Institutionen för molekylär medicin och kirurgi,
Karolinska Institutet
Kärlkirurgiska kliniken, Karolinska Universitetssjukhuset

Diabetes and Peripheral Arterial Disease

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Rehabsalen, Norrbacka S2:01, Karolinska Universitetssjukhuset

Fredagen den 30 november 2012, kl 09.00

av

Jonas Malmstedt
Bitr överläkare

Huvudhandledare:
Professor Jesper Swedenborg
Karolinska Institutet
Institutionen för molekylär medicin och kirurgi

Bihandledare:
Docent Gun Jörneskog
Karolinska Institutet
Institutionen för kliniska vetenskaper
Danderyds sjukhus

Professor Kerstin Brismar
Karolinska Institutet
Institutionen för molekylär medicin och kirurgi
Enheten för tillväxt och metabolism

Professor Eric Wahlberg
Linköpings universitet
Institutionen för medicin och hälsa

Fakultetsopponent:
Professor Mauri Lepäntalo
University of Helsinki, Finland
Faculty of Medicine, Department of Vascular Surgery

Betygsnämnd:
Docent Anna Norhammar
Karolinska Institutet
Institutionen för medicin
Enheten för kardiologi

Docent Bengt Lindblad
Lunds universitet,
Institutionen för kliniska vetenskaper
Enheten för kärlsjukdomar

Docent Lisa Juntti-Berggren
Karolinska Institutet
Institutionen för molekylär medicin och kirurgi
Enheten för signaltransduktion

ABSTRACT

Background: Diabetes mellitus increases the risk for peripheral arterial disease (PAD) early in life and the disease is likely to progress to advanced stages. Mechanisms responsible for premature PAD in diabetes are partly unknown. Leg ischaemia from PAD, together with other diabetic complications, is the key player in the pathway from ulceration to gangrene and infection, which ultimately results in major amputation. Infrainguinal bypass surgery (IBS) is carried out to restore leg perfusion and avoid amputations. Whether outcomes for this procedure are less favourable in patients with diabetes than in patients without diabetes is unclear.

Aims:

–To explore the impact of hyperglycaemia on outcome after IBS in patients with diabetes.

–To assess amputation-free survival (AFS) after IBS for critical limb ischaemia.

–To assess amputation-free survival (AFS) in patients with diabetes but without PAD during long term follow up.

–To investigate if receptor for advanced glycation end products (RAGE) and advanced glycation end products (AGE) are increased in plasma and vein grafts in diabetes patients.

–To investigate if the AGE-RAGE system predicts AFS and development of PAD, and if it is associated with AFS after IBS in patients with diabetes.

Results: In **Paper I**, we demonstrated an association between hyperglycaemia the first 48 hours after IBS and increased risk for wound complications, graft occlusion and amputation or death during the first 3 months in 91 patients with diabetes. Patients in the highest quartile of glucose exposure had an odds ratio of 13–14 in multivariate logistic regression.

In **Paper II**, we performed a nationwide, population-based cohort study and compared postoperative AFS in patients with and without diabetes. The analysis included data for 1 840 patients from the Swedish Vascular Registry who, during 2001–2003, underwent their first unilateral, below-knee, IBS procedure for critical limb ischaemia. Of these patients, 742 had diabetes and 1,098 did not. Patients were followed up until the end of 2005. Overall, 446 and 558 patients with and without diabetes, respectively, had undergone ipsilateral amputation or died by the end of the follow-up period. Patients with diabetes had a shorter AFS than patients without diabetes (2.3 years, 95% CI 1.9–2.8 years versus 3.4 years, 95% CI 3.1–3.7 years). The hazard ratio and incidence for ipsilateral amputation or death in patients with diabetes, adjusted for age, sex, smoking and other confounding variables, was 1.46 (95% CI 1.26–1.69) and 30.2 events per 100 person-years respectively. The incidence of amputation or death was 2.8 per 100 person-years, (95% CI 2.0 to 3.7) in the cohort of patients with type 2 diabetes who were free from PAD at start of follow up.

In **Paper III** and **IV** we showed that S100A12, a ligand to RAGE, is associated with AFS after IBS in patients with (n=38) and without (n=30) diabetes, and with AFS as well as development of PAD in a prospective longitudinal (10-year) population-based cohort (n=146) of patients with type 2 diabetes, free from signs of PAD at inclusion. Presence of AGE, RAGE and S100A12 were demonstrated in saphenous vein tissue with no difference between patients with and without diabetes.

Conclusions: Postoperative hyperglycaemia is associated with unfavourable outcome after IBS in patients with diabetes. Diabetes is associated with lower AFS after IBS for critical limb ischaemia. Plasma levels of S100A12 and RAGE components are elevated in PAD disease and markers of RAGE and its ligands are found in vein tissue used for bypass. This is consistent with a role for S100A12 in PAD complications by activation of the RAGE system. Higher plasma levels of S100A12 and the combined effect of RAGE components seem to be associated with AFS in patients with diabetes. Further study is needed to find methods of reducing this excess risk and prolonging AFS.

ISBN 978-91-7457-936-9