Adverse metabolic correlations relate to free-T3 levels in subclinical hypothyroidism; common FOXE1 polymorphisms associate with blood pressure

Anna de Lloyd¹, Lei Zhang¹, Ameen Bakhsh¹, Ilaria Muller¹, Alan Dodd², Hilary Durrant², Sarah Neal²
Carol Evans², Aled Rees³, Marian Ludgate³

Thyroid Research Group, School of Medicine, Cardiff University, UK
Department of Immunology & Biochemistry, University Hospital of Wales, Cardiff, UK

Introduction

The effects of mild subclinical hypothyroidism (SH; TSH<10 mU/L) on metabolic outcomes are unclear (Surks et al 2004). This may relate to differences in aetiology, including thyroid autoimmunity or genetic factors such as TSH-receptor mutations [TSHR-M] and FOXE1 polyalanine tract length [FOXE1-PTL] polymorphisms that are associated with altered thyroid function (Camilot et al 2005 & Medi et al 2011 respectively). We hypothesised that the metabolic manifestations of SH may depend upon its aetiology.

Aims of the study

• To see whether TSH correlates with metabolic parameters including blood pressure (BP) in an SH cohort (as a surrogate indicator of the effect of SH on metabolic parameters).
• To reveal associations between thyroid function parameters (free-T4, free-T3) and metabolic parameters in the SH cohort.
• To explore whether SH aetiology has a differential effect on metabolic parameters and BP.

Methods

A total of 208 adults (18-70 years) with primary untreated SH (TSH ≥ 5mU/L) were recruited and underwent a medical & lifestyle history, resting BP (mean of 3) and body mass index (BMI) measurement, genetic evaluation (for TSHR-M and FOXE1-PTL status), full thyroid function, anti-TPO antibody measurement (categorised as positive (+) or negative (-)), and metabolic assessments (HOMA-IR (surrogate measure of insulin resistance), full lipid profile (Total Cholesterol, LDL and HDL Cholesterol, Triglycerides and fasting glucose).

Associations were examined using stepwise multivariate regression analyses using Excel and Minitab 16 software.

The recruitment process is as described on poster EP-253

Results

Cohort characteristics; 75% female (consistent with the epidemiology of SH), 90% Caucasian (reflecting local ethnicity) and the median age of participants was 51 years. 50% were TPO antibody (+) and 6% (n=12) had loss of function TSHR-Ms. 60% of the cohort were homozygous for the 14 FOXE1-PTL polymorphism, and a 1/3rd had the 14/16 genotype.

TSH showed a small positive association with free-T3 (Correlation coefficient (R) +0.6, p<0.01) and a negative association with free-T4 (R -1.1, p<0.001) but no associations with metabolic factors including BP. Free-T3 showed a positive association with BP (Systolic R +0.9, p<0.001; Diastolic R +3, p=0.02), HOMA-IR (R +1.3, p=0.009) and Triglycerides (R +0.1, p=0.04). Free-T4 did not show any independent metabolic associations.

No metabolic associations were revealed for TSHR-M or TPO antibody status. The 14 FOXE1-PTL (the most prevalent genotype) was positively associated with free-T3 compared to ‘other’ genotypes (R +0.2, p=0.007) and negatively with BP (Systolic R -6, p=0.006; Diastolic R -4, p=0.01).

Conclusions

Free-T3 correlated positively with blood pressure and HOMA-IR in this cohort, irrespective of SH aetiology. An unexpected association between common FOXE1-PTL polymorphisms and blood pressure was revealed that will require further investigation. There were no independent associations between TSH and any of the metabolic parameters assessed.

References

• Surks MI, Ortiz E, Daniels GH, et al. Subclinical Thyroid Disease: Scientific Review and Guidelines for Diagnosis and Management. JAMA. 2004;291(2):228-238.

Stepwise regression model exploring the association between Blood Pressure and free-T3

In the stepwise regression models, N represents the number of subjects in each analysis, R represents the correlation coefficient between the expected parameters. The 95% confidence interval (CI) and p-values at each analysis step are provided. The minus (-) or plus (+) signs indicate the direction of the association.