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## 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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17

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44 **Abstract**

45

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,  $\chi$ -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](http://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 ( $\geq 3$  groups) for continuous data and  
182  $\chi$ -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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373

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375

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