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Prognostic significance of coronary flow reserve during acute hyperglycaemia
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Background: Although acute hyperglycaemia, including postprandial hyperglycaemia, attenuates vascular endothelial function independent of diabetes mellitus (DM), clinical implication of changes in coronary flow reserve (CFR) during acute hyperglycaemia remains unclear. This present study was conducted to evaluate the significance of changes in CFR during acute hyperglycaemia as a long-term predictor of acute coronary syndrome (ACS) in patients without DM.

Methods: Using transcranial Doppler echocardiography, we analyzed change in CFR before and 1 hour after an oral glucose loading in 62 non-DM patients (mean age: 58 years) during the periods of 2002 to 2004. HbA1c of all patients were less than 6.5%. CFR measurement was performed at the left anterior descending coronary artery or right coronary artery as the target vessels without any significant coronary stenosis. Patients with valvular disease, atrial fibrillation, artificial pacemaker, coronary artery bypass grafting, significant left ventricular (LV) hypertrophy, and chronic kidney disease (serum creatinine > 1.5 mg/dl) were excluded. Cox proportional hazards models were used to assess the risk of ACS caused by vascular events on the target vessels with adjustments for age, gender, use of anti-hypertensive medicines, use of statin, history of coronary intervention for the non-target vessels, body mass index, smoking, HbA1C, HOMA-R assessing insulin resistance.

Results: During a mean of 7.3 years of follow-up, 7 ACS (11.2%) occurred, CFR before a glucose loading (c-CFR: p=0.03, HR=1.98, 95% CI 1.04-0.68) and CFR after a glucose loading (a-CFR: p=0.01, HR=0.88, 95% CI 0.01-6.00) were significantly associated with incidence of ACS. Although both a-CFR (a-CFR: p=0.01, HR=0.88, 95% CI 0.01-6.00) and a-CFR were significantly associated with incidence of ACS after adjusting age and gender (model 1), its association was not observed by adding a use of anti-hypertensive medicines, a use of statin, and a history of coronary intervention (model 2). On the other hand, a-CFR was associated with incidence of ACS in the model 1 (p=0.01, HR=0.89, 95% CI 0.01-6.56) and model 2 (p=0.05, HR=0.80, 95% CI 0.01-2.06). In addition, after its association was preserved after adding body mass index, smoking, HbA1C, and HOMA-R (model 3: p=0.03, HR=0.004, 95% CI 0.00-0.65), and b-CFR (model 4: p=0.08, HR=0.003, 95% CI 0.00-0.95). Conclusion: CFR after glucose loading was an independent predictor for ACS on the target coronary artery amongst non-DM individuals. Impairment of CFR after acute hyperglycaemia might be a strong predictor of coronary events on the target vessels.

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Impaired arterial wall properties in patients with diabetic retinopathy: the role of inflammation
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Purpose: Diabetes Mellitus is associated with endothelial dysfunction and arterial stiffness. Diabetic Retinopathy (DR) is a complication of diabetes mellitus (mean age 65±y) healthy subjects. Patients with diabetes mellitus were divided in those with DR (53 subjects, mean age 68±9y) and those with no evidence of DR (NDR) (mean age 66±8y) healthy subjects. Patients with diabetes mellitus were divided in those with DR (53 subjects, mean age 68±9) and those with no evidence of DR (NDR) (mean age 66±6y). An ophthalmologist made the diagnosis of DR by ophthalmoscopy after pupillary dilatation. Endothelial function was evaluated by flow-mediated dilation (FMD) in the brachial artery, carotid-femoral pulse wave velocity (PWV) was measured as an index of arterial stiffness and augmentation index (AIx) as an index of reflected waves. Creatinine clearance was estimated based on MDRD formula, serum C-reactive protein levels and interleukin 6 (IL-6) levels were measured as markers of inflammatory status while glycosylated hemoglobin was used to evaluate adherence to treatment.

Results: Although there were no significant differences in sex, age and mean arterial pressure, ANOVA revealed that patients with DR compared to NDR patients and healthy subjects had impaired FMD (3.47±1.12% vs. 5.55±1.29%, p<0.001), I-85 ppm/sec (9.20±2.06/min/sec vs. 8.77±1.94/min/sec, p=0.001) and increased AIx (27.97±7.93% vs. 23.32±7.87%, p=25.47±2.88%, p=0.02). Interestingly, in diabetes mellitus subjects FMD was inversely correlated with IL-6 levels (r=-0.35, p<0.01). C-reactive protein levels were correlated with glycosylated hemoglobin (r=0.39, p=0.001) and positively correlated with creatinine clearance (r=-0.38, p=0.001). Moreover, DR compared to NDR subjects had impaired creatinine clearance (77.91±22.16 min/1.6 l vs. 86.83±18.97 min/1.6 l, p=0.04), glycosylated hemoglobin (7.40±0.85 g/dl vs. 6.02±0.60 g/dl, p=0.001) and log C-reactive protein levels (0.39±0.56 mg/dl vs. 0.11±0.50 mg/dl, p=0.01).

Conclusion: This study showed that DR patients have significantly impaired endothelial function and increased arterial stiffness compared to NDR patients and to healthy subjects. Moreover, the inverse association between vascular function, inflammatory status, renal function and adherence to treatment confirms the role of inflammation as the connective mechanism between diabetes progression, endothelial dysfunction and DR.

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Adverse epigenetic remodelling of p66Shc gene correlates with persistent endothelial dysfunction and oxidative stress in type 2 diabetics with optimal glycemic control
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Purpose: Hyperglycemic memory may explain why optimal glycemic control (OGC) has failed to improve cardiovascular outcomes in patients with diabetes. We recently reported that epigenetic regulation of the mitochondrial adaptor p66Shc, critically involved in oxidative stress, accounts for persistent endothelial dysfunction in diabetic mice with OGC. In the present study we hypothesise that p66Shc may be a determinant of vascular hyperglycemic memory in patients with type 2 diabetes.

Methods: 7 patients with newly-diagnosed type 2 diabetes (T2DM) and 7 age- and sex-matched healthy controls were studied (46±3 vs. 42±7 years, p=NS). After the enrolment, T2DM patients were assigned to OGC for 6 months with hypoglycaemic agents or insulin. Glycated haemoglobin (HbA1c) and continued urinary C-reactive protein (Cp) were used as markers of oxidative stress. Flow-mediated vasodilation (FMD) of the brachial artery was performed to assess endothelial function at baseline and follow up. Urinary levels of 8-isoprostaglandinF2α (8-isoPGF2α) were measured as a marker of oxidative stress. p66Shc mRNA expression and promoter-related epigenetic changes were assessed from peripheral blood monocytes. Acetylation of histones binding p66Shc promoter was determined by chromatin immunoprecipitation (ChIP) and methylation of CpG dinucleotides by real time PCR.

Results: HbA1c significantly differ in T2DM before and after OGC (9.4±2 vs. 9.1±1, p<0.001). Continuous blood glucose monitoring confirmed the restoration of a euglycaemic state (235±26 vs. 131±28 g/dl, p<0.05). As compared with controls, T2DM patients showed blunted FMD (6.8±1.9 vs. 8.6±1.4%, p<0.005), increased urinary 8-isoPGF2α levels (295±100 vs. 33±19 pg/ml, p=0.05) and p66Shc gene upregulation (0.18±0.06 vs. 0.05±0.03 AU, p<0.001). However, OGC did not rescue endothelial function (FMD 6.8±1.7), neither oxidative stress (292±8.54 pg/mI vs p66Shc upregulation 0.22±0.10, p=NS vs baseline). T2DM patients showed lysine 14 acetylation of histone 3 binding p66Shc promoter as well as hypomethylation of CpG dinucleotides, two critical epigenetic markers favouring p66Shc overexpression. Interestingly, these epigenetic changes remained despite OGC and significantly correlated with persistent endothelial dysfunction and oxidative stress.

Conclusions: Epigenetic regulation of p66Shc gene may contribute to the residual burden of vascular disease in T2DM patients with OGC.