What happens to thyroid function in long-term type 1 diabetes? A Winchester cohort study

AP Brooks
Honorary Consultant Physician, Specialist Diabetes Service
H Barbour
Consultant Biochemist, Department of Biochemistry
JSW Li Voon Chong
Consultant Physician, Specialist Diabetes Service
S Kibble
Research Assistant, Department of Biochemistry
D Schapira
Consultant Paediatrician, Paediatric Diabetes Clinic
G White
Senior Biochemist, Department of Biochemistry
E Williams
Consultant Paediatrician, Department of Paediatrics

1Hampshire Hospitals NHS Foundation Trust at the Royal Hampshire County Hospital, Winchester, UK

Correspondence to:
AP Brooks, MB ChB(Hons), MSc, MD, Honorary Consultant Physician, Specialist Diabetes Service, Hampshire Hospitals NHS Foundation Trust, Royal Hampshire County Hospital, Winchester SO22 5DG, UK; email: Andrew.Brooks@hhft.nhs.uk

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Abstract
In a cross-sectional analysis of 655 people with type 1 diabetes of a wide age range and duration of diabetes up to 50 years, the most common form of thyroid dysfunction was treated clinical hypothyroidism (under-activity) in 69 of 313 females (22%) and 26 of 342 males (7.6%). Only four patients (two of each sex) had episodes of thyroid over-activity.

Serum thyroid stimulating hormone (TSH mU/L) in 493 patients (208 females and 285 males) was remarkably steady.

After 10 years’ duration of type 1 diabetes the prevalence of treated clinical hypothyroidism in females increased from 1 in 6 for 10–29.9 years’ duration up to 1 in 3 for over 30 years, and respectively from 1 in 10 to 1 in 6 in males. Thyroid dysfunction, usually hypothyroidism, should be screened for annually using a serum TSH assay in all type 1 diabetes patients after 10 years’ duration.

In the first 10 years of type 1 diabetes thyroid dysfunction is rarer, but more variable, and must not be misdiagnosed because of its possible more severe consequences. Five of nine females who were hypothyroid were so at diagnosis of their diabetes; the other four became so in the first 12–24 months, and two had thyroid over-activity (one recurrent). Three males were already hypothyroid when diabetes was diagnosed and two developed over-activity.

New cases of type 1 diabetes should have their thyroid function assessed clinically with thyroid hormone levels, serum TSH and antithyroid antibodies, say six-monthly, for the first three years after diagnosis and on suspicion at any time thereafter. Copyright © 2015 John Wiley & Sons.

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Key words
type 1 diabetes; screening for thyroid dysfunction; hypothyroidism; serum TSH; antithyroid antibodies

Introduction
The clinical association between abnormal thyroid function (thyroid dysfunction), particularly thyroid under-activity (hypothyroidism), and type 1 diabetes is well known. The pathophysiological basis is the shared autoimmune process, and indeed this association was one of the factors which led to considering that type 1 diabetes has an autoimmune aetiology. Details of when this association is most likely in the course of long-term type 1 diabetes are not well documented. Perros and colleagues, for instance, found an overall prevalence of thyroid disease of 13.4% in a randomly selected group of 1310 adults of various ages with types 1 and 2 diabetes, but with no analysis of duration of diabetes.1

What is less well known is what happens to baseline thyroid function and serum pituitary thyroid stimulating hormone (TSH) levels in the long term in those who remain with normal thyroid function (euthyroid). This is an important question when considering the place of, and method for, screening for thyroid function abnormalities at the annual review, or some other time interval, in type 1 diabetes care.2 In addition, there are concerns about how subclinical hypothyroidism (also known as biochemical hypothyroidism), i.e. patients without symptoms but with a serum TSH level above an arbitrary cut-off value,3 may affect the prevalence of complications of type 1 diabetes in some populations,4 the growth of the youngest patients,5 and metabolic control in children and adolescents.6

A cohort of patients in whom there are carefully recorded accurate epidemiological, clinical and biochemical data over many years allows the study of the natural history of normal and abnormal thyroid function, and could contribute to answering these questions. The ascertainment and characteristics of such a cohort of white Caucasians of
Clinical thyroid status was known. In clinical thyroid status was accurately known in 655 patients, and serum TSH levels were known in 493 of these patients with normal thyroid function (euthyroid) that is not diagnosed as being hypothyroid (thyroid under-activity) and/or on L-thyroxine treatment.

<table>
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<th>10–19.9</th>
<th>20–29.9</th>
<th>30–39.9</th>
<th>40–49.9</th>
<th>Total</th>
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<td>12</td>
<td>17</td>
<td>20</td>
<td>11</td>
<td>69</td>
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<tr>
<td>Normal females</td>
<td>61</td>
<td>65</td>
<td>61</td>
<td>31</td>
<td>24</td>
<td>242</td>
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<tr>
<td>Hypothyroid males</td>
<td>3</td>
<td>6</td>
<td>3</td>
<td>11</td>
<td>3</td>
<td>26</td>
</tr>
<tr>
<td>Normal males</td>
<td>117</td>
<td>58</td>
<td>68</td>
<td>51</td>
<td>20</td>
<td>314</td>
</tr>
</tbody>
</table>

NB. In addition to these 651 patients 4 others had episodes of thyroid over-activity (total 655).

Table 1. Clinical thyroid function in 655 type 1 diabetes patients by duration of diabetes

both sexes, all ages of onset of type 1 diabetes and wide durations from newly diagnosed to over 50 years, have been previously described.7

This article reports the observations from this Winchester cohort on normal and abnormal thyroid function in type 1 diabetes.

Patients and methods
Clinical thyroid status, together with the dose of any L-thyroxine medication being taken, was noted at clinic attendance and annual diabetes review and recorded in the Diamond and Twinkle database systems (HiCom Technology) used in the specialist diabetes service and paediatric diabetes clinics in Winchester, Eastleigh and Andover of the former Winchester and Eastleigh Health Care Trust (WEHCT) for communication and audit purposes from 1995 onwards.

All type 1 diabetes patients were requested to have a serum TSH level measurement (mU/L, Beckman DCI Autoanalyser) either pre-clinic or at the clinic visit, as part of the annual review whether symptomatic or not of thyroid dysfunction.

A retrospective, cross-sectional audit was taken of those patients attending in one particular year (2010), and for each of these patients their chronological age at that point and duration of type 1 diabetes (‘diabetes age’) were known. Clinical thyroid status was accurately known in 655 patients, and serum TSH levels were known in 493 of these patients with normal thyroid function (euthyroid) that is not diagnosed as being hypothyroid (thyroid under-activity) and/or on L-thyroxine treatment.

Results
Clinical thyroid status was known in 655 patients with type 1 diabetes of whom 313 were females and 342 were males. Sixty-nine females were hypothyroid and on L-thyroxine medication (overall prevalence 22%), as were 26 of the 342 males (prevalence 7.6%). See Table 1 for a detailed breakdown by duration of diabetes. Only two females and two males had been recorded as having episodes of thyroid over-activity (‘hyperthyroid’) – that is, 0.6% of all 655 patients.

Table 2 shows the percentage prevalence of hypothyroidism for each sex and 10-year duration spans of their type 1 diabetes. It should be noted that not only is hypothyroidism least prevalent in the first 10 years of diabetes in both sexes, but also all three males were hypothyroid prior to the diagnosis of type 1 diabetes (one had Down’s syndrome), and five of the nine females were already hypothyroid. The other four females developed hypothyroidism in the first 12–24 months after diagnosis of type 1 diabetes.

In Table 3 serum TSH levels (mean and numerical range, mU/L) are shown for 208 females and 285 males who remained clinically euthyroid at the audit census point by 10-year divisions of duration of type 1 diabetes up to 49.9 years. Where serum TSH levels exceeded the cut-off point of, say, 5.50mU/L, these patients were not diagnosed on this basis alone as hypothyroid, but an appropriate clinical action was taken. They have not been put into the group of 95 diagnosed patients.

The scatter diagrams (Figures 1 and 2) show the distribution of serum TSH concentrations in 37 of the patients with clinically normal thyroid function and the longest durations of type 1 diabetes taken from the part of the cohort with 40–49.9 years’ durations. There is a wide distribution of levels, but no obvious upward trend with increasing duration, and therefore patient ages.

Discussion
How do these observations over a long period of time add to our knowledge, inform the questions about screening for thyroid dysfunction in type 1 diabetes, and potentially influence clinical practice?
The results of the serum TSH levels over up to 50 years add to our knowledge of the natural history of thyroid function. In this study the majority of patients with type 1 diabetes were not hypothyroid (560 out of 655, i.e. 85%), and their serum TSH levels (mU/L) were remarkably steady, particularly in males when viewed by 10-year intervals of duration with a mean value of between 1.90 and 2.15 for 285 results. In females there is a little more fluctuation, particularly in the second (10–19.9) and third (20–29.9) decades of duration where the highest (2.47) and lowest (1.90) means were found, as shown in Table 3. Statistical analysis using a paired t-test method showed no statistically significant differences between any of these mean serum TSH levels by 10-year divisions of duration for either sex. The scatter diagrams of serum TSH concentrations in those from the 40–49.9 years’ duration part of the cohort similarly show no clear linear increase in TSH with duration of type 1 diabetes. There is therefore overall no suggestion of an ‘ageing effect’ on thyroid function with a progressive, significant increase in mean or range of TSH levels to suggest a morbid running down of thyroid activity over time. Rodacki and colleagues in Brazil used cut-off levels for TSH of 0.5–2.49, 2.5–4.4 and >4.5mU/L when looking at the possible influence of TSH increases on complication rates in type 1 diabetes, within the subclinical hypothyroidism range, but the mean duration of diabetes in their cohort was 12.8 (±7.1 SD) years, with different ethnicity and sex distributions, making comparison difficult.

The observations in this study inform the questions about screening for thyroid dysfunction in type 1 diabetes in a positive way, and perhaps tell us something about why and how. In this cohort the overall prevalence of hypothyroidism is so high at 15%, or 1 patient in 7, that screening will be clinically very effective. Yes, hypothyroidism is 2–3 times more common in females than in males (22% vs 7.6%) but any condition which has a prevalence of 1 in 13 (7.6%) must surely be looked for. The prevalence doubles in females...
from 1 in 6 for a duration of 10–29.9 years to 1 in 3 when over 30 years’ duration, with corresponding figures for men of 1 in 10 to 1 in 6. Of particular interest is the behaviour of thyroid function in the first 10 years after diagnosis of type 1 diabetes in relation to screening. Only three males were known to be hypothyroid in this time period, but all were already hypothyroid at the time of diagnosis of their diabetes at ages five (the Down’s syndrome boy), 11 and 48 years. Likewise, five of the nine females who were hypothyroid were so at diagnosis of diabetes, and the other four became so in the first 12–24 months of diabetes. Their overall age range was 9–43 years. These changes reflect the intensity of the autoimmune reaction in early type 1 diabetes. All four patients who had episodes of thyroid over-activity did so in this initial 10 years of type 1 diabetes.

These observations do not answer the question as to whether measuring TSH alone is a good screening test, or whether adding antithyroid antibody tests, say in the first five years, would be helpful. The steady serum TSH levels in patients who remain euthyroid over many years suggest that if antithyroid antibody levels are insignificant at some point after diagnosis of type 1 diabetes they are likely to remain so, but without more facts this is conjecture. How may these observations influence clinical practice? Screening for thyroid (under) activity in asymptomatic patients with type 1 diabetes is good practice, should be done, and is probably safest on an annual frequency basis. Certainly, after five to 10 years’ duration, that should be the practice in both sexes. It may appear tempting not to test so frequently in males in the first 10 years, once they have been assessed fully (and this should include thyroid hormone levels, TSH, and antithyroid antibodies in all), but this is a sample of 120 in this cohort, and your population may be different. Incidentally, the two males who became thyrotoxic (over-active) did so in this time period as did the two females. In females there is no question but that thyroid (under) activity should be screened for annually whatever their duration of type 1 diabetes. Indeed, it should be positively looked for in the first three to five years, perhaps with six-monthly testing including antibody titres, and thereafter annually. Delayed diagnosis at the time of pregnancy in early type 1 diabetes could also have serious consequences and patients should have thyroid function tested at conception, in the third trimester, and at six weeks to six months after delivery.

In these days of increasingly fragmented diabetes care delivery, having an effective screening programme for thyroid dysfunction with a regulated process and a named person responsible for actioning the outcomes is a challenge for all trying to deliver high quality practical diabetes care.

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Declaration of interests
There are no conflicts of interest declared.

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3. Association of Clinical Biochemists, British Thyroid Association and British Thyroid Foundation. UK Guidelines for the Use of Thyroid Function Tests. 2006.