Diabetes & Metabolism xxx (2017) xxx–xxx

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Original article

Severe hypoglycaemia is a major predictor of incident diabetic retinopathy in Japanese patients with type 2 diabetes

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ARTICLE INFO

Article history:
Received 5 March 2017
Received in revised form 14 June 2017
Accepted 14 June 2017
Available online xxx

Keywords:
Diabetic retinopathy
Hypoglycaemia
Microvascular complications
Risk factors
Type 2 diabetes

ABSTRACT

Aim. – Hypoglycaemia is a common complication in diabetes patients. However, its relationship with retinopathy has not been well documented in patients with type 2 diabetes (T2D). This study aimed to investigate the associations between hypoglycaemia and the incidence and progression of diabetic retinopathy (DR).

Methods. – In this longitudinal cohort study, which was part of the Japan Diabetes Complications Study (JDCS), adult patients with T2D were recruited at 59 diabetes clinics across Japan. Their history of hypoglycaemia was assessed by standardized self-reported questionnaires. Severe hypoglycaemia was defined as having at least one episode with coma requiring an outpatients visit or hospitalization. Adjusted hazard ratios (HRs) for incidence and progression of DR over 8 years of follow-up were determined.

Results. – Of 1221 patients without DR, 127 (10.4%) had experienced non-severe hypoglycaemia within the previous year, whereas 10 (0.8%) reported severe hypoglycaemia episodes. During the 8-year follow-up involving 8492 person-years, 329 patients developed DR. In 410 patients with prevalent DR, the adjusted HRs for incident DR were 4.35 (95% CI: 1.98–9.56; $P < 0.01$) and, for progression of DR, 2.29 (95% CI: 0.45–11.78; $P = 0.32$) with severe hypoglycaemia.

Conclusion. – Having a history of severe hypoglycaemia was one of the strongest predictors of incident DR in patients with T2D, with a fourfold increased risk. Identifying patients with greater risks of DR based on their history of hypoglycaemia may help to personalize risk evaluation in patients with diabetes.

Introduction

Hypoglycaemia is the most common complication of intensive glucose-lowering therapy in diabetes patients. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which was prematurely stopped owing to increased mortality possibly related to hypoglycaemia, intensive glucose control in patients with type 2 diabetes (T2D) resulted in a threefold increase in hypoglycaemias requiring medical assistance [1]. Meta-analysis confirmed the adverse effects of intensive glucose control on hypoglycaemia [2], and similar associations were reported in a meta-analysis of the addition of dipeptidyl peptidase-4 inhibitors to sulphonylureas [3]. The prevalence of hypoglycaemia was estimated to be 45% for mild or moderate hypoglycaemia and 6% for severe hypoglycaemia in the entire study T2D population, whereas the prevalence was

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http://dx.doi.org/10.1016/j.diabet.2017.06.002
1262-3636/

50% for mild or moderate hypoglycaemia and 21% for severe hypoglycaemia in patients taking insulin [4]. It is well known that hypoglycaemia is a major cause of emergency hospitalizations in the elderly [5] and is life-threatening [6]. Moreover, a recent meta-analysis of six observational studies revealed that hypoglycaemia increases the risk of macrovascular complications threefold [7].

In earlier studies, rapid normalization of glucose status with intensive glucose management was suggested to have a potential role in aggravating the progression of diabetic retinopathy (DR), known as 'early worsening' [8]. The entire mechanism of this early worsening has not been fully elucidated, but hypoglycaemia is known to cause haemorheological changes, white cell activation, vasoconstriction, and the release of inflammatory mediators and cytokines [9]. Furthermore, fear of hypoglycaemia may have a negative impact by lowering adherence to diabetes management and glucose control regimens [10].

Data on microvascular complications related to hypoglycaemia in T2D are sparse. The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) study reported that hypoglycaemia increases major microvascular events [11]. Zhao et al. [12] reported that the risk of microvascular complications was increased in those who had hypoglycaemia within a year. However, it remains unknown whether hypoglycaemia specifically increases the incidence of DR, as the ADVANCE and Zhao et al. studies examined a composite outcome of new or worsening nephropathy or retinopathy. Also, a combined analysis of the ADVANCE and ACCORD studies suggested that the inconsistencies in the risk associations for microvascular complications between studies aiming at near-normalization of glucose might have been due to the balance between the beneficial effects of intensive glucose management and harmful effects of hypoglycaemia [13].

These lines of evidence have prompted our investigation into the associations between mild, moderate and severe hypoglycaemia and the incidence and progression of DR in a cohort of Japanese patients with T2D followed for 8 years.

Methods

Study cohort

The present study was part of the Japan Diabetes Complications Study (JDCS), an open-labelled randomized trial originally designed to evaluate the efficacy of a long-term therapeutic intervention that was mainly focused on lifestyle education [14,15]. Incidence rates of DR did not significantly differ between the two randomized groups in that trial; therefore, for our study, data from these two groups were combined [16]. Those eligible for the study were subjects previously diagnosed with T2D and aged 40–70 years, whose HbA_{1c} levels were $\geq$ 6.5% according to values established by the Japan Diabetes Society (JDS) and assays standardized by the Laboratory Test Committee of the JDS. From the outpatient clinics of 59 university and general hospitals nationwide specializing in diabetes care, 2205 patients were initially registered from January 1995 to March 1996. After excluding those with major ocular disease (such as glaucoma, dense cataract, history of cataract surgery), the population ultimately analyzed consisted of 1221 patients without DR (to assess incident DR) and 410 patients with DR (to assess progression of DR) [14,15]. Also analyzed were the follow-up data collected up to March 2003.

The protocol for the study, which was in accord with the Declaration of Helsinki and Ethical Guidelines for Clinical/Epidemiological Studies of the Japanese Ministry of Health Labour and Welfare, received ethics approval from the institutional review boards of all participating institutions. In addition, written informed consent was obtained from all enrolled patients.

Measurements

Extensive surveys using standardized self-reported questionnaires were conducted at baseline and at 5 years after study registration. Patients' history of hypoglycaemia was assessed by three items in the questionnaires:

- frequency of hypoglycaemia episodes within the previous year;
- frequency of coma due to hypoglycaemia within the previous year;
- and frequency of hypoglycaemia episodes requiring an outpatients visit or hospitalization within the previous year.

For our primary analysis, 'severe hypoglycaemia' was defined as the occurrence of at least one episode of hypoglycaemia with either coma or the need for an outpatients visit or hospitalization, based on the baseline questionnaires. Compliance with oral medications or insulin was assessed by the following four choices: takes (injects) every time; does not take (inject) occasionally; does not take (inject) frequently; and almost never takes (injects). Other measurements included treatments, physical examinations, blood pressure measurements, neurological/ophthalmological examinations and laboratory tests, including those for HbA_{1c}, fasting plasma glucose/insulin/C-peptide, serum lipids/creatinine/urea nitrogen and urinalysis. Plasma insulin was not measured in those treated with insulin analogues. HbA_{1c} assays were standardized by the JDS Laboratory Test Committee using JDS values. The US National Glycohemoglobin Standardization Program (NSGP) value for HbA_{1c} was calculated as follows: 0.25 + 1.02 $\times$ JDS value. All other laboratory measurements were done at each participating institution. Serum low-density lipoprotein (LDL) cholesterol was calculated using Friedewald's equation except when triglycerides were $>$ 400 mg/dL, in which case the LDL cholesterol data were treated as missing.

Outcome measures

The primary outcome of the present study was the incidence of DR in at least one eye. DR was evaluated annually by qualified ophthalmologists at each study institution using the International Clinical Disease Severity Scale for DR and for diabetic macular oedema disease with minor modifications [17]. Severity of DR was categorized into five stages: Stage 0, no retinopathy; Stage 1, haemorrhage and hard exudates; Stage 2, soft exudates; Stage 3, intraretinal microvascular abnormalities and venous changes, including beading, loops and duplication; and Stage 4, new vessels, vitreous haemorrhage, fibrous proliferation and retinal detachment. The incidence of DR was defined as having no signs of DR in either eye at baseline, but having mild-to-severe non-proliferative DR or proliferative DR (Stage 1 to Stage 4) confirmed at two consecutive follow-up years. This severity categorization is mostly comparable to the International Clinical Disease Severity Scale for DR Stages 1 and 2: mild-to-moderate non-proliferative diabetic retinopathy (NPDR); Stage 3: severe NDR; and Stage 4: proliferative diabetic retinopathy (PDR) [14]. To validate that the grading across study sites was consistent, fundus images were examined and evaluated by agreement of grading between local ophthalmologists and retinal specialists (R.K. and H.Y.). The estimated kappa statistic for agreement was 0.56 [95% confidence interval (CI): 0.52–0.59] and was above moderate.

The secondary outcome was time from registration to progression to Stage 3 or 4 DR in at least one eye. Another outcome was also examined in the sensitivity analysis: time from registration to a major microvascular event, defined as DR or overt nephropathy, whichever happened first. The incidence of overt nephropathy was defined by spot urinary albumin excretion $>$ 300 mg/g of creatinine in two consecutive samples.

Please cite this article in press as: Tanaka S, et al. Severe hypoglycaemia is a major predictor of incident diabetic retinopathy in Japanese patients with type 2 diabetes. Diabetes Metab (2017), http://dx.doi.org/10.1016/j.diabet.2017.06.002