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

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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 & Medici *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 (+ve) or negative (-ve)), and metabolic assessments (HOMA-IR (surrogate measure of insulin resistance), full lipid profile (Total Cholesterol, LDL and HDL Cholesterols, 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 +ve 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.

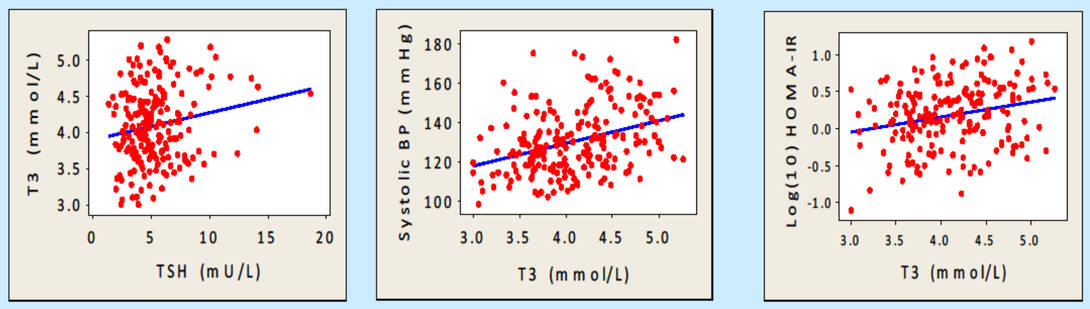
TSH showed a small positive association with free-T3 (Correlation coefficient (R) +0.6, p=0.01) and a negative association with free-T4 (R -1.1, p <0.001) but no associations with metabolic factors including BP. Free-T3 showed a positive association with BP (Systolic R +10, p <0.001; Diastolic R +3, p= 0.02), HOMA-IR (R +1.3, p=0.009) and Triglycerides (R +0.1, p-value 0.04). Free-T4 did not show any independent metabolic associations.

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

Results

Crude unadjusted associations across the cohort

TSH vs Free-T3 | Free-T3 vs Systolic BP | Free-T3 vs HOMA-IR



In these regression scattergraphs the red dots indicate individual subject values, and the blue line indicates the best linear relationship between these parameters.

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

	Systolic BP			Diastolic BP			
	N	R	95% C.I.	p-value	N	R	95% C.I.	p-value
Step 1; crude association between Blood Pressure and free-T3	207	+11	(+6.6, +15.4)	<0.001	206	+3.8	(+1, +6.5)	0.008
Step 2; Step 1 also adjusted for BMI (log^{10}BMI)	206	+9.6	(+5.2, +14)	<0.001	206	+3.1	(+0.4, +5.8)	0.037
Step 3; Step 2 also adjusted for FOXE1-PTL (14/14) polymorphism status	201	+11	(+6.7, +15.3)	<0.001	201	+3.8	(+1, +6.6)	0.008
Step 4; Step 3 also adjusted for age and male sex	201	+10.8	(+6.7, +15)	<0.001	201	+3	(+0.3, +5.7)	0.035
Step 5; Step 4 also adjusted for TPO antibody positivity, Activity status and TSH values (log^{10} TSH)	201	+10.8	(+6.6, +15)	<0.001	201	+2.7	(-0.1, +5.5)	0.058

Stepwise regression model exploring the association between Blood Pressure and FOXE1-PTL (14/14)

	Systolic BP			Diastolic BP			
	N	R	95% C.I.	p-value	N	R	95% C.I.	p-value
Step 1; crude association between Blood Pressure and FOXE1-PTL (14/14)	202	-4.7	(0.12, -9.5)	0.058	202	-2.7	(-5.6, +0.2)	0.07
Step 2; also adjusted for free-T3	202	-6.8	(-2.2, -11.4)	0.004	202	-3.5	(-6.4, -0.6)	0.02
Step 3; also adjusted for BMI (log^{10}BMI)	201	-7	(-10.9, -2.5)	0.003	201	-3.5	(-6.4, -0.6)	0.016
Step 4; also adjusted for age and male sex	201	-7.6	(-12, -3.7)	<0.001	201	-3.5	(-6.2, -0.8)	0.014
Step 5; also adjusted for TPO antibody positivity, Activity status and TSH values (log10 TSH).	201	-7.8	(-12, -3.6)	<0.001	201	-3.5	(-6.3, -0.7)	0.014

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

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

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