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Jonuscheit, Sven

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1 **The impact of diabetes mellitus and hyperglycaemia on the refractive status of the eye**

2

3 Sven Jonuscheit^{1,2}

4 ¹PhD

5 ²Department of Vision Sciences, Glasgow Caledonian University, Glasgow, United Kingdom

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12 **ABSTRACT**

13 **Purpose:** Diabetes mellitus is a condition of considerable concern globally, which can affect
14 the visual system in various ways, including changes to visual function, the integrity of the
15 ocular surface and the retinal microcirculation. The aim of this article is to provide an
16 overview on the perspectives around the relationship between diabetes and refractive status.

17 **Material and Methods:** Narrative literature review.

18 **Results:** The relationship between diabetes, hyperglycaemia and refractive error has been of
19 interest to clinicians and researchers for more than a century. This review shows that research
20 studies investigating the relationship have varied considerably in their design, methodology,
21 their outcome measures used, as well as their reported results. While some uncertainty
22 remains, there is evidence that short-term, drastic changes in blood glucose levels affect the
23 refractive status of human eyes leading to fluctuating and blurred vision.

24 **Conclusion:** Patients starting glycaemic treatment or undergoing adaptation to a new
25 treatment regime may present with considerable refractive changes and visual complaints.
26 Before considering the prescription of spectacle lenses, clinicians should ideally monitor
27 patients in whom glycaemic control has been initiated or is being adjusted until a stabilisation
28 of blood glucose levels has been confirmed.

29 **Keywords:** Diabetes, refraction, refractive error, variability

30

31

32 **ABSTRACT**

33 **Zweck:** Diabetes Mellitus ist eine Erkrankung von globaler Bedeutung, welche das visuelle
34 System auf verschiedene Weise beeinträchtigen kann, unter anderem durch Veränderungen

35 der Sehfunktion, der okulären Oberfläche und der retinalen Mikrozirkulation. Dieser Artikel
36 hat zum Ziel einen Überblick über den Zusammenhang zwischen Diabetes und refraktiven
37 Veränderungen zu geben.

38 **Material und Methoden:** Narrativer Literatur-Review.

39 **Ergebnisse:** Der Zusammenhang zwischen Diabetes und refraktivem Status ist für Praktiker
40 und Forscher seit mehr als einem Jahrhundert von Interesse. Studien, welche das Thema
41 untersuchten, haben eine Vielzahl von Studiendesigns, Methoden, festgelegte
42 Ergebnisparameter und Ergebnisdarstellungen verwendet. Während weiterhin Unsicherheiten
43 bestehen bleiben, gibt es Studienergebnisse welche deutlich nachweisen, dass es bei
44 kurzzeitigen und drastischen Veränderungen des Glukosespiegels im Blut zu kurzfristigen
45 und erheblichen Fluktuationen des refraktiven Status kommen kann.

46 **Fazit:** Patienten, bei welchen eine Einstellung des Glukosespiegel vorgenommen wird,
47 können erhebliche refraktive Veränderungen subjektiv und störend wahrnehmen. Eine
48 langfristige Versorgung mit Brillen oder Kontaktlinsen sollte erst in Betracht gezogen
49 werden, wenn sich der Glukosespiegel stabilisiert hat.

50 Schlüsselwörter: Diabetes, Refraktion, Refraktionsfehler, Variabilität

51

52 INTRODUCTION

53 Obtaining information on diabetes mellitus (DM) from patients is a standard element of
54 history taking prior to refractive assessment and clinical examination of ocular health. Asking
55 questions about DM allows practitioners to assess the risk of diabetic retinopathy and to put
56 any refractive complaints, which may be due to poorly controlled hyperglycaemia, into
57 context. The latter is especially important if a patient has reported a recent temporary
58 fluctuation in vision, which constitutes a common complaint in patients with DM and
59 hyperglycaemia.

60

61 **Epidemiology and types of diabetes mellitus**

62 DM is a chronic systemic condition and a primary cause of morbidity and mortality globally.
63 The estimated prevalence in adults worldwide in 2019 was 422 million (8.5%) and around
64 1.5 million deaths were attributed to the condition.^{1,2}

65 There are three different types of DM including type 1, type 2 and gestational diabetes. DM
66 type 1 is rarer than DM type 2 and associated with deficient insulin production, leading to a
67 need for daily injections of insulin. The causes of DM type1 are still uncertain and there is
68 no known prevention available. DM type 2 is considerably more common than DM type 1

69 and characterised by what is thought an ineffective use of insulin by the body. It has been
70 reported that approximately one quarter of adults in the United States have been diagnosed
71 with DM type 2.³ This type has been shown to be associated with obesity and physical
72 inactivity as well as genetic factors and processes related to ageing.³ Although DM type 2
73 used to be a condition that was primarily diagnosed in adults, the World Health Organization
74 (WHO) reports that it is now more frequently detected in children. Gestational DM refers to
75 elevated blood sugar levels (hyperglycaemia) above normal values, but below levels of DM,
76 during pregnancy. This type is considered by the WHO as a risk factor for the development
77 of DM type 2 later in life.¹

78

79 **Hyperglycaemia**

80 All types of DM carry health risks that are associated with hyperglycaemia, which describes
81 an imbalance between glucose production by the body (liver), glucose uptake through
82 nutrition and glucose uptake by target tissues such as muscle. The imbalance leads to greater
83 than normal glucose levels, which are used to diagnose DM and to monitor treatment
84 efficacy.³ To monitor changes, fasting plasma glucose as well as haemoglobin A_{1c} (HbA_{1c})
85 levels can be measured.⁴

86

87 **Effect of diabetes and hyperglycaemia on ocular structures**

88 The consequences of DM range from mild systemic and ocular findings to severe and life-
89 threatening complications. These complications include microvascular changes, stroke,
90 blindness, coronary heart disease, kidney disease and amputations.² Research studies have
91 investigated the impact of DM on ocular structures and functions. Several effects on the
92 ocular surface have been reported, including reduced tear film stability and secretion and
93 reduced corneal sensitivity.⁵ Central corneal thickness has been shown to be increased in
94 DM^{6,7} and poor glycaemic control can lead to decreased corneal endothelial cell density.⁷ A
95 recent major review confirmed that people living with DM have altered corneal endothelial
96 morphology such as increased pleomorphism, polymegathism and decreased endothelial cell
97 density. These structural changes appear to be associated with functional changes including
98 reduced endothelial pump and barrier functions, leading to greater corneal thickness and
99 hypoxic stress.⁸

100 Dry eye has been reported to be common in DM type 2^{9,10} and to be related to a reduction in
101 quality of life.¹⁰ Studies reviewing the associations between DM and peripheral changes have

102 suggested that corneal nerve changes due to DM present an opportunity for the early
103 detection of peripheral neuropathy and early treatment.¹¹
104 Hyperglycaemia has been shown to cause diabetic keratopathy, but also to be a cause of
105 retinal and choroidal cell death.¹² Recently, lower corneal optical density has been reported in
106 people with DM in comparison to non-diabetic individuals.¹³ In contrast to the negative
107 impact DM can have on the ocular surface, the condition is not thought to be a significant
108 risk factor for glaucomatous optic neuropathy.¹⁴

109

110 However, DM does not only affect the ocular surface and the anterior segment of the ocular
111 system. Diabetic retinopathy (DR) is a major and potentially sight threatening microvascular
112 complication of DM affecting the posterior segment. DR represents the leading cause of
113 preventable blindness in people of working age,¹⁵ affecting about a third of people with
114 DM.¹⁶ Hyperglycaemia is commonly the underlying factor for the development of DR, even
115 though there is a long list of associated risk factors including hypertension, dyslipidaemia,
116 DM duration and ethnic origin.¹⁵ Early detection of DR is paramount to minimise visual
117 impairment. To facilitate early detection, diabetic retinal screening programmes are in
118 operation in many countries and have been shown to be successful and effective in
119 identifying people developing DR and associated complications such as visual impairment. In
120 Scotland, a national Diabetic Retinal Screening programme was rolled out in 2006. People
121 with DM aged 12 years and older are invited to attend either community or hospital-based
122 retinal screening clinics (note: these are not ophthalmology clinics). Following a brief patient
123 history and assessment of habitual and best-corrected visual acuity, fundus photographs are
124 obtained and evaluated to identify clinical signs of DR.¹⁷ Patients with non-proliferative
125 forms of DR are monitored at regular intervals at screening clinics, e.g. at 6- or 12-months
126 intervals. People with more severe presentations and potentially proliferative DR or signs of
127 maculopathy are referred for detailed examination at the ophthalmology hospital department.
128 Overall, about 4% of patients require ophthalmology referral, (once the screening programme
129 has been fully established). The most common cause for ophthalmology referral is macular
130 oedema.¹⁷

131

132 With both, anterior and posterior ocular structures affected by DM, it seems reasonable and
133 logical to assume that structural changes may have a noticeable impact on the refractive
134 status of the visual system. These functional changes are primarily due to underlying
135 pathophysiology that is linked to biochemical changes in response to hyperglycaemia.

136

137 *Aims*

138 This invited review was devised to provide a succinct overview of the current knowledge and
139 key aspects of DM and its impact on the refractive system in adult humans. A particular focus
140 was placed on acute changes in refractive status.

141

142 **METHODS**

143 **Literature search strategy, inclusion and exclusion criteria**

144 A literature search was carried out on 25 April 2020, using a set of keywords including
145 ‘diabetes’, ‘refraction’, ‘refractive error’, ‘myopia’, ‘hyperopia’ and keyword combinations
146 to scrutinise the electronic database of the National Library of Medicine (*MEDLINE*) through
147 the EBSCO host access at a university library. MEDLINE is a major database and currently
148 contains more than 27 million references to journal articles in life sciences from more than
149 5,200 journals, ranging from the year 1966 to the present day. Articles published in English
150 language and covering the topic of this review were included. A manual search was
151 conducted for relevant systematic reviews on the topic, including the Cochrane Database of
152 Systematic Reviews. The website of the World Health Organization was searched for
153 relevant reports and general patient information on diabetes mellitus.

154

155 **RESULTS**

156 The focus of this review has been on the effect of DM on refraction, which has been
157 considered for at least a century. Table 1 provides a summary of the included studies and
158 highlights the various outcome measures that have been reported in studies which
159 investigated the relationship between refractive error and DM. The studies included in this
160 review are presented in ascending chronological order by year of publication.

161

162 An early example is a paper by Duke-Elder, who presented a series of three cases that were
163 examined at St. George’s Hospital in London in the 1920s. In this case series, it is suggested
164 that a reduction in blood glucose could lead to hyperopic refractive error and an increase in
165 glucose levels can lead to a more myopic refractive status.¹⁸ The first of these cases was a
166 patient who was admitted to hospital with severe symptoms of DM and the refractive changes
167 (hyperopic shift) were observed suddenly within a day and followed the start of insulin
168 therapy, which led to temporary hypoglycaemia. The acute hyperopic shift was found to be

169 reversible, but also quite variable during the period in which the insulin dosage (and blood
170 glucose) was adjusted.

171 The second case also described a patient who was admitted to hospital in a severe, DM-
172 related health state. Following initiation of insulin treatment, a considerable hyperopic shift
173 with considerable astigmatism was observed. Similar to the first case, this acute change in
174 refraction normalised once blood glucose levels had been stabilised and normalised.

175 The third case was a long-term diabetic patient who was also suffering from what appeared to
176 have been severe underlying health problems. In this patient, a drastic myopic shift was
177 observed alongside an increase in blood glucose. Even though no meaningful statistical
178 analysis can be undertaken based on these three cases, the paper nevertheless presents a
179 useful insight into early observations of refractive shifts in patients with acute changes in
180 blood glucose levels.

181

182 More recently, a Danish study was conducted to investigate the impact of DM on refraction
183 in twins.¹⁹ Data were obtained from the Danish Twin Register and a total of 43 twin pairs
184 were examined. A key outcome of the study was the observation that studies of relations
185 between refraction and duration of DM showed diverging results. In the monozygotic (MZ)
186 group, a tendency to reduced axial length and corresponding hyperopia with increasing
187 duration of DM was found. However, in the dizygotic (DZ) group of same sex twins the
188 opposite tendency was found. Increasing lens thickness and decreasing anterior chamber
189 depth with increasing DM duration have been confirmed in this study. The authors conclude
190 that insulin-dependent DM may influence refractive status on different levels.¹⁹

191

192 Okamoto and colleagues observed refractive changes during intensive glycaemic control.²⁰ A
193 transient hyperopic shift occurred in all 28 participants with a reduction in blood glucose
194 levels, with a minimum change of 0.50 D and a mean change in refraction of 1.47 ± 0.87 D.

195

196 These findings were confirmed by a clinical study that reported transient variation in
197 refractive status in diabetic individuals, although no clear trend in either a myopic or
198 hyperopic direction was observed.²¹

199

200 Further evidence was provided by a study that investigated the effect of acute
201 hyperglycaemia on retinal thickness and refraction, which reported that a small hyperopic
202 shift can occur when acute hyperglycaemia was induced,²² which is in contrast to those

203 studies reporting a hyperopic shift during intensive glycaemic control. However, this effect
204 was observed in only one study participant and the authors concluded that ocular refraction
205 was not affected by hyperglycaemia.

206

207 Lin and colleagues, in a small case series, also reported transient hyperopia due to intensive
208 glucose reduction.⁴

209

210 Another paper considered and reviewed aspects around the crystalline lens in relation to
211 blood glucose levels.²³ The authors discuss refractive index gradients within the lens and
212 applied mathematical modelling to determine whether and how such gradients impact on
213 refraction. In their paper, they report that there is no simple linear correlation between blood
214 glucose and refraction, at least in relation to short-term changes over several weeks.

215 Even though the authors discuss recent work, which suggests that starting therapy to control
216 hyperglycaemia leads to a hyperopic shift within a few days to weeks, followed by a gradual
217 return to baseline over a several weeks to months, they conclude that refractive changes occur
218 relatively slowly (several weeks) and suggest that the transient nature implies that two
219 mechanisms are involved. The absence of axial changes or curvature changes of ocular
220 components suggests that changes in refractive index indeed play a role. In summary, the
221 important finding was that it appears possible to account for any observed hyperopic shift
222 after initiation of therapy for hyperglycaemia and the subsequent recovery based on changes
223 in the distribution of refractive index within the lens.²³

224

225 Huntjens, Charman and colleagues carried out a study to investigate how short term changes
226 in blood glucose affect refractive components in individuals with type 1 and type 2 DM.²⁴
227 For this clinical study, 41 long-term diabetic and 20 non-diabetic (control) participants were
228 recruited and data were collected throughout the day at broadly two-hourly intervals between
229 8.00 and 20.00 hours. Various clinical measurements including objective refraction,
230 aberrations, anterior chamber depth, lens thickness and corneal thickness were collected, one
231 eye of each participant was randomly selected for statistical analysis. The study showed that
232 short-term fluctuations of blood glucose levels did not cause acute changes in refractive error,
233 aberrations, or anterior biometric parameters.²⁴

234

235 In a recent ex-vivo study, a bovine lens model was used to assess optical changes in
236 hyperglycaemia as well as in response to reductions in hyperglycaemia (back to normal

237 glucose levels, simulating treatment onset).²⁵ Back vertex focusing distance and equatorial
238 lens diameter were measured. From these data back vertex focal length and longitudinal
239 spherical aberration were derived. A statistically non-significant trend towards myopia with
240 increasing hyperglycaemia was observed. Similarly, a hyperopic shift was noted for changes
241 from hyperglycaemia to normal glucose levels, which was also not statistically significant.
242 Overall, the results suggest that there is no consistent crystalline lens induced refractive
243 change following exposure to hyperglycaemia for periods of up to 5 days.²⁵

244

245 Zhu and colleagues assessed the frequency of under-corrected refractive error among diabetic
246 individuals in Shanghai, China.²⁶ Data were collected through a community-based study that
247 involved a survey of 649 people aged 60 years and older living with DM. A range of clinical
248 measurements was carried out including refraction, best-corrected visual acuity, tonometry,
249 slit-lamp biomicroscopy and fundus photography. A key finding of the study was the
250 observation that undercorrected refractive error occurred in approximately 17% of the
251 participants, thus providing an indirect indication of a possible link between DM and
252 refractive status.²⁶ Similar studies have been carried out, for example in India, where a high
253 prevalence of refractive error was observed in diabetic individuals (type 2) aged 40 years and
254 older.²⁷

255

256 In another study carried out in China, Song et al. set out to determine the prevalence of
257 refractive error and the association with glycaemic control in adults living with type 2 DM.²⁸
258 A total of 839 participants were included in the analysis, 96% of whom presented with some
259 form of refractive error. Haemoglobin A_{1C} (HbA_{1C}) levels were found to be associated with
260 refractive status in that myopic individuals had higher and hyperopic individuals lower levels
261 of HbA_{1C}. Overall, this may provide some, albeit not necessarily robust, evidence of a
262 potential link between glycaemic control and refractive error and the authors recommend
263 further longitudinal research to assess the relationship between glycaemic control and
264 refractive status over time.²⁸

265

266 DISCUSSION AND CONCLUSIONS

267 The impact of poor glycaemic control and hyperglycaemia on the refractive status in humans
268 has been a topic of interest to the clinical and research community for at least a century. Yet,
269 the studies reviewed here provide examples of the diversity of study designs, research
270 methods, outcome measures used and resultant findings. For example, study designs included

271 observational case series,^{18 4} cohort studies,¹⁹ clinical cross-sectional studies using human
272 participants,^{4,20-22} population-based studies,²⁶ ex-vivo animal studies²⁵ and mathematical
273 modelling studies.²³ The variety of study designs and methodological approaches applied
274 makes a direct comparison of the outcomes difficult. However, together these studies indicate
275 that there is remaining uncertainty and that there is no consistent or robust association
276 between glycaemic status, glycaemic control and refractive error, or changes in refraction.
277 However, there seems to be sufficient evidence to support the notion that short-term and
278 reversible changes in refraction can occur in some individuals, for example in situations
279 where blood glucose levels either drop or rise drastically. Similarly, the initiation of treatment
280 to normalise blood glucose levels appears to cause a change in refraction, frequently in the
281 form of a hyperopic shift. These refractive changes are not usually long-lasting and should
282 thus not be considered in the long-term refractive management of patients.

283 The time course of the refractive changes varies, but the studies reviewed indicate reasonably
284 strongly that a stabilisation of refractive status can be achieved within weeks of initiating or
285 adjusting normoglycaemic treatments. The exact timeline needs to be determined for each
286 individual patient. To determine the time point of refractive stability, regular follow-up
287 appointments to assess the refractive status should be arranged, e.g. at 2-4 weekly review
288 intervals, but always dependent on the individual situation of the patient. These follow-up
289 appointments would allow for any trends such as any hyperopic shifts to be measured.

290 Ophthalmic appointments could be coordinated in line with general medical appointments,
291 potentially facilitating comparative assessments of blood glucose and refraction monitoring
292 (where feasible).

293 Even though it is not possible to provide a definitive guide on when exactly refractive
294 stability will be achieved, clinicians should ideally monitor patients in whom glycaemic
295 control has been initiated or is being considerably adjusted and wait for a stabilisation of
296 blood glucose levels before considering the prescription of spectacle lenses. Communicating
297 the need to wait to patients is critical to ensure patients are fully aware of the reasons their
298 visual problems are not being managed with spectacles immediately. The monitoring of
299 blood glucose and its stabilisation are typically overseen by general medical practitioners or
300 DM specialists. If patients present with visual complaints and unmet refractive needs, there is
301 an opportunity for interdisciplinary, collaborative care of such patients, involving close
302 communication between optometrist and medical practitioner as well as the exploration of
303 short-term solutions for the patient in order to help them achieving best possible visual

304 outcomes while their glucose levels are being brought under control and spectacle prescribing
305 can commence.

306

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310

311 *Disclosure*

312 The author has no proprietary interest in any of the materials and methods mentioned in the
313 article.

314

315 *Ethics statement*

316 This article reviewed the published literature and did not use any patient or other identifiable
317 data. Ethical approval was thus not required.

318

319 **The Author**

320 Dr. Sven Jonuscheit

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322 E-Mail

323 Sven.Jonuscheit@gcu.ac.uk

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 404 with type 2 diabetes and its association with glycaemic control. Clin. Exp. Optom.
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406

407 **Table legend:**

408 Table 1. Summary of key characteristics of included articles.

409

410

411

412

413

414

415 Table 1. Summary of key characteristics of included articles.

416

First author	Year	Main outcome measures	Effect of changes in blood glucose levels directly measured?
Duke-Elder	1925	<ul style="list-style-type: none"> • Refractive error 	Yes
Løgstrup	1997	<ul style="list-style-type: none"> • Refractive error • Axial length • Corneal radius • Lens thickness • Spearman's correlation coefficient 	No
Okamoto	2000	<ul style="list-style-type: none"> • Plasma glucose levels • Onset and peak of hyperopic change • Baseline refraction • Change in refraction 	Yes
Sonmez	2005	<ul style="list-style-type: none"> • Plasma glucose levels • Baseline refraction • Lens power 	Yes
Wiemer	2008	<ul style="list-style-type: none"> • Change in refraction • Retinal thickness 	Yes
Lin	2009	<ul style="list-style-type: none"> • Baseline refraction • Change in refraction 	Yes
Rani	2010	<ul style="list-style-type: none"> • Refractive error (prevalence) • Odds ratios 	No

Charman	2012	<ul style="list-style-type: none"> • Crystalline lens model 	No
Huntjens	2012	<ul style="list-style-type: none"> • Mean spherical equivalent • Central corneal thickness • Axial length • Aberrations 	Yes
Mehta	2015	<ul style="list-style-type: none"> • Bovine lens model, ex-vivo • Back vertex focusing distance • Equatorial lens diameter 	Yes
Zhu	2017	<ul style="list-style-type: none"> • Refractive error (prevalence) • Visual acuity • Intraocular pressure • Odds ratios 	No
Song	2018	<ul style="list-style-type: none"> • Refractive error (prevalence) 	No

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