

Knowledge of thyroid eye disease in Graves' Disease patients with and without orbitopathy

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1 **Title Page**

2

3 **Knowledge of Thyroid Eye Disease in Graves' Disease Patients With and**
4 **Without Orbitopathy**

5

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22

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44 **Abstract**

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46 **Background**

47

48 Thyroid Eye Disease (TED) develops in around 25% of those with Graves' Disease
49 (GD). Patients with TED may present late to ophthalmologists, when debilitating
50 orbital inflammatory changes have already occurred. The reasons for this are
51 multifactorial, but poor knowledge of TED in GD patients may be contributory. We
52 aimed to assess the knowledge of TED in those with established TED, GD without
53 orbitopathy and control subjects.

54

55 **Methods**

56

57 A validated, anonymised questionnaire, with 20 knowledge-based questions, was
58 prospectively completed by 100 GD patients, 100 TED patients and 100 age- and
59 sex-matched controls (with no history of thyroid disease or TED) in two tertiary
60 referral Thyroid and Orbital Diseases clinics. Demographic data and details of
61 highest educational level, disease duration and follow-up were gained. Residence
62 post-code was used to determine Index of Multiple Deprivation (2015) quintile.
63 Knowledge score was established for each of the study groups of interest. Statistical
64 analysis was undertaken with Kruskal-Wallis test, χ -squared test and multivariable
65 logistic regression.

66

67 **Results**

68

69 There was no significant difference in median knowledge scores (out of 20) between
70 GD (13.71, range 9-18) and TED (14.25, range 9-18) patients. However, both groups
71 had significantly higher scores than controls (11.53, range 4-16) ($p < 0.001$).
72 Multivariable analysis determined no particular independent factor associated with
73 lower knowledge score. There were a number of important areas in which patient
74 knowledge of TED was poor. While almost all (99% TED, 89% GD) knew that TED
75 involved orbital tissue inflammation, a large proportion (60% TED, 50% GD) were
76 unaware that TED may develop in the absence of hyperthyroidism or did not know
77 that cigarette smoking is associated with more severe TED (21% TED, 33% GD).

78

79 **Conclusions**

80

81 TED patients had equivalent levels of TED knowledge to GD patients without
82 orbitopathy. While subjects in both disease groups had greater knowledge than
83 controls, each had significant misconceptions regarding aspects of TED diagnosis,
84 management and treatment. These findings should guide the future provision of
85 patient information for TED, with educational materials being targeted to address
86 existing gaps in knowledge.

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94 **Introduction**

95

96 Previous studies have demonstrated that increased patient knowledge of a disease
97 results in earlier presentation to health services, better insight into that condition,
98 reduced anxiety and increased compliance with treatment (1). This is especially
99 important in Thyroid Eye Disease (TED), an inflammatory condition of the orbital
100 tissues which occurs in around 25% of those with the autoimmune hyperthyroidism,
101 Graves' Disease (GD) (2). GD develops before or at the same time as TED in
102 around 80% of cases (3) and of those with GD who do develop TED, around 70%
103 will develop orbital manifestations within 12 months of their GD diagnosis (4).

104

105 However, evidence also exists that patients present late with TED, with a mean time
106 from development of ocular symptoms to TED diagnosis of 9 months (5). This
107 represents a lost opportunity for early intervention (e.g. with early
108 immunosuppression or targeted smoking cessation) with the possible prevention or
109 reduction of the subsequent physically and psychosocially debilitating effects of TED.

110

111 While it might be expected that a proportion of patients with GD will search the
112 internet for information about ocular problems related to autoimmune thyroid
113 disease, it has been demonstrated that online information regarding TED is of poor
114 readability. This means that patients may not be able to fully understand the potential
115 morbidity associated with TED, nor the available strategies to reduce the impact of
116 early symptoms, such as the use of topical lubricants, as well as those to prevent
117 development of severe TED, including smoking cessation (6).

118

119 To our knowledge, no study to date has objectively assessed the level of knowledge
120 of TED either in patients with TED or those with GD, who are at risk of subsequently
121 developing TED. We aimed to assess and compare TED knowledge between GD
122 patients (with and without ocular or orbital manifestations) and controls, to identify
123 any misconceptions about TED and to determine factors that may predict poorer
124 understanding of TED.

125

126 **Methods**

127

128 The study model was based on previous research assessing patient knowledge of
129 glaucoma by Danesh-Meyer et al (2008) (1). Recruitment sites for the study were the
130 Thyroid Clinic of University Hospital Birmingham, UK (TED and GD subjects) and the
131 Orbital Diseases Clinic of Birmingham and Midland Eye Centre, UK (TED subjects
132 only). The study followed the principles of the Declaration of Helsinki and was
133 approved by the research and development departments of both hospital trust
134 recruitment sites.

135

136 Study subjects were recruited into three groups – those with established TED, those
137 with GD but no manifestations of ocular or orbital disease, and age- and sex-
138 matched controls. Patients were eligible for inclusion in the GD group if they had this
139 diagnosis made by a consultant endocrinologist on the basis of abnormal thyroid
140 function tests (overt hyper- or hypothyroidism) either at the time of recruitment, or
141 previously, as well as raised concentrations of thyroid stimulating hormone receptor
142 (TSH-R) antibodies. Overt hyperthyroidism was defined as undetectable serum TSH
143 concentrations with raised serum free T4 and or free T3 concentrations. Overt

144 hypothyroidism was defined as raised serum TSH concentrations with reduced
145 serum fT4 concentrations. Subjects were eligible to be included in the TED group if
146 they had the above criteria for GD, in addition to a diagnosis of TED made by a
147 consultant ophthalmologist, for 6 months or more on the basis of signs of orbitopathy
148 (e.g. proptosis, periocular swelling, strabismus/ocular movement restriction). The
149 control group was recruited randomly from patients, family members and friends
150 attending non-thyroid and non-orbit out-patient clinics at University Hospital
151 Birmingham. Exclusion criteria for control subjects included a personal or family
152 history of thyroid dysfunction or TED.

153

154 An anonymized questionnaire was developed for GD, TED and control subjects
155 (Supplementary Data), the first section of which sought demographic information
156 (age, sex, ethnic origin), level of educational attainment (no qualifications, secondary
157 school education, vocational qualifications, university degree or higher degree) and
158 first language spoken at home. Residence post code was used to determine an
159 Index of Multiple Deprivation (IMD) 2015 score using the GeoConvert website
160 (www.geoconvert.ukdataservice.ac.uk). The questionnaire also asked if information
161 about TED had been sought and, if relevant, the sources of information used to
162 research TED. Finally, subjects were questioned about their GD and TED diagnosis
163 and duration, the treatment they had received (anti-thyroid drugs, radioiodine,
164 thyroidectomy) and, in the case of TED subjects, whether they had received
165 immunosuppressive therapy, orbital radiotherapy or surgery (orbital decompression,
166 squint or eyelid surgery).

167

168 The second section of the questionnaire comprised 20 true/false format questions.
169 These questions were written and discussed at a focus group of two endocrinologists
170 and two ophthalmologists, with the aim being to explore patient knowledge of TED
171 diagnosis, disease-modifying factors and treatment. Feedback on the questions was
172 requested from members of the UK-based TED charity, Thyroid Eye Disease
173 Charitable Trust (TEDct) to ensure that the questions were of sufficient quality and
174 importance. The questionnaire was piloted on 10 TED patients prior to the
175 commencement of the full study. Following this validation period the questionnaire
176 was personally administered to, and completed by, all study subjects while they were
177 in the out-patient clinic environment, ensuring that it was not possible for participants
178 to search for the correct answers to questions while completing the questionnaire.

179

180 Statistical analysis was undertaken for non-normally distributed data using Mann-
181 Whitney test (2 groups) and Kruskal-Wallis test (≥ 3 groups) for continuous data and
182 χ -squared test for categorical data. Multivariable logistic regression was undertaken
183 to determine if differences in knowledge scores were associated with any
184 independent variable. Analyses were undertaken using Prism version 5.0 (GraphPad
185 Software, La Jolla, CA, USA) and SPSS version 18 (IBM, Chicago, IL). $P < 0.05$ was
186 considered statistically significant.

187

188 **Results**

189

190 The study was undertaken over a 12-month period with 300 consecutive subjects
191 recruited. There were 100 TED, 100 GD and 100 control subjects in each study
192 group. The groups were well-matched for age and gender.

193

194 The overall TED knowledge scores for each of the study groups are shown in Figure
195 1. Median knowledge score (out of 20) in the TED group was 14.25 (range 9-18), in
196 the GD group 13.71 (range 9-18) and in the control group 11.53 (range 4-16). There
197 was no significant difference between the scores of the TED and GD group, but both
198 of these groups scored significantly higher than the controls ($P<0.001$). The
199 proportion of correct answers for each of the groups was significantly different for
200 some, but not all, of the 20 questions (Table 1).

201

202 Univariate analyses determined no significant difference in TED knowledge scores
203 according to age, gender, ethnicity, level of highest educational attainment, first
204 language or IMD 2015 score. Similarly, there was no significant difference in TED
205 knowledge scores in relation to disease duration following diagnosis of GD or TED,
206 the duration of follow-up in the Thyroid or Orbit Clinic, whether they had ever been
207 seen and assessed by an ophthalmologist, whether they had received steroids or
208 orbital radiotherapy for TED or indeed whether they had undergone emergency or
209 rehabilitative surgery for TED. Furthermore, multivariable analysis determined that
210 there was no factor independently associated with higher or lower TED knowledge
211 score in any of the study groups.

212

213 **Discussion**

214

215 To our knowledge, this is the first study to evaluate the level of TED knowledge in
216 GD patients with and without orbitopathy. While GD and TED patients scored
217 significantly higher than controls from a statistical point of view, the actual practical

218 difference in knowledge scores (2 to 3 points higher than the controls) for GD and
219 TED patients is likely to be insignificant. Indeed, TED patients only scored
220 significantly higher than controls in 13 out of the 20 questions (65%), while GD
221 patients scored higher than controls in 8 out of the 20 questions (40%).

222

223 It is perhaps surprising that those with a longer duration of GD or TED, or TED that
224 had required steroid treatment, orbital radiotherapy or surgical intervention, did not
225 score more highly. Similarly, those with a shorter duration of GD or TED may have
226 been anticipated to score more highly, as they may have been expected to have
227 sought out relevant information more recently, or more recently had contact with their
228 endocrinologist or ophthalmologist. However, this did not prove to be the case. This
229 may also indicate that recent attempts by endocrinologists and ophthalmologists to
230 educate those with GD and TED were unsuccessful.

231

232 In univariate analysis no significant difference was observed in knowledge scores by
233 age, sex, ethnicity, highest educational attainment, first language, IMD 2015 score or
234 duration of follow-up in the Thyroid or Orbit Clinic. Likewise, no factor was found to
235 be independently associated with higher or lower TED knowledge scores on
236 multivariable analyses.

237

238 Studies evaluating patient knowledge of other diseases have noted that higher
239 educational level and socioeconomic status are associated with earlier presentation
240 to medical services, increased knowledge of disease and better compliance with
241 treatment regimens (1). Other studies have shown higher knowledge scores for
242 diseases such as glaucoma and diabetic retinopathy in those whose first language is

243 English (1, 7, 8), mainly as the questionnaires in these studies were written in
244 English. We did not find such an association in our study. Studies assessing
245 conditions such as uveitis have also determined patient knowledge of their own
246 condition to be poor (9).

247

248 Significant misconceptions were identified in key areas that may impact upon drivers
249 for worse TED in GD patients, such as the importance of good thyroid function
250 control and the crucial role of smoking in TED. While both GD and TED patients
251 scored significantly higher than controls in terms of demographic aspects of TED
252 (e.g. questions 4 and 7), only 50% of GD and 40% of TED patients knew that TED
253 does not necessarily only occur in those with hyperthyroidism (question 1). This
254 might result in euthyroid or hypothyroid GD patients becoming complacent in having
255 a perception that they are less likely to develop TED, even if experiencing ocular
256 symptoms. Likewise, whilst GD and TED subjects scored relatively highly regarding
257 TED pathogenesis (e.g. questions 8, 12, 16, 17 and 20), only 67% of GD and 79% of
258 TED patients knew about the association between smoking and more severe TED.
259 Furthermore, knowledge of the surgical management of TED appeared poor, with
260 GD and TED subjects overestimating the effectiveness of thyroidectomy in treating
261 TED (question 9), overestimating the tendency of radioiodine to worsen TED
262 (question 15), and demonstrating poor knowledge regarding the role of orbital
263 radiotherapy and orbital decompression (questions 18 and 19) in the management of
264 some TED patients. It is also important to note that around two-thirds of GD and TED
265 subjects perceived that psychological stress made TED worse (question 5). While no
266 published literature currently exists regarding an association between stress and

267 TED, the weighting that the GD and TED patient groups gave to this area suggests
268 that it may be an interesting avenue for further research.

269

270 Those with TED are known to have delay to presentation from their initial experience
271 of ocular symptoms, with recent Europe-wide data determining that the median
272 period is 9 months (although with a range of 0 to 552 months) (5). Similarly, in a
273 multicentre United Kingdom audit, the mean time from initial symptoms of TED to
274 diagnosis was over 27 months, and from first visit to any doctor with ocular
275 symptoms to TED diagnosis of over 9 months (10). The reasons for this are
276 multifactorial, but may include the patient themselves not presenting sufficiently early
277 as initial symptoms of grittiness and soreness may be perceived as being due to
278 'allergy' or 'conjunctivitis'. Nevertheless, this duration is shorter than in earlier studies
279 from 15 years ago when the median time from symptoms to diagnosis was 16
280 months (with a range of 0 to 720 months) (11). This is important, as studies have
281 shown that treatments may be more efficacious when a diagnosis of TED is made
282 earlier (12). In addition, delay to diagnosis may result in increased time to
283 intervention, with the possibility of developing morbidity including loss of vision,
284 diplopia and disfigurement, but also loss of work, income (13), reduced quality of life,
285 social status, as well as negative psychosocial consequences (14).

286

287 The objectives of the Amsterdam declaration on Thyroid Eye Disease in general
288 were to minimize the morbidity associated with TED and improve the patients'
289 experience and quality of life and to prevent the development of TED in people at
290 high risk (15). There has been an increasing recognition of the importance of early
291 diagnosis of TED, with agencies such as the UK Thyroid Eye Disease Amsterdam

292 Declaration Implementation Group (TEAMeD) advocating that GD patients be issued
293 with 'early warning cards' to prompt them to seek urgent assessment if ocular
294 symptoms develop (16). Clinical assessment tools, such as Diagnosis of Graves'
295 Orbitopathy (DiaGO) (17) to aid endocrinologists in making an earlier diagnosis of
296 TED in GD patients have also been devised. However, if patients do not adequately
297 understand their medical condition, these may be of lesser utility. Patient and public
298 involvement in TED has been attempted (18) and in the United Kingdom there are
299 support agencies such as Thyroid Eye Disease Charitable Trust (TEDct) and British
300 Thyroid Foundation (BTF). There are also numerous websites with patient
301 information for people with TED. However, studies have indicated that the actual
302 readability of the information on these websites is poor, and therefore may not be
303 understood by GD and TED patients (6).

304

305 Endocrinologists and ophthalmologists need to have an understanding of the level of
306 knowledge their patients with GD, with and without ocular manifestations, have about
307 TED. In the former group of patients good understanding may result in medical
308 advice being sought in good time. In the latter, patient knowledge and understanding
309 may result in better motivation to make necessary lifestyle modifications, adhere to
310 treatment regimens and have an awareness of the available treatment modalities.
311 Endocrinologists and ophthalmologists also need to know which areas of TED
312 knowledge may be deficient, so that these can be effectively targeted and
313 emphasized during the usually short clinic attendances that may be afforded in busy
314 out-patient clinics. **Despite time and resource limitations we as physicians still have**
315 **responsibility for ensuring that we appropriately counsel our patients regarding**
316 **important aspects of GD with and without orbitopathy.**

317

318 The answers given by GD and TED patients in this study demonstrate a number of
319 misconceptions that endocrinologists and ophthalmologists need to be aware of and
320 try to overcome. Our findings indicate the need to tailor educational efforts and
321 materials to deficient areas and to focus on important aspects of TED knowledge
322 with the aim of dispelling misconceptions.

323

324 We recommend that endocrinologists and ophthalmologists undertake similar
325 surveys of the knowledge of their own GD and TED patients to more accurately
326 gauge patient knowledge, as a surrogate of local performance in GD and TED
327 patient education and information retention. We acknowledge that it is not possible
328 for us to guarantee the wider applicability of the results of this survey to other
329 national and international specialist clinics. However, the city in which the study was
330 undertaken is a very culturally and ethnically diverse region of the United Kingdom
331 and our respondent population was large and truly represented an unbiased regional
332 cross-section. There are also more holistic means of assessing patient knowledge
333 beyond True/False format questionnaires (e.g. structured interviews), but our data
334 does demonstrate 'real-world' responses of GD and TED patients to extremely
335 pertinent questions regarding their presentation, assessment and treatment.

336

337 In summary, this is the first study to evaluate the level of TED knowledge in GD
338 patients with and without orbitopathy, and to provide a comparison with the
339 knowledge levels of the public in general. GD and TED knowledge scores were
340 significantly higher than controls from a statistical point of view, but not necessarily
341 from a practical point of view. Significant misconceptions and knowledge 'gaps' in

342 important areas were observed. These data should be used to inform future
343 decisions about the provision of patient information for those with GD and TED and
344 will facilitate the tailoring of educational materials to these patients.

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372 Birmingham & Midland Eye Centre, UK.

373

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375

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