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Hyperthyroxinemia is positively associated with prevalent and incident type 2 diabetes mellitus in two population-based samples from Northeast Germany and Denmark

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Abstract *Background and Aims:* A potential causal relationship between thyroid function and type 2 diabetes mellitus is currently under debate, but the current state of research is limited. Our aim was to investigate the association of thyroid hormone levels with prevalent and incident type 2 diabetes mellitus (T2DM) in two representative studies.
Methods and Results: Analyses are based on data from the Study of Health in Pomerania (SHIP), a German population based cohort with 4308 individuals at baseline and 3300 individuals at a five-year follow-up, and from INTER99, a Danish population-based randomized controlled trial with 6784 individuals at baseline and 4516 individuals at the five-year-follow-up. Serum thyroid-stimulating hormone (TSH) and free thyroxine (fT4) concentrations were measured in both studies, while free triiodothyronine was measured in SHIP only. T2DM was defined by self report or intake of anti-diabetic medication.

Neither in SHIP nor in INTER99 we detected significant associations of serum TSH levels with prevalent or incident T2DM. Serum fT4 levels were significantly positively associated with prevalent T2DM in SHIP and INTER99. In longitudinal analyses baseline levels of fT4 were significantly positively associated with incident T2DM in SHIP (RR per pmol/L = 1.07; 95%-CI = 1.05–1.10), while this association barely missed statistical significance in INTER99 (RR per pmol/L = 1.03; 95%-CI = 0.99–1.06). In SHIP baseline fT3 levels were significantly associated with incident T2DM (RR per pmol/L = 1.21; 95%-CI = 1.16–1.27).
Conclusion: We demonstrated positive associations of thyroid hormones with prevalent and incident type 2 diabetes mellitus suggesting that hyperthyroxinemia may contribute to the pathogenesis of this condition.

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Introduction

A potential causal relationship between thyroid function and type 2 diabetes mellitus is currently under debate. Both hyper- and hypothyroidism may be involved in the pathogenesis of type 2 diabetes mellitus due to their effects on insulin resistance [1,2]. Data from two cross-sectional population-based studies from Norway (HUNT-2 and HUNT-3) point towards an association between hyperthyroidism and type 2 diabetes mellitus, particularly in males [3]. However, findings from the two studies were somewhat inconsistent, because associations were predominantly seen in data of HUNT-2, but not in HUNT-3. Likewise, findings regarding the association between hypothyroidism and type 2 diabetes mellitus are also conflicting. While in data from HUNT [3] and one smaller patient study [4] no significant association between hypothyroidism and type 2 diabetes was observed, three studies in patient populations identified hypothyroidism as a risk factor for type 2 diabetes mellitus [5–7]. A longitudinal study [6], with 59,597 individuals from a matched cohort of users and nonusers of statin, showed that hypothyroidism was associated with an increased risk of incident type 2 diabetes mellitus. Furthermore, a population-based study from Spain showed that individuals with low-normal serum TSH levels had a lower risk for hyperglycemia than those with high-normal serum TSH levels [8].

Except HUNT, no other population-based study investigated the association between thyroid dysfunction and type 2 diabetes mellitus [3]. In HUNT, thyroid dysfunction was mainly defined by self-reported diagnosis of hyper- and hypothyroidism rather than by thyroid hormone levels. Furthermore, Norway is a region of iodine repletion and it is unknown whether the association between thyroid dysfunction and type 2 diabetes mellitus is similar in other populations with different iodine status. Except one patient study [6], no longitudinal data on the association between thyroid function and type 2 diabetes mellitus is available.

Considering the very limited information on the relation between thyroid function and type 2 diabetes mellitus, we aimed to investigate the associations of thyroid biomarkers defined by serum levels of thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), and free thyroxine (fT4) with prevalent and 5-year-incident type 2 diabetes mellitus in two cohort studies from Germany and Denmark conducted in regions of former iodine deficiency.

Methods

Study population

Data was obtained from the Study of Health in Pomerania (SHIP) and INTER99.

SHIP is a population-based cohort study conducted in Northeast Germany [9]. A sample from the population aged 20–79 years was drawn from population registries comprising 6267 eligible subjects. Examinations were performed between 1997 and 2001. The baseline SHIP population (SHIP-0) included 4308 Caucasian participants (response 68.8%). Between 2002 and 2006 all participants were re-invited for an examination follow-up (SHIP-1), in which 3300 subjects took part (1589 men and 1711 women; 83.5% of all eligible subjects). The median follow-up time was 5.0 years (minimum, 4.4 years; maximum, 8.6 years; 17,315 person-years).

Inter99 is a Danish population-based randomized controlled trial (CT00289237, ClinicalTrials.gov) and investigated the effects of lifestyle intervention on CVD [10]. Overall, 12,934 persons between 30 and 60 years that lived in 11 municipalities of the South-Western part of Copenhagen County were randomly selected from population registries, of which 6784 (52.5%) participated at baseline examinations between 1999 and 2001. Participants were randomized into a high and a low intensity intervention group (A and B, respectively). In the present analysis, Inter99 data was considered observational, and data from the 5-year follow-up was used for definition of incident type 2 diabetes mellitus.

In both studies all participants gave informed written consent and both studies followed the recommendations of the Declaration of Helsinki. Approval for SHIP and INTER99 were given by the local Ethics Committees.

From cross-sectional analyses in SHIP-0 we excluded 548 individuals with missing data in any of the considered variables comprising 3760 individuals. From longitudinal analyses we further excluded 276 individuals with type 2 diabetes mellitus at baseline and 795 individuals with missing follow-up data comprising a study population of 2689 individuals. In INTER99 data from 6206 individuals with complete data was used for cross-sectional analyses. After exclusion of 381 individuals with type 2 diabetes mellitus at baseline and 2010 individuals without follow-up data, longitudinal analyses were carried out in 3815 individuals of INTER99.

Assessments

In both studies age, sex, and type 2 diabetes mellitus were assessed by computer-assisted personal interviews performed by certified staff at baseline and follow-up. In SHIP all participants were asked to bring all medications taken 7 days prior to the time of examination and medication data were obtained online using the IDOM program (online drug-database leaded medication assessment) and categorized according to the Anatomical Therapeutical Chemical (ATC) classification index. In SHIP thyroid medication was defined by the ATC code H03, anti-diabetic medication by the ATC code A10, insulin medication by the ATC code A10A, and metformin intake by the ATC code A10BA02. In INTER99 antidiabetic medication was assessed by interview, but information on thyroid medication was not available. In SHIP diagnosed type 2 diabetes mellitus at baseline and follow-up was defined by self-reported diabetes in the interview or intake of anti-diabetic medication, while in INTER99 type 2 diabetes mellitus at baseline and follow-up was defined solely anamnestically from the interviews. In both studies height and weight were

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