Hypoglycaemia is associated with the absence of a decrease in diurnal macular thickness in patients with diabetic macular oedema

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Abstract

Aim. – Spontaneous diurnal variations measured by optical coherence tomography (OCT) have been reported in diabetic macular oedema (DME) together with a daytime decrease in central macular thickness (CMT). For this reason, this study aimed to investigate the influence of acute glucose and blood pressure changes on daytime variations in CMT in patients with DME.

Methods. – In this prospective observational study of type 1 (n = 4) and type 2 (n = 18) diabetic patients with DME, OCT scans, capillary blood glucose, and systolic and diastolic blood pressure measurements were performed at 9 a.m., 12 a.m., 3 p.m., 6 p.m. and again at 9 a.m. the day after. At the same time, the study protocol included simultaneous ambulatory blood pressure and glucose monitoring over a 24-h period. Hypoglycaemic episodes, defined as glucose values < 60 mg/dL, were also recorded.

Results. – CMT decreased consistently between 9 a.m. and 6 p.m. in 10 patients (from 374 ± 82 μm to 337 ± 72 μm; P = 0.01) and increased or remained steady in 12 others (from 383 ± 136 μm to 390 ± 149 μm; P = 0.58), with a significant difference in CMT absolute change between the two groups (P < 0.001). In the study population as a whole, the lower the mean diurnal blood glucose, the smaller the decrease in CMT during the day (P = 0.027). Also, eight (67%) of the 12 patients with a flat CMT profile experienced a diurnal hypoglycaemic event whereas none of those with a CMT decrease had hypoglycaemia (P = 0.002).

Conclusion. – Hypoglycaemic events may explain the lack of diurnal CMT decrease in diabetic patients with DME. However, further studies need to be conducted to evaluate whether having no diurnal CMT decrease is associated with a poorer visual prognosis and whether it can be modified by better glucose control.

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Keywords: Type 1 diabetes mellitus; Type 2 diabetes mellitus; Diabetic macular oedema; Hypoglycaemia; Optical coherence tomography

Résumé

Association entre hypoglycémie et absence de diminution diurne de l’épaisseur maculaire chez des patients atteints d’œdème maculaire diabétique.

Objectif. – Des variations spontanées diurnes de l’épaisseur maculaire centrale (EMC) mesurée par tomographie par cohérence optique, notamment une diminution au cours de la journée, ont été rapportées dans l’œdème maculaire diabétique (OMD). Le but de cette étude est d’évaluer l’influence des fluctuations aiguës de la glycémie et de la pression artérielle sur l’EMC chez des patients atteints d’OMD.

Méthodes. – Etude prospective observationnelle chez des patients diabétiques de type 1 (n = 4) ou 2 (n = 18) atteints d’OMD. Une tomographie en cohérence optique ainsi que la mesure de la glycémie capillaire et de la pression artérielle ont été réalisées à 9 h, 12 h, 15 h, 18 h et le lendemain à 9 h. Le même jour et durant 24 h, étaient enregistrées de façon simultanée les variations tensionnelles et glycémiennes à l’aide respectivement d’un holter tensionnel et d’un holter glycémiéque. Les épisodes hypoglycémiques, définis par une glycémie inférieure à 0,60 g/L, ont été parallèlement colligés.

Résultats. – L’EMC diminuait régulièrement de 9 h à 18 h chez dix patients (de 374 ± 82 à 337 ± 72 μm, P = 0.01) et augmentait ou restait stable chez les 12 autres patients (de 383 ± 136 à 390 ± 149 μm, P = 0.58), avec une différence significative dans les variations absolues observées entre les deux groupes (P < 0.001). Dans l’ensemble de la population, plus la glycémie diurne moyenne était basse, moins l’EMC diminuait durant la journée (P = 0.027). En outre, huit (67 %) des 12 patients dont l’EMC restait stable ou augmentait durant la...
journée ont présenté une hypoglycémie diurne alors que, chez les patients dont l’EMC diminuait au cours de la journée, aucun épisode d’hypoglycémie n’a été constaté \( (P = 0.002) \).

**Conclusion.** – Les épisodes hypoglycémiques pourraient expliquer l’absence de diminution diurne de l’EMC chez les patients diabétiques atteints d’OMD. Des études complémentaires doivent être réalisées afin d’évaluer si cette absence de baisse diurne de l’EMC est associée à un plus mauvais pronostic visuel et pourrait être modifiée par un meilleur contrôle glycémique.

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**Mots clés :** Diabète de type 1 ; Diabète de type 2 ; Œdème maculaire diabétique ; Hypoglycémie ; Tomographie en cohérence optique

### 1. Introduction

Diabetic macular oedema (DME) is the main cause of visual loss in patients with diabetes and leads to poor vision in about 10% of patients after several years [1,2]. Spontaneous diurnal variations in DME measured by optical coherence tomography (OCT) have been reported. Polito et al. [3] showed that macular thickness tended to be greater in the morning and decreased during the day in 40% of patients with DME, while Larsen et al. [4] reported an overnight thickness increase in most (91%) diabetic patients with DME. Yet, several studies have also reported diurnal macular thickness variations, observing that macular thickness did not decrease, and even increased, in a number of patients with DME [3,5,6]. How can these differences in macular thickness variation be accounted for among patients? Several factors such as posture effects [7], body temperature, light exposure, blood pressure (BP) and hormonal changes have been suspected [3,6–8], but no clear answer has yet been formulated. Furthermore, acute changes in systemic factors and the influence of spikes on the evolution of DME have so far been poorly investigated.

Chronic high BP and sustained high blood glucose constitute independent risk factors for the incidence of diabetic retinopathy and DME [9,10]. However, despite optimal HbA1c levels and BP control, a number of patients still experience severe DME. Therefore, it appears to be of interest to determine whether hypoglycaemic events might be an additional factor in the development of microvascular complications and, in particular, whether they might influence the course of DME. The purpose of the present study was to investigate the influence of acute glucose and BP changes on spontaneous diurnal variations in central macular thickness (CMT) in patients with DME.

### 2. Methods

The study adhered to the tenets of the Declaration of Helsinki and was approved by the medical ethics committee of the Saint-Antoine Hospital (Paris, France). Eligible subjects were any patients over 18 years of age with a clinical diagnosis of type 1 or 2 diabetes, and presenting with clinically significant macular oedema involving the centre of the macula and a CMT > 250 \( \mu \text{m} \) on OCT. Exclusion criteria included DME associated with retinopathy that required laser treatment, eye surgery or laser photocoagulation performed within 6 months of study inclusion, any previous vitrectomy, all cases of non-DME, pregnancy, dialysis and any general diseases requiring systemic steroid therapy. In cases of bilateral oedema, the eye with the greater macular thickness was included. A Stratus OCT3 system (Carl Zeiss Meditec, Dublin, CA, USA) was used to measure macular thickness. CMT was defined as the mean thickness of the central 1000-\( \mu \text{m} \)-diameter area. A variation of >12% of the total CMT was considered significant and not due to variability of the measurement as part of the Stratus machinery.

Patients were followed for 24 h. The study protocol included two daytime visits (V1 and V2); in the interim, patients went home for the night. Patients’ baseline characteristics, including age, type and treatment of diabetes, glycated haemoglobin (HbA1c) levels and past medical history of any general (including hypertension) or ophthalmological diseases, were recorded. Macular thickness measurements of both eyes using OCT scans, capillary blood glucose (Accu-Chek®, Roche Diagnostics, Mannheim, Germany) and systolic and diastolic BP measurements were performed at 9 a.m., 12 a.m., 3 p.m., 6 p.m. (V1) and again at 9 a.m. the day after (V2). From V1 at 9 a.m. to V2 at 9 a.m. the next day, ambulatory 24-h BP monitoring (ABPM; Diasys Integra II, NOVACOR, Rueil-Malmaison, France) and simultaneous continuous glucose monitoring (CGM; Medtronic, Minneapolis, MN, USA) were recorded. For 24-h BP monitoring, measurements were taken at 15-min intervals during the day (from 8 a.m. to 11 p.m.) and at 30-min intervals at night (from 11 p.m. to 8 a.m.). Glucose levels were also monitored on an ambulatory basis over a 24-h period. The monitor continuously measured subcutaneous tissue interstitial glucose levels, recording values every 5 min on average, giving a total of 288 readings per day. The mean 24-h blood glucose and standard deviation (SD), and hypoglycaemic events, defined as a glucose value < 60 mg/dL (3.3 mmol/L), were also recorded [11,12]. Patients were encouraged to maintain their usual lifestyles, diets and treatments during the monitoring period.

#### 2.1. Statistical analysis

Analyses were performed using SPSS software version 14.0 for Windows (Chicago, IL, USA). Results were expressed as mean, SD, range and median values. The data collected were processed with non-parametric tests (Wilcoxon-based tests when appropriate). Correlations between variations of CMT and systemic parameters were calculated by determining Spearman’s correlation coefficient. Multivariate analysis was used to estimate the independent association between hypoglycaemia and the diurnal CMT profile. Significance was considered as a \( P \) value < 0.05.
3. Results

3.1. Baseline characteristics of the population

The study population included 22 diabetic patients (86% male). Four patients had type 1 diabetes and 18 had type 2, including 10 using insulin therapy. The mean ± SD age and duration of diabetes were 60 ± 12 years and 18 ± 13 years, respectively. Mean HbA1c was 7.3 ± 1.3% (median: 7.1%). Mean 24-h blood glucose calculated from CGM data was 150 ± 45 mg/dL. Twelve patients experienced hypoglycaemia (<60 mg/dL) either during the day (n = 8) or at night (n = 4). Mean systolic and diastolic 24-h ABPM values were 132 ± 15 mmHg and 76 ± 10 mmHg, respectively. Eighteen patients were taking antihypertensive drugs.

3.2. Diurnal evolution of central macular thickness

Mean CMT values were 379 ± 144 μm at 9 a.m., 374 ± 121 μm at 12 midday, 370 ± 120 μm at 3 p.m., 366 ± 121 μm at 6 p.m. and 392 ± 135 μm the following day at 9 a.m. In 10 patients, CMT decreased consistently from 9 a.m. to 6 p.m. (from 374 ± 82 μm to 337 ± 72 μm; P = 0.01) and increased or remained steady in 12 other patients (from 383 ± 136 μm to 390 ± 149 μm; P = 0.58), with a significant difference in CMT absolute change between the two groups (−37 μm vs. +7 μm; P < 0.001; Fig. 1). The principal characteristics and metabolic and BP parameters according to CMT diurnal variations are presented in Table 1. There were no significant differences in mean age, body mass index, gender and type of diabetes between the two groups.

3.3. Central macular thickness diurnal variation and blood glucose profile or hypoglycaemic events (<60 mg/dL)

For the study population as a whole, the lower the mean diurnal blood glucose (CGM) value, the smaller the decrease in CMT during the day (P = 0.027). Fig. 2 shows the minimum value for diurnal blood glucose, which was significantly lower in patients without CMT decreases compared with those with CMT decreases (P = 0.025).

Eight patients had at least one daytime value <60 mg/dL recorded by CGM, although no value was <40 mg/dL. These asymptomatic hypoglycaemic episodes occurred in the morning (n = 1) or between 4 p.m. and 8 p.m. (n = 7) and were followed by a median 27% rise in systolic BP. All of these patients with hypoglycaemic events had a flat CMT profile, whereas no hypoglycaemia was registered in patients whose CMT decreased (P = 0.001). After adjusting for diurnal BP parameters and baseline CMT values, hypoglycaemic events maintained a significant association with a flat CMT profile (P = 0.004).

4. Discussion

Our present study findings suggest that, in patients with DME, hypoglycaemic episodes are associated with no decrease in diurnal CMT. Previous studies failed to demonstrate a link between glucose levels and CMT variations probably because of the limitations of a glucose profile obtained from intermittent finger sticks [7]. However, a weak negative correlation between changes in retinal thickening and blood glucose was reported by the Diabetic Retinopathy Clinical Research Network (http://DRCK.net) in 2006 [6].

Recurrent iatrogenic hypoglycaemia is seen in most people with type 1 diabetes and in many of those with advanced type 2 diabetes [11]. In our present study, CGM allowed the detection of minor unrecognized hypoglycaemic episodes in 12 out of 22 patients (55%). This rate is in accordance with those in the literature [13]. Moreover, intensive treatment can increase the number of hypoglycaemic episodes [9]. This was the case in our present patients, whose blood glucose was well controlled (median HbA1c value: 7.1%), whereas in other studies of diurnal variation of CMT, mean HbA1c values were around 7.8% [6,7].

During acute hypoglycaemia, a batch of counterregulatory hormones is released, including catecholamines such as epinephrine and norepinephrine, that activates the
Characteristics of patients without and with a diurnal decrease in central macular thickness (CMT).

<table>
<thead>
<tr>
<th></th>
<th>Whole study population (n = 22)</th>
<th>Without diurnal CMT decrease (n = 12)</th>
<th>With diurnal CMT decrease (n = 10)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60 ± 12</td>
<td>58 ± 13</td>
<td>63 ± 12</td>
<td>0.254</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td>0.571</td>
</tr>
<tr>
<td>Female (n/n total)</td>
<td>3/3</td>
<td>2/3</td>
<td>1/3</td>
<td>0.631</td>
</tr>
<tr>
<td>Male (n/n total)</td>
<td>19/19</td>
<td>10/19</td>
<td>9/19</td>
<td></td>
</tr>
<tr>
<td>Type of diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1 (n/n total)</td>
<td>4/4</td>
<td>2/4</td>
<td>2/4</td>
<td></td>
</tr>
<tr>
<td>Type 2 (n/n total)</td>
<td>18/18</td>
<td>10/18</td>
<td>8/18</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.5 ± 3.4</td>
<td>27.3 ± 3.8</td>
<td>28.0 ± 3.1</td>
<td>0.923</td>
</tr>
<tr>
<td>Baseline CMT at 9 a.m. (µm)</td>
<td>379 ± 114</td>
<td>383 ± 136</td>
<td>374 ± 82</td>
<td>0.670</td>
</tr>
<tr>
<td>Absolute difference between CMT at 9 a.m. and 6 p.m. (µm)</td>
<td>−12 ± 30</td>
<td>7 ± 23</td>
<td>−37 ± 21</td>
<td>0.001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.3 ± 1.3</td>
<td>7.1 ± 1.2</td>
<td>7.5 ± 1.4</td>
<td>0.448</td>
</tr>
<tr>
<td>24-h mean glucose by CGM (mg/dL)</td>
<td>156 ± 45</td>
<td>148 ± 45</td>
<td>166 ± 45</td>
<td>0.235</td>
</tr>
<tr>
<td>Diurnal mean glucose by CGM (mg/dL)</td>
<td>156 ± 55</td>
<td>136 ± 47</td>
<td>180 ± 55</td>
<td>0.025</td>
</tr>
<tr>
<td>Diurnal hypoglycaemiaa [n/n total (%)]</td>
<td>8/22 (36)</td>
<td>8/12 (67)</td>
<td>0/10 (0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Daytime ABPM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>136 ± 17</td>
<td>139 ± 17</td>
<td>132 ± 15</td>
<td>0.222</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>78 ± 11</td>
<td>82 ± 12</td>
<td>74 ± 8</td>
<td>0.165</td>
</tr>
<tr>
<td>Pulse pressure (mmHg)</td>
<td>58 ± 12</td>
<td>58 ± 11</td>
<td>57 ± 13</td>
<td>0.716</td>
</tr>
</tbody>
</table>

Data are presented as means ± standard deviation (SD) or n (%). BMI: body mass index; CGM: continuous glucose monitoring; ABPM: ambulatory blood pressure monitoring; BP: blood pressure. NB: to convert fasting blood glucose to millimoles per liter (mmol/L), multiply by 0.0555.

* Patients with vs. without a diurnal CMT decrease.

aData glucose < 60 mg/dL.

sympathoadrenal system, resulting in a potential increase in BP and heart rate [14]. As it had previously been shown that hypoglycaemia is followed by a hypertensive spike in everyday life [15] and that a high BP constitutes an independent risk factor for DME [10], a hypoglycaemia-induced BP increase might be one of the mechanisms underlying the absence of a diurnal CMT decrease in our present patients. Interestingly, seven of the eight hypoglycaemic events recorded happened in the afternoon, and the diurnal ABPM tended to be higher in patients with a flat CMT profile. In any case, a transient BP elevation of short duration with no impact on ABPM is apparently sufficient to increase the risk of diabetic complications, as white-coat hypertension has been associated with an increased risk of diabetic retinopathy [16]. Diabetic retinopathy has also been associated with a late-afternoon BP increase in normotensive patients with type 2 diabetes [17].

While DME is mainly due to retinal–blood barrier breakdown secondary to an increased vitreous vascular endothelial growth factor (VEGF) level, Dantz et al. [18] demonstrated in healthy men that acute hypoglycaemia is associated with an increased level of serum VEGF. In pregnant rabbits, intravitreal VEGF concentrations correlated with plasma VEGF levels [19], thereby suggesting that systemic VEGF diffuses into the retinal and vitreous spaces. A recent study has also shown that levels of serum VEGF were higher in patients with diabetic retinopathy than in healthy patients; however, no correlation was found between CMT and serum VEGF levels [20].

In addition, cortisol serum levels are at their highest in the morning and at their lowest at around 6 p.m., as is also the CMT in some patients with macular oedema. Polito et al. [7] found a positive correlation between changes in CMT and serum cortisol levels (r = 0.69, P = 0.024).

The main limitations of our present study are the small sample size, the lack of precise information regarding duration of DME because of an unknown onset of the disease and the absence of cortisol serum measurements. The present authors also have no clear explanation for why the four patients without a CMT decrease presented with no associated hypoglycaemic events.

Strengths of this study include:

- the use of CGM to capture the blood glucose profile;
- the significant number of diurnal hypoglycaemic events (8/22 patients);
- the simultaneous monitoring of glucose and BP with point-to-point analysis (and calculation of not only mean values).

In conclusion, hypoglycaemic events may explain the lack of diurnal CMT decrease in diabetic patients with macular oedema. However, further studies need to be conducted to evaluate whether this absence of diurnal CMT decrease is associated to poorer visual prognosis and whether it can be modified by better glucose control. Considering the prevalence of hypoglycaemic events among diabetic patients, confirmation of these results could be of considerable interest in clinical practice.

**Disclosure of interest**

SFB has received fees for lectures and consultations from Eli Lilly and Novartis NS, BD declare no conflicts of interest within the field of this report.
JB declares no conflicts of interest within the field of this report.

PJG has received fees for lectures and consultations from AstraZeneca, BMS, Eli Lilly, GSK, Medisense, Novartis, Novo Nordisk, Roche, Sanofi-Aventis, Servier, Takeda and Therval.

PM has received fees for lectures and consultations from Eli Lilly, Takeda, Novartis, Allergan and Fovea Pharmaceutical.

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