus excluded homebound subjects. Reasons for not being able to participate in MEC examinations may well have included severe knee OA. The use of KL grade >2 as the accepted definition of RKOA in NHANES III may have reduced our sensitivity for classifying disease. Indeed, NHANES III defined chondrocalcinosis as corresponding to a KL grade of 1.[28] Chondrocalcinosis would be more likely to affect the patellofemoral compartment of the knee and the NHANES definition may have missed such secondary OA changes because of the absence of lateral views.

Table 6. Descriptive statistics for sub-sample characteristics by TPOAb groups.

TPO >35				TPO ⩽35			
Categorical variables	***n***	**Weighted %**	**SE of weighted %**	**Categorical variables**	***n***	**Weighted %**	**SE of weighted %**
RKOA				RKOA			
Yes	59	35.4	5.9	Yes	927	38.0	1.4
No	84	64.6	5.9	No	1221	62.0	1.4
sRKOA				sRKOA			
Yes	20	11.9	3.2	Yes	351	13.3	0.9
No	123	88.1	3.2	No	1797	86.7	0.9
Chondrocalcinosis				Chondrocalcinosis			
Yes	9	7.6	2.8	Yes	192	7.3	0.7
No	134	92.4	2.8	Nosysymsym	1956	92.7	0.7
Age				Age			
60–69	66	51.5	5.0	60–69	976	50.1	2.2
70–79	55	38.9	4.5	70–79	699	34.3	1.6
80 and above	22	9.6	3.0	80 and abovsym	473	15.6	1.8
Gender				Gender			
Male	30	21.9	3.0	Male	1045	43.9	1.4
Female	113	78.1	3.0	Female	1103	56.1	1.4
Race/ethnicity				Race/ethnicity			
Non-Hispanic White	84	83.0	2.3	Non-Hispanic White	1219	83.1	2.0
Non-Hispanic Black	17	5.1	1.1	Non-Hispanic Black	400	7.7	1.1
Mexican American	32	2.6	0.9	Mexican American	439	2.3	0.3
Others	10	9.3	1.6	Others	90	6.9	1.5
Education				Education			
Less than or equal to 12	113	69.8	4.1	Less than or equal to 12	1693	71.3	2.8
Greater than 12	29	30.2	4.1	Greater than 12	443	28.7	2.8
BMI				BMI			
Underweight/normal	47	34.8	5.5	Underweight/normal	707	34.9	2.3
Overweight	54	41.4	4.9	Overweight	895	40.2	1.5
Obese	42	23.9	4.6	Obese	542	24.9	1.2

(Continued)

Table 6. (Continued)

TPO >35				TPO ⩽35			
Categorical variables	***n***	**Weighted %**	**SE of weighted %**	**Categorical variables**	***n***	**Weighted %**	**SE of weighted %**
Occupation				Occupation			
Manual	72	45.9	4.8	Manual	1225	47.1	2.5
Non-manual	71	54.1	4.8	Non-manual	923	52.9	2.5
Smoking				Smoking			
Yes	29	17.6	5.5	Yes	463	20.0	2.1
No	114	82.4	5.5	No	1684	80.0	2.1
TSH levels				TSH levels			
Hyperthyroidism	13	8.8	2.7	Hyperthyroidism	84	3.7	0.6
Euthyroidism	70	43.5	3.4	Euthyroidism	1899	89.0	1.0
Hypothyroidism	60	47.7	3.7	Hypothyroidism	165	7.3	0.8
Thyroid disease				Thyroid disease			
Yes	26	19.0	4.6	Yes	119	7.3	0.8
No	117	81.0	4.6	No	2027	92.7	0.8
Diabetes				Diabetes			
Yes	24	11.3	3.0	Yes	331	11.6	1.1
No	119	88.7	3.0	No	1815	88.4	1.1
Gout				Gout			
Yes	4	2.5	1.8	Yes	125	6.3	1.1
No	139	97.5	1.8	No	2023	93.7	1.1
Lupus				Lupus			
Yes	0	0.0	0.0	Yes	6	0.6	0.4
No	143	100.0	0.0	No	2141	99.4	0.4
Goiter				Goiter			
Yes	7	6.6	2.7	Yes	48	2.4	0.4
No	136	93.4	2.7	No	2099	97.6	0.4
Continuous variables	***n***	**Mean**	**SD**	**Continuous variables**	***n***	**Mean**	**SD**
TPOAb	143	133.10	102.10	TPOAb	2148	1.23	3.60
TgAb	143	49.88	224.81	TgAb	2148	5.88	59.27
T4	142	8.33	2.74	T4	2146	8.59	2.22
RFP	142	6.76	45.63	RFP	2136	47.48	358.59
CRP	142	0.63	1.05	CRP	2145	0.54	0.90
Age	143	69.72	6.75	Age	2148	70.70	7.60
BMI	143	27.45	5.82	BMI	2144	27.05	4.97

BMI, body mass index; CRP, C-reactive protein; *n*, sample size; RKOA, radiographic knee osteoarthritis; RFP, rheumatoid factor; SD, standard deviation; SE, standard error; sRKOA, symptomatic radiographic knee osteoarthritis; T4, thyroxine; TgAb, anti-thyroglobulin antibody; TPOAb, anti-thyroid peroxidase antibody; TSH, thyroid-stimulating hormone.

The association of the thyroid autoantibodies, perhaps in dose-dependent fashion, could suggest the relevance of immunological mechanisms as well as hormonal mechanisms in influencing the development of chondrocalcinosis and perhaps secondary OA. Further studies including longitudinal or prospective studies without the limitations of a cross-sectional design would need to examine more closely the relative risk and the associations with inflammatory markers and serum mediators including CRP and serum complement constituents, to look for likely mechanisms of tissue injury that could be immunologically rather than purely hormonally mediated. In a preliminary analysis of the relationship between TPOAb and CRP we found that CRP was significantly positively correlated with TPOAb ($p < 0.001$). However, this was with an $R^2 = 0.0129$ which showed a relatively weak relationship. Firm evidence of such a relationship would need to be ascertained in further studies, and future work would need to collect comprehensive thyroid, inflammatory mediator and immunological data alongside clinical and demographic information, further developing the objectives of NHANES III to understand disease etiology and investigate the natural history of rheumatic diseases.

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Authors' contributions

Study concept: CET. Study design: CET, KB, WW. Data acquisition and retrieval: CET. Data analysis: WW, CET, KB. CET, WW, KB and SW were responsible for interpretation of the data and for drafting, revising and approving the final submitted manuscript.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Ethics approval

The study was approved by the Albert Einstein College of Medicine IRB IRB no. 11-04-142E, reference no. 069596, approval date 10/19/2020.

Patient consent

Patient consent for publication was not required. The patient consent process is described in detail in the manual of operations and procedures for NHANES III referenced in the manuscript.

ORCID iD

Clement E Tagoe https://orcid.org/0000-0003-4306-1340

Data availability statement

The data source exists in the public domain. Data analyses by the authors are available on reasonable request by contacting the corresponding author.

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