Atherosclerosis 245 (2016) 222–227

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

The paradoxical association of adiponectin with mortality rate in patients with type 2 diabetes: evidence of synergism with kidney function

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ARTICLE INFO

Article history:
Received 19 October 2015
Received in revised form
15 December 2015
Accepted 19 December 2015
Available online 22 December 2015

Keywords:
Adipokines
Renal dysfunction
Mortality
Type 2 diabetes

ABSTRACT

Background: The paradoxical relationship between high adiponectin and increased mortality, described in several clinical subsets, has been reported only once in type 2 diabetes (T2D) and only in selected elderly patients.
We investigated this relationship in unselected patients with T2D and, then, addressed its possible modulation by several demographic and clinical conditions, known to affect *per se* mortality rate.
Methods: Patients from the Gargano Mortality Study (GMS; N = 897, follow-up = 10.5 ± 3.7 years; 290 events) and the Foggia Mortality Study (FMS; N = 529, follow-up = 7.1 ± 2.5 years; 143 events), were investigated.
Results: For each SD adiponectin increase, HRs (95% CI) for all-cause mortality were 1.30 (1.19–1.43) in GMS, 1.43 (1.26–1.64) in FMS and 1.34 (1.24–1.45) in the combined studies. This association was independent of the possible confounding effect of demographics, adiposity measures, diabetes-related features, kidney function-related parameters and medications ($p = 9.34 \times 10^{-9}$). While no interaction was observed between adiponectin and sex, age, smoking habits, BMI, waist circumference, HbA1c, diabetes duration, micro-/macro-albuminuria and medications, a strong interaction was observed with GFR, with a significant adiponectin-mortality association observed in individuals with GFR≥ but not those with GFR < 60 ml/min/1.73 m^2; p for adiponectin-by-GFR status interaction = 2.13×10^{-6}).
Conclusion: This is the first study reporting a paradoxical association of adiponectin with all-cause mortality in a large sample of unselected diabetic patients and indicating that such counterintuitive effect is observed only among patients with preserved kidney function. Further studies are needed to address if the strong interwoven effect of adiponectin and GFR turns to be useful in improving previously validated tools for predicting mortality in T2D.

1. Introduction

The rate of mortality in patients with type 2 diabetes (T2D) is twice as much that in non-diabetic individuals [1]. This makes diabetes a leading risk factor for all-cause mortality worldwide (IDF Diabetes Atlas Update 2014) [2]. Unfortunately, the exact pathogenic mechanisms, underlying such increased risk are only partially understood [1], thus making it difficult to set up predicting and preventing strategies aimed at reducing mortality rate in T2D.

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http://dx.doi.org/10.1016/j.atherosclerosis.2015.12.026
0021-9150/

Adiponectin, a 244-amino acid protein secreted by adipocytes, despite its insulin-sensitizing, anti-inflammatory, and endothelial protective effects [3,4], is an independent positive predictor of all-cause mortality. Such paradoxical effect, which has been described in the general population [5–9] and in several clinical sets [10–21], has been reported only once in patients with T2D and only in the subset of elderly individuals [22].

To investigate whether the counterintuitive relationship between adiponectin and all-cause mortality is observed also in unselected patients with T2D and, if so, to address its possible modulation exerted by several demographic and clinical conditions, known to affect *per se* the risk of all-cause mortality, we analyzed data from over 1400 patients with T2D from central-southern Italy, followed over time for several years.

2. Materials and methods

2.1. The Gargano Mortality Study (GMS)

One thousand and twenty-eight patients with type 2 diabetes (ADA 2003 criteria) were consecutively recruited from November 1st, 2000 to September 30th, 2005 at the Endocrine Unit of IRCCS "Casa Sollievo della Sofferenza" in San Giovanni Rotondo (Apulia, central-southern Italy), for a study having all-cause mortality as the end-point [23–26]. The only exclusion criterion was the presence of poor life expectancy due to non diabetes-related disorders. This cohort was followed until 31st, December 2014. All-cause mortality was the only predetermined end point of this study. At follow-up, the vital status of study patients was ascertained by two authors, either by telephone interview with the patient or his/her relatives or by queries to the registry office of cities of residence. The last follow-up was carried out by queries to the Italian Health Card (http://sistemats1.sanita.finanze.it/wps/portal/portalets/cittadinots/ts).

Serum total adiponectin was measured in 897 participants (87.3%) constituting the eligible sample for the present analysis.

2.2. The Foggia Mortality Study (FMS)

One thousand one hundred and fifty-three patients with type 2 diabetes (ADA 2003 criteria) were consecutively recruited at the Endocrine Unit of the University of Foggia (Apulia, central-southern Italy) from 7th, January 2002 to 30th, September 2008 for a study having all-cause mortality as the end-point [23,27]. Also in this case, the only exclusion criterion was the presence of poor life expectancy due to malignancies. This cohort was followed until 31st, March 2015. All-cause mortality was the only predetermined end point of this study. At follow-up, the vital status of study patients was ascertained by two authors, either by telephone interview with the patient or his/her relatives or by queries to the registry office of cities of residence.

Serum total adiponectin was measured in 529 participants (45.9%), who constituted the eligible sample for the present analysis.

2.3. Examination at baseline

Clinical data were obtained from a standardized interview and examination. Body mass index (BMI) was calculated by dividing the weight (in kilograms) by squared height (in meters). Smoking habits, anti-hypertensive, anti-dyslipidemic, and glucose-lowering treatments were also recorded at the time of examination. No thiazolidinediones (TZDs) were ever used in these patients. Data regarding medications were confirmed by review of medical records. Individuals who reported smoking cigarettes regularly during the year before the examination were considered current smokers. Diabetes duration was calculated from the current age and the age at diagnosis of diabetes.

In the two studies, blood samples were collected between 8:00 and 9:00 AM after an overnight fast. Serum aliquots were stored at −80 °C.

Urinary albumin and creatinine concentrations were determined the same morning of the clinical examination on an early morning first-void sterile urine sample by the nephelometric method (Nephelometer Analyzer; Behring, Germany) and the Jaffe's reaction-rate method (737 Autoanalyser; Hitachi, Tokyo, Japan), respectively.

GFR was estimated (eGFR) by using the Chronic Kidney Disease Epidemiology Collaboration (CKD–EPI) formula [28].

2.4. Ethics

The study protocols and the informed consent procedures were approved by the Institutional Ethic Committee of Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) "Casa Sollievo della Sofferenza" and the University of Foggia, respectively. All participants gave written informed consent.

2.5. Measurement of circulating adiponectin levels

Serum adiponectin concentrations were measured by a commercial ELISA (Alpco, Salem, NH) at the Research Unit of Diabetes and Endocrine Diseases at "Casa Sollievo della Sofferenza", as previously described [29]. Inter- and intra-assay coefficients of variation were 7.0 and 6.6%, respectively.

2.6. Statistical methods

Patients' baseline characteristics are reported as mean ± SD and percentages for continuous and categorical variables, respectively.

In both prospective studies, the time variable was defined as the time between the baseline examination and date of the event (i.e. all-cause mortality), or, for subjects who did not experience any event, the date of the last available clinical follow-up. Incidence rates for the endpoint of interest were expressed as the number of new events per total number of person years (py). Univariate and multivariable Cox proportional hazards regressions analyses were performed to assess the association between adiponectin and the event occurrence. Risks were reported as HRs along with their 95% CI per SD increase in adiponectin levels.

Pooled data analyses were performed in an individual patient data meta-analysis fashion [30] (i.e. adjusting for "study sample"), after checking for heterogeneity (i.e. the presence or absence of a significant exposure-by-sample interaction).

Six separate models were evaluated and only covariates that were significantly related to the outcome or to adiponectin were included. The first model was adjusted only for "study sample" (i.e. GMS and FMS); in the second model demographics (i.e. sex, age and smoking habits) were added to the previous model; in the third model adiposity measures (i.e. BMI and waist circumference) were added to the second model; in the fourth model diabetes-related parameters (i.e. disease duration and HbA1c) were added to the third model (in this case, age was excluded from the analysis because of its collinearity with diabetes duration); in the fifth model kidney function parameters [i.e. albumin creatinine ratio (ACR) and eGFR] were added to the third model (in this case, sex and age, were excluded because both are already present in the CKD–EPI formula); finally, in the sixth model medications (i.e. glucose-lowering, anti-hypertensive and anti-dyslipidemic treatments) were added to the third model.