Contents lists available at ScienceDirect

Primary Care Diabetes

journal homepage: http://www.elsevier.com/locate/pcd

Original research

Sialic acid and incidence of hospitalization for diabetes and its complications during 40-years of follow-up in a large cohort: The Värmland survey

Payam Khalili[a,b,*], *Johan Sundström*[c], *Johan Jendle*[b,d], *Fredrik Lundin*[e], *Ingmar Jungner*[f], *Peter M. Nilsson*[b,g]

[a] *Department of Cardiology and Acute Internal Medicine, Central Hospital, Karlstad, Sweden*
[b] *Faculty of Health Sciences and Medicine, Örebro University, Örebro, Sweden*
[c] *Department of Medical Sciences, Uppsala University, Uppsala, Sweden*
[d] *Endocrine and Diabetes Center, Central Hospital, Karlstad, Sweden*
[e] *Statistical Unit, Värmland County Council, Karlstad, Sweden*
[f] *Department of Medicine, Clinical Epidemiological Unit, Karolinska Institute, Stockholm, Sweden*
[g] *Department of Clinical Sciences, Lund University, Skåne University Hospital, Malmö, Sweden*

ARTICLE INFO

Article history:
Received 3 July 2013
Received in revised form 9 May 2014
Accepted 3 June 2014
Available online 1 July 2014

Keywords:
Epidemiology
Diabetes mellitus
Inflammation
Population
Sialic acid

ABSTRACT

Aim: To examine the association of sialic acid (SA) with first recorded diabetes mellitus-related hospitalization.

Methods: From a population-based study in Värmland, Sweden, between 1962 and 1965, 87,035 men and women were selected and followed for first recorded diabetes-related hospitalization until 2005. The association of SA was calculated and stratified for gender by Cox's proportional hazards models. Adjustments were made for conventional risk factors and socioeconomic status. Association analyses were made for comparisons between SA-levels above and below median.

Results: The mean age was 47.2 (SD 13.0) years and the total numbers of incident diabetes-related hospitalizations in men and women were 3445 and 3273, respectively. Hazard ratios per one standard deviation of SA were 1.12 (95% CI: 1.08–1.17, $p < 0.0001$) in men and 1.17 (95% CI: 1.13–1.22, $p < 0.0001$) in women. Interaction analyses indicated a relatively higher SA-associated risk in women than in men with above median SA levels.

Conclusions: In this large population-based cohort followed for more than 40 years, elevated SA, as a marker of systemic inflammation, was independently associated with risk of diabetes and diabetes-related hospitalizations.

* *Corresponding author at*: Department of Cardiology and Acute Internal Medicine, Central Hospital, SE-652 30 Karlstad, Sweden. Tel.: +46 54 617 421; fax: +46 54 617 069.
E-mail addresses: payam.khalili@liv.se, payamkhalili@yahoo.com (P. Khalili).

http://dx.doi.org/10.1016/j.pcd.2014.06.002
1751-9918/

1. Introduction

Diabetes mellitus is associated with micro- and macrovascular complications, including the detrimental effect of hyperglycaemia and other cardiovascular risk factors. Chronic inflammation could play an important role for the development of these complications, as well as for hyperglycaemia and diabetes itself. Elevated inflammatory markers such as C-reactive protein (CRP), interleukin 6 (IL-6) and white cell count have been associated with features of the metabolic syndrome and the prediction of incident type 2 diabetes [1]. Among the various pathogenic features induced by metabolic abnormalities in diabetes, oxidative stress and increased inflammatory responses appear to be some of the first detectable abnormalities [2,3] that trigger several other mechanisms involved in diabetes-associated endothelial dysfunction. Inflammatory markers have previously been shown to predict incident type 2 diabetes in population-based studies, for example acute phase reactants such as CRP [4], and risk scores including various cytokines [5].

Sialic acid (SA) is the common name for biological compounds derived from neuraminic acid and occurs mainly as part of terminal positions of glycoprotein and glycolipid oligosaccharide side-chains. In humans, a large quantity of SA is found in inflammatory markers such as orosomucoid, α1-antitrypsin, haptoglobulin, ceruloplasmin, fibrinogen, complement proteins and transferrin [6]. SA has also been positively correlated to levels of tumour necrosis factor-alpha (TNFα), IL-6, and high sensitive-CRP (hs-CRP) [7]. Furthermore, increased levels of SA have been observed in various inflammatory disorders [8], malignancies [9], as well as cardiovascular disease [10] and diabetes [9]. In patients with established type 2 diabetes it has been suggested that complications are associated with increased SA levels [9]. Finally it has also been reported that SA levels decline during treatment with metformin [11].

In this large prospective, observational cohort study, with 40-years of follow-up, we hypothesized that increasing levels of SA is associated with the risk of diabetes-related hospitalization. Since various known biomarkers, such as hs-CRP and insulin improved the risk prediction for type 2 diabetes differently in women and in women [12,13] we also aimed to examine the biological interaction between SA and gender.

2. Subjects and methods

2.1. Study sample

During 1962–1965 a general health survey was carried out among residents of the geographical area of the county of Värmland as well as in a minor part of the county of Gästrikland, Sweden [14,15]. All inhabitants aged 25 years or older were offered a health examination, including measurement of blood pressure, height, and weight. Blood and urine tests were performed. The primary aim of the original survey was to detect pre-symptomatic disease in the general population.

In total 97,273 individuals underwent the baseline screening. No data on emigration during follow-up is available. To minimize the risk of bias when possible emigrants contribute with too long follow-up time, individuals were followed-up long-term until their 81st birthday. Additionally, as no data on previous diabetes or usage of drugs were available at screening we excluded individuals with incident diabetes events or diabetes-associated complications during the first five years of follow-up from further analyses in order to avoid potential influences by pre-existing diabetes and co-morbidities.

After exclusion of individuals with extreme data on blood pressure levels, SA, cholesterol, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), defined as outliers (>75th centile + 3 × interquartile range) or (<25th centile − 3 × interquartile range), and individuals with missing data on systolic blood pressure, diastolic blood pressure, SA, cholesterol and socioeconomic position, we finally included 42,639 men and 44,396 women.

2.2. Baseline examinations

The screening included measurement of blood pressure in the sitting position which was measured to the nearest 10 mmHg with a sphygmomanometer by use of an appropriate cuff, reflecting a simplified screening approach from the early 1960s. Height (m) and weight (kg) were measured in light in-door clothing, and body mass index (BMI; kg/m^2) calculated. Blood samples were drawn from non-fasting subjects and were chilled on ice during overnight transport to the central laboratory for analysis. All chemical analyses were run on the automated analytical laboratory (MEKALAB) in Stockholm. The SA concentration was analyzed by Svennerholm's method [16] and a modified Liebermann–Burchard's method described by Zak et al. [17,18] was used for the analyses of total cholesterol. AST and ALT were analyzed by a method described by Reitman and Frankel [19] and expressed in Karmen units (U) [20].

2.3. Follow-up procedures in national registers

Using the unique 10-digit personal identification number assigned to each Swedish citizen, we linked our cohort with national registers provided by the Swedish Board of Health and Welfare. Subjects have been followed up until end of 2005 for first non-fatal or fatal diabetes event treated in hospital, as diagnosed either as diabetes mellitus type 1, diabetes mellitus type 2 or as any diabetes related complication (based on International Classification of Disease: ICD 7th version; 260. 8th and 9th versions 250 and ICD 10th versions: E10–E11 and E13–E14). The total number of person-years at risk was 1,223,006 for men and 1,401,528 for women.

We also linked our cohort with data from the Swedish population and housing census in 1960 ("Folk- och Bostadsräkningen", FoB, Statistics Sweden) to obtain data on socioeconomic position. Subjects were stratified into social categories based on their occupation as: (a) non-manual workers at higher level, (b) non-manual workers at intermediate level, (c) non-manual workers at lower level, (d) farmers, (e) skilled and unskilled workers, or (f) others.