Can J Diabetes 40 (2016) 258–263

Contents lists available at ScienceDirect

Canadian Journal of Diabetes

journal homepage: www.canadianjournalofdiabetes.com

Original Research

Incidence and Risk Factors Involved in the Development of Nephropathy in Patients with Type 1 Diabetes Mellitus: Follow Up Since Onset

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ARTICLE INFO

Article history:
Received 5 September 2014
Received in revised form
16 September 2015
Accepted 17 November 2015

Keywords:
glycated hemoglobin
low-density cholesterol
nephropathy
type 1 diabetes

ABSTRACT

Objectives: Estimation of the incidence of nephropathy as well as potential risk factors involved in its onset in a cohort of patients with type 1 diabetes who were followed from diagnosis.
Methods: We studied 716 patients, who were followed for a mean (standard deviation [SD]) of 10.1 (SD: 5.3) years. We analyzed the influence of demographic characteristics and levels of glycated hemoglobin (A1C), lipids and blood pressure during the course of the disease by univariate and multivariate survival methods.
Results: The cumulative incidence of nephropathy was 2.6%, 6.3% and 11.9% at 5, 10 and 15 years of evolution, respectively. The factors associated with increased risk for nephropathy were systolic blood pressure and A1C levels. An increment of 10 mm Hg in systolic blood pressure increases the risk by 36%, and an increment of 1% in A1C levels raises the risk by 13% at 5 years since onset and 68% at 10 years, and it doubles the risk at 15 years. Women have higher risk than men (hazard ratio 1.79; p=0.024).
Conclusions: Our study suggests that female gender and high levels of A1C and systolic blood pressure throughout the course of the disease are the main factors associated with an increased risk for development of nephropathy in patients with type 1 diabetes mellitus.
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Mots clés :
hémoglobine glyquée
cholestérol à faible densité
néphropathie
le diabète de type 1

RÉSUMÉ

Objectifs : Estimation de l'incidence de la néphropathie ainsi que les facteurs de risque potentiels impliqués dans son apparition dans une cohorte de patients atteints de diabète de type 1 qui ont été suivis d'un diagnostic.
Méthodes : Nous avons étudié 716 patients, qui ont été suivis pendant une durée moyenne (écart type []) de 10,1 (SD: 5.3) ans. Nous avons analysé l'influence des caractéristiques démographiques et des niveaux d'hémoglobine glyquée (A1C), les lipides et la pression artérielle au cours de l'évolution de la maladie par la survie univariée et multivariée méthodes.
Résultats : L'incidence cumulée de la néphropathie a été de 2,6%, 6,3% et de 11,9% à 5, 10 et 15 années d'évolution, respectivement. Les facteurs associés à un risque accru de néphropathie étaient la pression artérielle systolique et les niveaux d'A1C. Une augmentation de 10 mm Hg dans la pression artérielle systolique augmente le risque de 36%, et une augmentation de 1% du taux d'HbA1c augmente le risque de 13% à 5 ans depuis le début et 68% à 10 ans, et il double le risque à 15 ans. Les femmes ont un risque plus élevé que les hommes (hazard ratio 1,79; p=0,024).
Conclusions : Notre étude suggère que le sexe et des niveaux élevés de femmes A1C et la pression artérielle systolique pendant toute la durée de la maladie sont les principaux facteurs associés à un risque accru de développement de la néphropathie chez les patients avec diabète de type 1.
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http://dx.doi.org/10.1016/j.jcjd.2015.11.008

Introduction

Diabetic nephropathy is one of the most serious complications in patients with type 1 diabetes. It includes several stages, microalbuminuria being an early marker of structural renal disease. The prevalence of microalbuminuria ranges from 12% to 25% at 10 years of evolution (1) and from 30% to 40% after 20 years (2,3). Of patients with microalbuminuria, half evolve to more advanced stages while 50% to 60% return to normal albuminuria values (4). Although the incidence of this complication appears to be decreasing (5), it remains the most common cause of end stage renal disease and increases cardiovascular risk for these patients (6–9).

Several risk factors have been associated with the onset of nephropathy, apart from glycemic control (10), such as glycemic variability (11,12), duration of the diabetes, hypertension (13), smoking (14), plasma lipid levels (15–17), body mass indexes (BMIs) (18) and genetic predisposition. Contradictory data have been published regarding factors, such as sex (19) or age at diagnosis (20), with most of the studies referring to pediatric populations.

The objectives of this study were to estimate the risk for nephropathy in its various phases and to assess the variables related to its onset and progression in a cohort of patients who had type 1 diabetes; no limits were placed on age at onset, and the patients had been followed since diabetic onset in a longitudinal study.

Methods

This was an observational, retrospective follow-up study. The subjects of the study were patients with onset of type 1 diabetes between January 1990 and December 2008 who were treated in the Navarra Hospital Complex between January 1990 and December 2010. The cohort included 716 patients. The regional Ethical Review Board of Navarra approved this study.

Type 1 diabetes was diagnosed according to the clinical criteria recommended by the World Health Organization (21). The clinical diagnostic criteria were those previously validated by Molback (22).

According to the medical protocol followed, all patients had at least 1 scheduled outpatient appointment per year. The information for the study was obtained from the electronic health records of the Navarre Health Service. We gathered information about age, sex, GAD65 and IA2 autoantibodies at onset for all patients. At the initial visit and for every visit through follow up, we included weights; BMIs, systolic blood pressure (SBP) and diastolic blood pressure (DBP) (BP was obtained after patients rested for 5 minutes in the sitting position); smoking status and analytic data, such as lipid profiles and A1C levels. When patients had more than 1 determination of these covariates in a year, we computed the arithmetic mean in the case of continuous variables, whereas for the categoric variables, we chose the value that had lasted longest during that year.

Urinary albumin excretion was measured in each patient at least once a year by nephelometry (Beckman Coulter, Sharon Hill, Pennsylvania, US) between 1990 and 2006 and by immunoturbidimetry (Roche Diagnostics, Risch-Rotkreuz, Switzerland) between 2006 and 2010. In line with current American Diabetes Association recommendations, microalbuminuria was defined as urinary albumin excretion rates of 20 to 200 mg/g in the first morning urine test in at least 2 of 3 consecutive samples. The minimum time between samples was 3 months. Macroalbuminuria was defined as albumin excretion rates >200 mg/g. Kidney failure was defined by values of creatinine ≥1.2 mg/dL or calculation of creatinine clearance <60 mL/min/1.73 m^2 using the Cockcroft-Gault formula at 2 consecutive study visits. For total risk estimates, we considered nephropathy as presenting at least 1 of the renal outcomes, i.e. as presenting microalbuminuria (including reverted microalbuminuria) or/and macroalbuminuria or/and kidney failure. Possible causes of kidney disease other than diabetes were ruled out.

Between 1990 and 1997, A1C levels were measured by several techniques: Abbott IMX (Abbott Laboratories, Lake Bluff, Illinois, USA); Ciba Corning Glycomat (Ciba Corning Diagnostics, Walpole, Massachusetts, USA); and Merck (Merck Millipore, Darmstad, Germany) and Menarini (Menarini Diagnostics, Florence, Italy) high pressure liquid chromatography (HPLC); after 1997, by HPLC (Adams A1C HA, Menarini Diagnostics, Florence, Italy); reference range: 4.1% to 6.2%. In 2005, the laboratory of the hospital complex obtained the level II certification of traceability of the Diabetes Control and Complications Trial (DCCT) Reference Method through the National Glycohemoglobin Standardization Program. Previous A1C level determinations were standardized to the DCCT reference range (4.05% to 6.05%) (23).

Cholesterol, HDL cholesterol and triglycerides (TGs) were measured by GPO-PAP (Roche Diagnostics). LDL cholesterol was calculated by using the Friedewald equation. Serum creatinine was measured by the Jaffé method (Roche Diagnostics). Determination of anti-GAD and anti-IA2 antibodies was performed using the RIA technique (Medipan Diagnostica, Blankenfelde-Mahlow, Germany).

This study was supported by a grant from the Carlos III Institute of Health (PI10/02715) and a grant from the Government of Navarre (53/2008)

Statistical analysis

The characteristics of the patients at disease onset were summarized using frequencies and percentages, means and standard deviations (SDs). The cumulative incidence of nephropathy for the global sample was estimated and graphed using Kaplan-Meier curves, and confidence intervals based on the cumulative hazard were derived for 3 time points of the follow up: 5, 10 and 15 years since onset. Data were right-censored when no nephropathy event occurred throughout follow up or because of loss to follow up or death.

The effects of demographic-, clinical- and analytic-related variables on nephropathy were assessed through a 2-step procedure. First, univariate Cox-proportional regression models were fitted using the covariates as fixed variables (characteristics at diabetes onset) and as time-dependent variables (characteristics during follow-up). The proportional assumption implicit in the Cox-regression modelling was assessed using weighted residuals and, when violated, an interaction term with time was included in the models. The possible modifying effect of age group was also evaluated and, when appropriate, models were adjusted or stratified by age group. This step, which was complemented graphically with plots of the stratified cumulative incidence curves obtained with the Kaplan-Meier method, provided the signification of the covariates and the estimation of the hazard ratios. In the second step, a multivariate regression model was fitted with the variables that had turned out to be significant or marginally significant ($p<0.1$) in the previous step.

A p value of <0.05 was considered statistically significant. All analyses were performed using the R statistical package, v. 2.13 (R Foundation for Statistical Computing. Vienna, Austria).

Results

We followed 716 patients with type 1 diabetes from onset: 280 patients with onset younger than 15 years of age and 436 with onset older than 15. The mean (SD) follow up was 10.1 (5.3) years, ranging from 2 (those with onset in 2008) to 21 years (those with onset in

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