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Abdominal aortic aneurysms – glycaemic status and mortality

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ABSTRACT

Aims: The prevalence of diabetes mellitus (DM) and mortality with respect to glycaemic status in patients with abdominal aortic aneurysms (AAA) was evaluated. Glycaemic status was assessed by an oral glucose tolerance test (OGTT) and by HbA_{1c}.

Methods: Sixty-six patients with AAA admitted to the vascular surgery unit for elective surgery between October 2006 and September 2007 were included. Seven patients had previously known DM. OGTT and HbA_{1c} results were available from 58 patients. The patients were categorized as having DM, prediabetes and normoglycaemia according to the WHO's and American Diabetes Association's criteria.

Results: The prevalence of newly diagnosed DM according to the OGTT and HbA_{1c} results were 12% and 14% respectively. Mean follow-up time was 68 months and all-cause mortality 43%. HbA_{1c} was an independent predictor for mortality in the DM category. Hazard ratio of all-cause mortality in the DM category defined by the HbA_{1c} values was 6.35, 95% [CI 1.49–27.1]; $p = 0.01$.

Conclusions: DM defined by $HbA_{1c} \geq 6.5\%$ is an important determinant of mortality following surgical treatment for AAA. Half the patients with AAA and DM were unaware of their DM diagnosis. All patients with AAA should be tested for DM using HbA_{1c}. The results should be confirmed in a larger prospective study.

1. Introduction

The diagnosis of diabetes mellitus (DM) is defined as either fasting plasma glucose levels (FPG) ≥ 7.0 mmol/L, and/or two-hour oral glucose tolerance test (OGTT) ≥ 11.1 mmol/L or an HbA_{1c} value of ≥ 48 mmol/mol (6.5%) (American Diabetes Association, 2010; World Health Organization, 2006).

Previous studies have revealed a higher DM prevalence in patients with peripheral arterial disease (PAD) (Astor, Softeland, Daryapeyma, & Jonung, 2010; Selvin & Erlinger, 2004) compared to general populations (Cowie et al., 2006; Midthjell & CMYLCPSC, 2010) and populations at risk of developing DM (Peter et al., 2011).

When comparing the diagnostic modalities for the diagnosis of DM (HbA_{1c} and the OGTT including FPG and/or 2 h-post glucose value), it has been shown that they to a significant degree define different individuals as having DM (Cowie et al., 2010; Doerr et al., 2011; Hjellestad, Astor, Nilsen, Softeland, & Jonung, 2013; Lauritzen, Sandbaek, Skriver, & Borch-Johnsen, 2011; Midthjell & CMYLCPSC, 2010; Peter et al., 2011; Rathmann et al., 2012). In a cohort of patients with peripheral arterial disease located in western Norway, the total prevalence of pathologic glucose metabolism was substantially higher when based on HbA_{1c} values than when based on the OGTT. The two parameters largely defined different patients with DM (Hjellestad et al., 2013). No studies could be found comparing the prevalence of DM by the two criteria in patients with abdominal aortic aneurysm (AAA).

Up to one third of patients with type 2 DM are unaware of their DM diagnosis (World Health Organization, 2006), and are therefore untreated and at high risk of developing vascular complications. Patients with AAA and DM defined by OGTT have a higher risk of complications and shorter long-term survival compared with AAA patients without known DM - although studies have reported inconsistent results (Theivacumar, Stephenson, Mistry, & Valenti, 2014). Further, the impact of DM and prediabetes on mortality in patients with AAA, based on the OGTT and the HbA_{1c} values, is not known.

It is of vital importance to inform about the high level of dysglycaemia in AAA patients to improve diagnostics and treatment of dysglycaemia and improve clinical outcome.

The aim of this study was to evaluate the prevalence of DM and prediabetes in AAA patients, and the mortality with respect to glycaemic status assessed by OGTT and HbA_{1c}.

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2. Methods

2.1. Patient Selection

This study was a prospective cohort study including patients with abdominal aortic aneurysms admitted for surgical treatment for their AAA. The initial study population consisted of 345 patients admitted consecutively to the vascular surgery unit for elective surgery between October 2006 and September 2007. The vascular pathologies were carotid stenosis, AAA, iliac occlusive disease and infrainguinal occlusive disease. Sixty-six of these patients had AAA, and were included in the present study. Seven patients had previously known DM. HbA_{1c} value was missing in one patient. An OGTT was performed on the remaining 58 patients and the results were included for further analysis. Fasting glucose and HbA_{1c} values were analyzed in all patients. The research protocol was approved by the Regional Committee for Medical Research Ethics (REK vest 14109).

2.2. Diagnostic Tests

An OGTT was performed on 58 patients. Fasting glucose and HbA_{1c} values were measured in all participants. The OGTT was performed by orally administering a standard dose of 75 g anhydrous glucose dissolved in water after a minimum of eight hours overnight fasting. Plasma glucose levels were measured in a fasting state prior to administering the anhydrous glucose and again two hours after administration. Venous whole blood, drawn in containers with glycolytic inhibitors (citrate and fluoride) and centrifuged within one hour from venous sampling to separate plasma, was used for the OGTT glucose measurements.

The OGTT plasma glucose levels were analysed using Modular P (Roche Diagnostics). The OGTT results were categorized into three groups according to the WHO 1999 criteria: 1/DM defined as fasting plasma glucose (FPG) ≥ 7.0 mmol/l and/or two-hour value (2-h-value) ≥ 11.1 mmol/l, 2/prediabetes, which consists of IGT defined as FPG < 7.0 mmol/L and a 2-h-value between 7.8 mmol/L and 11.1 mmol/L, and IFG defined as fasting glucose value between 6.1 mmol/L and 7.0 mmol/L with a normal 2-h-value and 3/normal glucose metabolism defined as FPG < 6.1 mmol/L and a 2-h-value < 7.8 mmol/L.

HbA_{1c} values were measured in all participants through a single blood sample using Variant II HPLC system (Biorad). The HbA_{1c} results were categorized as: DM, prediabetes and normoglycaemia. The diagnostic limit of HbA_{1c} is ≥48 mmol/mol (6.5%) according to the WHO statement of 2011. The American Diabetes Association definition of prediabetes at 39–46 mmol/mol (5.7–6.4%) was used since the WHO has not yet made a statement on the HbA_{1c} diagnostic range of prediabetes.

External quality assessment of all equipment used for analysis was performed by NOKLUS. NOKLUS is a national institution certified by The National Institute of Technology (NS-EN ISO 9001:2000), and run by a committee consisting of representatives from The Norwegian Health Ministry, The Norwegian Medical Association and The Norwegian Association of Local and Regional Authorities. NOKLUS is quality checked by The European Reference Laboratory for Glycohemoglobin in the Netherlands.

2.3. Other Variables

Information about age (continuous), sex (men/women), smoking habits (yes/no), aortic diameter (continuous), body mass index (BMI) (kg/m^2), state of anaemia (yes/no), reduced renal function (yes/no), coronary artery disease (yes/no), cerebrovascular disease (yes/no), established peripheral occlusive disease (yes/no) and medical treatment (the use of statins, platelet inhibitors and antihypertensive medication) (yes/no) at time of inclusion was obtained from the patients' medical records. The presence of reduced renal function was defined based on estimated glomerular filtration rates (eGFR), calculated by The Modification of Diet in Renal Disease Equation.

Surgical treatment for AAA was either open surgery or an endovascular procedure. Patients with high age and comorbidities were more likely to be treated with an endovascular procedure while younger patients and patients without comorbidities were more likely to be treated with open surgery.

2.4. End Points and Follow-Up

The study was closed on the 11th of August 2014. Mean follow-up time of the study population was 71 months [range: 0–100]. Follow-up time for each participant was defined as the number of months from the date of surgical intervention to the date of death, or to the date of study closure. Mortality rates were verified by the Norwegian civil registry. The primary end point was death of all cause.

2.5. Statistical Analysis

Data were analysed using R version 3.2.1 (R Core Team, 2015) software for Windows. All p values were 2-sided, and values <0.05 were considered statistically significant. The data were presented as mean ± standard error for continuous data, and as number and percentage for categorical data. Associations between categorical variables were analysed using χ^2 test. When the expected number of observations in one or more categories was ≤ 5, the Fisher's exact test was used. The Kaplan–Meier survival function was used to describe the percentage of survivors since study inclusion. To test for difference in survival functions across glycaemic categories based on both the OGTT and the HbA_{1c} value, the log-rank test was used.

Associations of OGTT and HbA_{1c} glycaemic categories with all-cause mortality were further estimated as hazard ratios with 95% confidence intervals (CIs) using Cox regression models. The time from study inclusion until death was used as the measure of event free time. All patients were monitored until censoring with 11th of August 2014 as the final day of follow-up. The hazard ratios were estimated by crude models as well as after controlling for age, platelet inhibitor and statin. The three covariates were selected among 11 covariates, measured at study inclusion, by using a stepwise method stated in literature (Collet, 2015). The covariates initially explored were age, the use of platelet inhibitor, BMI, sex, hypertension, reduced renal function, coronary artery disease, smoking status, the use of statin, the use of antihypertensive medication and established peripheral occlusive disease. Based on a test and inspection of scaled Schoenfeld residuals, it was verified that the proportional-hazards assumption was fulfilled for all variables in the final models.

3. Results

Baseline characteristics of all participants are presented in Table 1. The study population was an elderly population with a high prevalence of comorbidities. The majority of the participants were former or current smokers. Patients who died during follow-up had significantly higher age and more often a history of cerebrovascular disease at baseline. They were more likely to be treated with an endovascular procedure than open surgery in comparison with patients who were alive at end of the study.

3.1. Glycaemic Status

The prevalence of newly diagnosed DM, prediabetes and normoglycaemia, in patients with AAA is summarized in Table 2. The HbA_{1c} criteria and the OGTT results largely classified different patients as having newly diagnosed DM. The total prevalence of DM in this