Diabetes & Metabolism xxx (2017) xxx–xxx

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

Review

Early worsening of diabetic retinopathy after rapid improvement of blood glucose control in patients with diabetes

S. Feldman-Billard [a,*], É. Larger [b,c], P. Massin [d], for the Standards for screening, surveillance of ocular complications in people with diabetes SFD study group

[a] Service de médecine interne, CHNO des Quinze-Vingts, 28, rue de Charenton, 75571 Paris cedex 12, France
[b] Département hospitalo-universitaire, service de diabétologie, hôpital Cochin, Paris, France
[c] Inserm U1016, Institut Cochin, université de Paris René Descartes, Paris, France
[d] Centre d'ophtalmologie Breteuil, centre Broca, hôpital Lariboisière, Paris, France

ARTICLE INFO

Article history:
Received 2 October 2017
Received in revised form 27 October 2017
Accepted 29 October 2017
Available online xxx

Keywords:
Bariatric surgery
Early worsening of diabetes retinopathy
Insulin intensive treatment
Pancreas transplantation

ABSTRACT

Aim. – To review the frequency, importance of and risk factors for "early worsening of diabetic retinopathy" (EWDR) after rapid improvement of blood glucose in patients with diabetes.
Methods. – This was a systematic review of key references (PubMed 1980–2016) and the current international recommendations for the above-mentioned topics.
Results. – EWDR has been described during intensive treatment (IT) in patients with uncontrolled type 1 or 2 diabetes, and after pancreas transplantation or bariatric surgery. EWDR arises in 10–20% of patients within 3–6 months after abrupt improvement of glucose control, and in nearly two times that proportion in patients with advanced baseline diabetic retinopathy (DR). While EWDR is often transient and predominantly driven by the development of cotton-wool spots and intraretinal microvascular abnormalities in patients with no or minimal DR, it can lead to irreversible retinal damage in patients with advanced DR before IT. Its identified risk factors include higher baseline levels and larger magnitudes of reduction of HbA_{1c}, longer diabetes durations and previous severity of DR.
Conclusion. – Intensive diabetes treatment inducing a rapid fall in glucose should prompt vigilance and caution, particularly in patients with long-term and uncontrolled diabetes and DR prior to IT. Careful retinal examination should be performed in all patients before initiating IT; however, in patients with severe non-proliferative or proliferative DR, panretinal photocoagulation therapy should be performed immediately. During the year following IT, quarterly eye monitoring is required in patients at high risk of EWDR (long-term uncontrolled diabetes, previous advanced DR), whereas follow-up every 6 months can be applied in patients with short-term diabetes and no/minimal DR before IT. To date, there is no evidence that controlling the speed or magnitude of HbA_{1c} decreases will reduce the risk of EWDR in patients with diabetes.

Introduction

Diabetic retinopathy (DR) is a leading cause of vision loss and affects more than 100 million people globally [1]. Besides diabetes duration, the strongest predictor of the development and progression of DR, hyperglycaemia and hypertension are well-established modifiable risk factors [2]. Studies provide evidence that intensive treatment (IT) to lower glycaemic levels, compared with conventional therapy (CT), can reduce the development and progression of DR in both type 1 (T1D) [3] and 2 diabetes (T2D) [4,5].

Near-normalization of blood glucose levels is thus an important goal of DR monitoring. However, studies 30 years ago demonstrated a paradoxical early aggravation of DR called "early worsening of diabetic retinopathy" (EWDR) during insulin IT in young T1D patients with a long history of uncontrolled diabetes [6–10]. While in some patients EWDR was temporary and limited, in others, laser treatment was necessary and severe retinal damage occurred. In the years since then, accurate determination of the prevalence and risk factors for EWDR after rapid improvement of glucose control have been an issue of debate in the literature. In addition, the mechanism behind this unfavourable outcome has still not been completely elucidated.

The aim of this article is to review the frequency, importance of and risk factors for EWDR after dramatic decreases of HbA_{1c} in T1D

* Corresponding author.
E-mail address: sfeldman@15-20.fr (S. Feldman-Billard).

https://doi.org/10.1016/j.diabet.2017.10.014
1262-3636/

and T2D patients, excluding pregnant women. Based on the available data up to 2017 and in accordance with the opinions of the *Société francophone du diabète* (SFD; French Society of Diabetes) study group for standards of screening and surveillance of ocular complications in people with diabetes [11], a preventative strategy, including close eye monitoring and treatment, was validated by both the SFD and *Société française d'ophtalmologie* (SFO; French Society of Ophthalmology).

Materials and methods

Rapid improvement of blood glucose control in the setting of chronic hyperglycaemia has been observed in the following clinical situations: during insulin IT in uncontrolled T1D and T2D patients; after pancreatic or islet-cell transplantation; and, more recently, after bariatric surgery. To analyze the DR outcomes reported to date in the literature in these situations, a systematic literature search was performed in The Cochrane Library and Medline (PubMed) databases. Of all studies published between 1980 and 2017, randomized controlled trials, cohort studies and retrospective or case series reporting the incidence or progression of DR following a rapid drop in blood glucose were included. In addition, the recommendations of ophthalmological (Australian, UK, US) and diabetes (American Diabetes Association) societies were also analyzed [12–15].

Although rapid improvement of blood glucose control was not precisely defined in terms of speed and/or magnitude of HbA_{1c} reductions in these studies, decreases in HbA_{1c} of $\geq 1.5\%$ over 3 months (for example, an HbA1c decrease from 9% to 7.5% over that time) or $>2\%$ over a 6-month period were commonly reported. However, DR progression during the first year after rapid improvement in blood glucose is usually considered EWDR, and most studies provided outcome data on retinal status (non-proliferative and proliferative DR). Recent investigations have also analyzed macular thickness based on optical coherence tomography (OCT) following rapid falls in blood glucose.

Results

Clinical findings

EWDR after IT in T1D patients

The first observations of progression to severe DR were reported 30 years ago following insulin pump therapy (continuous subcutaneous insulin infusion [CSII]) in young T1D patients with uncontrolled diabetes. In a study published in 1984 including 19 T1D patients, four of them with severe non-proliferative DR and long-term uncontrolled diabetes evolved within 3–6 months of CSII to severe proliferative DR (PDR), whereas no change or discrete EWDR was observed among those with minimal-to-moderate non-proliferative DR before CSII [6].

Randomized controlled trials

From 1983 onwards, numerous controlled trials reported the incidence or progression of DR within the first few years of IT (Table 1) [7–10,16–20]. These studies all share a similar methodology. Patients were randomized to IT (subcutaneous multiple insulin injections or CSII) or continued their usual treatment (CT), usually 1–2 insulin injections. Most patients had non-proliferative DR at baseline, except for some patients free of DR in the Oslo study [8] and Diabetes control and complications trial (DCCT) in a primary-prevention cohort [3]. In addition, in the DCCT [3], the most severe form of DR was a criterion for non-inclusion, given the EWDR cases observed in the Oslo study [8]. All patients had HbA_{1c} levels $>8.5\%$ at baseline and, in some studies, nearly 10% [7–9]. Blood glucose control improvements were rapid in most cases in the first 3 months [3,9] of IT, with 1–3% reductions in HbA_{1c} levels at 1 year. Conversely, patients randomized to CT showed either no or slight improvement in glucose control, and their HbA_{1c} levels remained significantly higher than in IT patients. The duration of follow-up ranged from <1 year (8 months in the Kroc collaborative study [9]) to ≥ 1 year [3,7,8,15,17] and, in three studies, monitoring was extended beyond 6 years [3,10,18–20]. Ophthalmological examinations were performed at least annually, although early assessment was scheduled within the first few months of IT in two studies. Patients in the Oslo study underwent eye examinations 2 months before randomization, and at 3, 6 and 12 months thereafter [8]. Retinal status was also evaluated in a subgroup of DCCT patients at 3 months [3,10]. Furthermore, the criteria for DR progression differed (2 or 3 steps of progression as per the Early treatment of diabetic retinopathy study [ETDRS] scale, need for laser treatment, presence of vitreous haemorrhage) across these studies.

In 1983, the Steno study, including 30 patients with long-term T1D (~20 years) and moderate non-proliferative DR, reported progression to PDR after 1 year of CSII [7]. Later, the Kroc and Oslo studies and DCCT reported less-serious retinal damage, mostly cotton-wool spots and intraretinal microvascular abnormalities [3,8–10]. In the Oslo study, half the patients treated with CSII (7/15) or multiple injections (8/15) had EWDR at 3 months compared with none in the CT group (0/15; $P<0.01$) [17]. In the Kroc collaborative study, 47% (15/32) of CSII patients worsened at 8 months vs 27% (9/33) in the CT group [9]. Of the DCCT patients who underwent eye examination at 3 months, EWDR was observed in 11% (21/197) with IT vs 3.6% (7/192) with CT. At 6 months, EWDR was observed in nine IT and six CT DCCT patients and, within the first 12 months, was described primarily in patients in the secondary-prevention cohort: 13% (93/711) of IT (13/348 in primary- and 80/363 in secondary-prevention cohorts) vs 7.6% (55/728) of CT patients (7/378 in primary- and 48/350 in secondary-prevention cohorts) for an odds ratio (OR) of 2.06 ($P<0.001$). In addition, 25 patients progressed to an advanced stage, including two high-risk PDR cases requiring laser treatment within 1 year [10].

Nevertheless, EWDR is often transient, with regression of retinal signs after 12 months in the Oslo study in all except four patients [8] and in nearly half of the DCCT patients [10]. In fact, a recent randomized study of 51 T1D patients demonstrated no differences in cases of EWDR after 1 year of CSII compared with multiple daily insulin injections, with HbA_{1c} reduced by 1.6% in the former vs 0.3% in the latter ($P<0.0001$) [21].

Meta-analysis

Extended follow-ups have clearly demonstrated the ocular long-term benefits of insulin IT even in patients with EWDR [3,18]. In the Stockholm diabetes intervention study (SDIS), decreased DR and vision loss appeared at 5 years of monitoring following IT [19,20], and even earlier in other studies, although the benefit is primarily the reduced risk of DR. In a recent Cochrane review of 12 clinical trials involving a total of 2230 patients, the relative risk (RR) of DR occurrence was reduced by 73% at the end of follow-up in IT compared with CT patients [22]. In a 2015 meta-analysis of 24 studies involving 9302 patients, the risk of developing DR was halved by IT compared with CT (RR: 0.43, 95% CI: 0.23–0.83) and by CSII vs three insulin injections (RR: 0.45, 95% CI: 0.24–0.83), irrespective of HbA_{1c} [23]. Moreover, IT reduced DR progression by nearly a third in the meta-analysis (RR: 0.63, 95% CI: 0.43–0.92) [23] and in the Cochrane review (39%) [22].

Please cite this article in press as: Feldman-Billard S, et al. Early worsening of diabetic retinopathy after rapid improvement of blood glucose control in patients with diabetes. Diabetes Metab (2017), https://doi.org/10.1016/j.diabet.2017.10.014