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

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. 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. In iodine replete populations Hashimoto’s thyroiditis is the commonest cause of hypothyroidism. 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. 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).
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. 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. 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. 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 ofAITD.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 mIU/mL, <0.39 mIU/mL and >4.6 mIU/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...
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/m² (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, \( p > 0.05 \) (TABLE 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...
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 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  |

**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             |

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

| Predictor                  | β     | SE   | PR    | p-value | 95% CI of PR |
|----------------------------|-------|------|-------|---------|--------------|
|                            |       |      | 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<sup>a</sup>         | 0.217 | 0.08 | 1.242 | <0.006  | 1.063 | 1.451 |
| Race/ethnicity<sup>b</sup> |       |      |       |         |      |      |
| 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<sup>c</sup>      |       |      |       |         |      |      |
| 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<sup>d</sup>     |       |      |       |         |      |      |
| 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.

<sup>a</sup>Compared with male.
<sup>b</sup>Compared with Non-Hispanic White.
<sup>c</sup>Compared with 12 years and below of educational level.
<sup>d</sup>Compared to euthyroidism.

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 \( \leq 351 \text{IU/ml} \) (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 forAITD and RKOA, sRKO A, 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              | \( \beta \) | 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| \textbf{0.040} | 1.013        | 1.791        |
| Age                    | 0.342       | 0.08| 1.408| <\textbf{0.001} | 1.209        | 1.641        |
| BMI                    | 0.502       | 0.06| 1.651| <\textbf{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 \textit{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<sup>a</sup> | 0.046 | 0.21| 1.047| 0.826   | 0.692        | 1.584        |
| Race/ethnicity<sup>b</sup> | | | | | |
| 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<sup>c</sup> | | | | | |
| 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.

<sup>a</sup>Compared to male.
<sup>b</sup>Compared to Non-Hispanic White.
<sup>c</sup>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. The validity of our data is supported by similar findings to the study of Dillon et al. on RKOA. They demonstrated that both RKOA and sRKO A 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  |          | β       | SE       | PR       | p-value  |          |
|           |         |          |          |          | 95% CI of PR |         |          |          |          | 95% CI of PR |
|           |         |          |          |          | 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  |
| Femalea   | −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.

aCompared to male.
bCompared to 60–69 years old.
cCompared 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.

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 |               |                |
|----------------|---------|---------------|---------------|---------|---------------|---------------|
|                | n       | Weighted %    | SE of weighted % | n       | Weighted %    | SE of weighted % |
| **Categorical variables** |         |               |               |         |               |               |
| RKO A          |         |               |               |         |               |               |
| Yes            | 59      | 35.4          | 5.9           | Yes     | 927           | 38.0          | 1.4          |
| No             | 84      | 64.6          | 5.9           | No      | 1221          | 62.0          | 1.4          |
| sRKO A         |         |               |               |         |               |               |
| 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 |       |               |               |         |               |               |
| Yes            | 9       | 7.6           | 2.8           | Yes     | 192           | 7.3           | 0.7          |
| No             | 134     | 92.4          | 2.8           | No      | 1956          | 92.7          | 0.7          |
| 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 abov   | 473           | 15.6          | 1.8          |
| 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 |         |               |               |         |               |               |
| 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      |         |               |               |         |               |               |
| 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            |         |               |               |         |               |               |
| 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)

| 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.

Acknowledgements
The authors would like to thank Ruth Eisenberg for preliminary analysis of the data set.

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.

Funding
The authors received no financial support for the research, authorship, and/or publication of this article.

CDC disclaimer
The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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.

References
1. Vanderpump MP. The epidemiology of thyroid disease. Br Med Bull 2011; 99: 39–51.
2. McLeod DS and Cooper DS. The incidence and prevalence of thyroid autoimmunity. Endocrine 2012; 42: 252–265.
3. Dayan CM and Daniels GH. Chronic autoimmune thyroiditis. N Engl J Med 1996; 335: 99–107.
4. Caturegli P, De Remigis A and Rose NR. Hashimoto thyroiditis: clinical and diagnostic criteria. Autoimmun Rev 2014; 13: 391–397.
5. Hollowell JG, Staehling NW, Flanders WD, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab 2002; 87: 489–499.
6. Addimanda O, Mancarella L, Dolzani P, et al. Clinical associations in patients with hand osteoarthritis. Scand J Rheumatol 2012; 41: 310–313.
7. Becker KL, Ferguson RH and McConahey WM. The connective-tissue diseases and symptoms associated with Hashimoto’s thyroiditis. N Engl J Med 1963; 268: 277–280.
8. Biro E, Szekeanecz Z, Czirjak L, et al. Association of systemic and thyroid autoimmune diseases. Clin Rheumatol 2006; 25: 240–245.
9. Somers EC, Thomas SL, Smeeth L, et al. Autoimmune diseases co-occurring within individuals and within families: a systematic review. *Epidemiology* 2006; 17: 202–217.

10. Tomer Y. Mechanisms of autoimmune thyroid diseases: from genetics to epigenetics. *Annu Rev Pathol* 2014; 9: 147–156.

11. Tagoe CE, Zezon A and Khattri S. Rheumatic manifestations of autoimmune thyroid disease: the other autoimmune disease. *J Rheumatol* 2012; 39: 1125–1129.

12. Bazzichi L, Rossi A, Giuliano T, et al. Association between thyroid autoimmunity and fibromyalgic disease severity. *Clin Rheumatol* 2007; 26: 2115–2120.

13. Tagoe CE, Sheth T, Golub E, et al. Rheumatic associations of autoimmune thyroid disease: a systematic review. *Clin Rheumatol* 2019; 38: 1801–1809.

14. Tagoe CE, Zezon A, Khattri S, et al. Rheumatic manifestations of euthyroid, anti-thyroid antibody-positive patients. *Rheumatol Int* 2013; 33: 1745–1752.

15. Khoury EL, Hammond L, Bottazzo GF, et al. Presence of the organ-specific ‘microsomal’ autoantigen on the surface of human thyroid cells in culture: its involvement in complement-mediated cytotoxicity. *Clin Exp Immunol* 1981; 45: 316–328.

16. Weetman AP, Cohen SB, Oleisky DA, et al. Terminal complement complexes and C1/C1 inhibitor complexes in autoimmune thyroid disease. *Clin Exp Immunol* 1989; 77: 25–30.

17. Ahmad J, Blumen H and Tagoe CE. Association of antithyroid peroxidase antibody with fibromyalgia in rheumatoid arthritis. *Rheumatol Int* 2015; 35: 1415–1421.

18. Gulvdog I, Reitsma LC, Johnsen L, et al. Thyroidectomy versus medical management for euthyroid patients with hashimoto disease and persisting symptoms: a randomized trial. *Ann Intern Med* 2019; 170: 453–464.

19. Jones AC, Chuck AJ, Arie EA, et al. Diseases associated with calcium pyrophosphate deposition disease. *Semin Arthritis Rheum* 1992; 22: 188–202.

20. Chaissen CE, McAlindon TE, Felson DT, et al. Lack of association between thyroid status and chondrocalcinosis or osteoarthritis: the Framingham Osteoarthritis study. *J Rheumatol* 1996; 23: 711–715.

21. Hellevik AI, Johnsen MB, Langhammer A, et al. Incidence of total hip or knee replacement due to osteoarthritis in relation to thyroid function: a prospective cohort study (The Nord-Trondelag Health Study). *BMC Musculoskelet Disord* 2017; 18: 201.

22. Felson DT, Anderson JJ, Naimark A, et al. The prevalence of chondrocalcinosis in the elderly and its association with knee osteoarthritis: the Framingham study. *J Rheumatol* 1989; 16: 1241–1245.

23. Wang Y, Wei J, Zeng C, et al. Association between chondrocalcinosis and osteoarthritis: a systematic review and meta-analysis. *Int J Rheum Dis* 2019; 22: 1175–1182.

24. Plan and operation of the Third National Health and Nutrition Examination Survey, 1988–94. Series 1: programs and collection procedures. *Vital Health Stat 1* 1994; 32: 1–407.

25. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *PLoS Med* 2007; 4: e296.

26. Kellgren JH and Lawrence JS. Radiological assessment of osteo-arthritis. *Ann Rheum Dis* 1957; 16: 494–502.

27. Dillon CF, Rasch EK, Gu Q, et al. Prevalence of knee osteoarthritis in the United States: arthritis data from the Third National Health and Nutrition Examination Survey 1991–94. *J Rheumatol* 2006; 33: 2271–2279.

28. U.S. Department of Health and Human Services (DHHS). National Center for Health Statistics. Third National Health and Nutrition Examination Survey, 1988–94, NHANES III Knee osteoarthritis X-ray data file (Series 11, No. 11A). Hyattsville, MD: Centers for Disease Control and Prevention. 2001. Accessed at https://wwwn.cdc.gov/nchs/data/nhanes3/11a/xray-acc.pdf

29. Price AJ, Alvand A, Troelsen A, et al. Knee replacement. *Lancet (London, England)* 2018; 392: 1672–1682.

30. Gunter EW, Lewis BG and Koncikowski SM. Laboratory procedures used for the third National Health and Nutrition Examination Survey, 1988–94, NHANES III Knee osteoarthritis data from the Third National Health and Nutrition Examination Survey 1991–94. *Ann Rheum Dis* 1995; 45: 316–328.

31. Kellgren JH and Lawrence JS. Radiological assessment of osteo-arthritis. *Ann Rheum Dis* 1957; 16: 494–502.

32. Silverwood V, Blagojevic-Bucknall M, Jinks C, et al. Current evidence on risk factors for knee osteoarthritis in older adults: a systematic review and meta-analysis. *Osteoarthritis Cartilage* 2015; 23: 507–515.
33. Foreman SC, Gersing AS, von Schacky CE, et al. Chondrocalcinosis is associated with increased knee joint degeneration over 4 years: data from the Osteoarthritis Initiative. *Osteoarthritis Cartilage* 2020; 28: 201–207.

34. Shrestha A, Cohen HW and Tagoe CE. Association of spinal degenerative disc disease with thyroid autoimmunity. *Clin Exp Rheumatol* 2016; 34: 296–302.

35. Richette P, Bardin T and Doherty M. An update on the epidemiology of calcium pyrophosphate dihydrate crystal deposition disease. *Rheumatology (Oxford)* 2009; 48: 711–715.

36. Williams ED and Doniach I. The post-mortem incidence of focal thyroiditis. *J Pathol Bacteriol* 1962; 83: 255–264.

37. Stassi G and De Maria R. Autoimmune thyroid disease: new models of cell death in autoimmunity. *Nat Rev Immunol* 2002; 2: 195–204.

38. Simmonds MJ. GWAS in autoimmune thyroid disease: redefining our understanding of pathogenesis. *Nat Rev Endocrinol* 2013; 9: 277–287.

39. Spencer CA, Hollowell JG, Kazarosyan M, et al. National Health and Nutrition Examination Survey III Thyroid-Stimulating Hormone (TSH)–thyroperoxidase antibody relationships demonstrate that TSH upper reference limits may be skewed by occult thyroid dysfunction. *J Clin Endocrinol Metab* 2007; 92: 4236–4240.