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Vagotomy and subsequent development of diabetes – A nested case–control study

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ABSTRACT

Background. Vagal signaling is involved in gastric emptying and the secretion and effect of a number of hormones regulating gluco-metabolic processes and, thus, crucial for metabolic homeostasis.

Purpose. We hypothesized that vagotomy would increase the risk of developing type 2 diabetes and examined the association between vagotomy and subsequent development of diabetes.

Methods. A nested case–control study was conducted with information on cases and controls from the Danish National Patient Registry. Cases included individuals with a diabetes diagnosis subsequent (>12 months) to the first registration of vagotomy and/or upper gastrointestinal disease in the period 1977–2011. Controls had no subsequent diagnosis of diabetes and were matched by incidence density sampling, age and gender. Logistic regression analyses were conducted.

Results. 501,724 diabetes patients and 1,375,567 matched controls were included in the analysis. Vagotomy was performed on 2772 individuals and 148,489 individuals had an upper gastrointestinal diagnosis. In this combined population, 30,902 were diagnosed with diabetes. The mean follow-up was 16 years. The unadjusted odds ratio for developing diabetes following vagotomy was 0.64 (95% confidence interval (CI): 0.58–0.71) and did not change in an adjusted analysis (0.64, 95% CI: 0.58–0.70). When restricting the multivariate-adjusted analysis to patients with type 2 diabetes and type 1 diabetes, respectively, the multivariate odds ratios were 0.79 (95% CI: 0.70–0.89) and 0.75 (95% CI 0.53–1.08), respectively.

Conclusion. Vagotomy was associated with a significantly decreased risk of developing type 2 diabetes in a population of patients with upper gastrointestinal disease.

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1. Introduction

The scientific and clinical interest in vagally targeted treatments of type 2 diabetes, e.g. transcutaneous vagus stimulation, is increasing [1,2]. Vagotomy was previously a common treatment for peptic ulcer. The primary types of vagotomy are full truncal vagotomy, in which both vagal trunks are resected, and super selective vagotomy, in which only the nerves supplying the fundus and body of the stomach are cut [3]. The vagus is the main nerve relaying parasympathetic signals. It plays an important role in the regulation of metabolic homeostasis via mechanisms including gastrointestinal, pancreatic, and hepatic processes [4]. Decreased and/or dysregulated vagal activity in obesity and comorbidities, e.g. type 2 diabetes, have been reported [4]. On the other hand, some evidence suggests that vagotomy and vagal blockade, respectively, may result in weight-loss and improved glycemic control in obese patients [5–7], but especially truncal vagotomy is complicated by dumping syndrome and diarrhea [8]. In rodent studies of obesity, vagotomy reduces diet-induced weight gain and reduces intra-abdominal fat [2]. Obesity is highly associated with metabolic syndrome [9,10] and insulin resistance [11].

Vagal afferents from the gastrointestinal tract and liver integrate nutritional, hormonal and metabolic signals to the brain, and vagal efferents innervate the liver, pancreas and the gastrointestinal tract [12,13]. As an example of this signaling pathway, the glucose-lowering and appetite-reducing hormone glucagon-like peptide-1 (GLP-1) is worth mentioning. GLP-1 is secreted into circulation from enteroendocrine L cells in the small intestinal epithelium in response to intraluminal content of nutrients. In addition to its endocrine signaling pathway, GLP-1 also activates intestinal vagal afferents relaying to the brain stem and, subsequently, vagal efferents to the pancreas and other target organs (e.g. the stomach where GLP-1 reduces gastric emptying) [14,15]. Thus, substrates in the gastrointestinal lumen elicit neuronal activation in vagal afferents and brain areas of satiety highlighting the role of vagus in the brain-gut axis [16–18]. An intact and functional vagus may, therefore, be crucial for metabolic homeostasis and other functions such as gastric emptying.

The objective of this nested case–control study was to examine the association between vagotomy and subsequent development of diabetes in a group of patients with upper gastrointestinal disease. We hypothesized that truncal vagotomy increased the risk of developing type 2 diabetes, whereas superselective vagotomy had a minor or no effect on the risk of developing diabetes.

2. Methods

A nested case–control design was used to investigate the association between vagotomy and development of diabetes. The study was conducted on a Danish population-based sample. In Denmark the entire population is assigned a civil registration number, which is a unique personal identifier that allows linkage between several registries [19]. From 1977 to 1995 all inpatient visits are registered in the Danish National Patient Registry among these also surgical procedures. From 1996, inpatient visits, outpatient visits, and emergency room contacts are registered in the Danish National Patient Registry. Diagnoses are coded as International Classification of Diseases (ICD) 8 in the period 1977–1993 and coded by ICD 10 from 1994 and forward. All ICD diagnosis codes used in this study are displayed in Supplemental Tables 1 and 2.

From Statistics Denmark, a cohort of diabetes patients (n = 501,724) was assembled based on prescription data from the Register of Medicinal Product Statistics and diagnoses from the Danish National Patient Registry. One-to-four controls for each diabetes patient (n = 1,375,567) were assigned. Non-diabetes patients who underwent vagotomy or had a previous diagnosis of ulcer, esophagitis, gastritis, or gastric reflux disease were selected as the final cohort and the first registration of these diagnoses was set as the index date. This cohort selection was performed to match the vagotomized patients. Vagotomy was defined as a surgical procedure code of 34310, 34820, 42620, 42621, 42680, 42681, 42720, 42740, 42742, 42744, 42749, or 44700 from the Surgical Procedures Classification (1977–1995) and as a surgical procedure code of KJDG from the Nordic Classification of Surgical Procedures (1996 and onwards). The selection process is depicted in Fig. 1.

Cases were individuals with a diabetes diagnosis subsequent to the first registration of vagotomy, ulcer, esophagitis, gastritis, or gastric reflux disease in the period 1977–2011. Diabetes was defined by ICD 8 and ICD 10 codes from the Danish National Patient Registry and also by the use of glucose-lowering drugs based on Anatomical Therapeutic Classification (ATC) codes (A10). The validity of the diabetes diagnosis in Denmark is high [20]. The ATC codes were extracted from the Register of Medicinal Product Statistics, which from 1994 and onwards has registered all prescribed medical products purchased by the Danish population.

All cases prior to the diagnosis of vagotomy, ulcer, esophagitis, gastritis, or gastric reflux disease were excluded. Furthermore, to avoid prevailing diabetes all cases within the first year of vagotomy, ulcer, esophagitis, gastritis, or gastric reflux disease were excluded.

Controls were individuals without a diagnosis of diabetes. Controls were matched four to one with cases based on the following parameters; analysis time (follow-up period), ten year age groups, and gender. The end of study was defined as the time of diagnosis of diabetes or the 31st of December 2011. Individuals were censored at date of emigration or death if applicable.

Data on comorbidities were obtained from the Danish National Patient Registry. A Charlson comorbidity index (CCI) was calculated for each case and control based on diagnoses before the end of study or censoring date. The CCI consists of major diseases and predicts ten year mortality [21]. We excluded ulcer, diabetes and diabetes with end-stage organ damage as items in the score as these constituted outcome measures and selection criteria. Furthermore, data on previous alcohol-related diagnoses, pancreatitis, hyperthyroidism, and hypothyroidism were collected.

2.1. *Statistical Analysis*

Unpaired T-test was performed to compare characteristics of cases and controls and a Bartlett's test was used to determine