Introduction

The role of the thyrotropin receptor (TSHR) in bone is unclear. TSHR-deficient mice have low bone mineral density (BMD) and focal osteosclerosis despite normal thyroid hormones (suggesting TSH function, in bone, is important) [Abe et al. 2003]. Subclinical Hypothyroidism (SH) has various aetiologies including thyroid autoimmunity and inactivating TSHR mutations (TSHR-M). In TSHR-deficiency & TSHR-M elevated TSH compensates for reduced TSH function [Camilo et al. 2005], whereas in thyroid autoimmunity it compensates for reduced thyroid synthetic responsiveness (infiammation mediated). We hypothesised different bone effects in SH relating to these causes.

Aims of the study

- To explore whether TSH associates with BMD and bone turnover (BT) in an SH cohort.
- To explore whether aetiology of SH influences BMD and BT.

Methods

208 adults (18-70 years of age) with primary untreated SH (TSH ≥5mU/L) and free of known bone disease were recruited.

A medical/lifestyle history, anthropometric data and blood samples were collected (free-T3, free-T4, TSH, anti-TPO antibodies (categorised as positive (+ve) or negative (-ve)), BT markers (CTX, PINP)). Mutational screening of the entire TSHR coding region was undertaken by dHPLC and confirmed by direct sequencing.

A DXA bone scan (Lumbar Spine (LS) and hip) generated Z-scores (relative to age/sex-matched normals (BMD-Z)). These are expressed as a number of standard deviations (SD) the subjects value lies above or below the mean. The relationship between parameters of interest were explored using stepwise multivariate regression analyses using Excel and Minitab software.

The subject recruitment process is summarised in the flow diagram below.

Subjects identified by the Department of Biochemistry and GP letters sent out n = 1537

Not willing or left the practice n=114 (16%)

Not responding or willing to participate n=159 (34%)

Permission given to approach the subject n=463 (67%)

Willing and booked n=220 (48%)

Study Subjects n=208

GP responses n=693 (45%)

Not suitable n=116 (17%)

Not suitable or study closed n=84 (18%)

Failed to participate n=15 (7%)

Stratification by SH aetiology showed no influence of TSHR-M on BMD-Z (despite lower free-T3 relative to TSH (R= -0.34, p<0.001) but TPO +ve associated negatively with BMD-Z at all sites (R= -0.65, p<0.001). Male gender associated negatively with BMD-Z at all sites (R= -0.38, p<0.001). The BT markers did not associate with either thyroid function or BMD.

Conclusions

SH appears to have a negative effect on BMD in adults. Negative associations between BMD and free-T3, TSH, male gender and TPO antibody positivity are revealed. If these associations reflect causation it indicates that bone health should be actively evaluated in SH, particularly in those who are male, have thyroid autoimmunity, and in those with any additional risk factors for Osteoporosis.

References