distance, ejection fraction, number of involved arteries, triglycerides, cholesterol, LDL, fibrinogen, D-dimers, antithrombin III, protein S and C, creatinin, glycaemia, histories of myocardial infarction, stroke, diabetes, arterial hypertension and previous revascularization, as well as number of other concurrent diseases.

We developed Cox-proportional model for identification of variables, associated with cardiovascular events, and multivariate regression model to define the predictors of mortality.

Results: We registered 126 cardiovascular events during three years follow-up(incidence of 0,05% for fatal and 0,57% for non-fatal events). Hazard ratios for cardiovascular events onset were: 1,07 for plasma level of fibrinogen (4,92+1,22 g/L), 2,55 for plasma value of D-dimers (983+315 μg/L) and 1,01 for protein S activity (61,2%+33,9%). Mortality of 6,67% was found in patients with diabetic polyvascular disease.

The variables independently associated with mortality found by multivariate analysis were fibrinogen (r = 0,21, p 0,02, score 2,78), D-dimers (r = 0,94, p 0,01, score 17,24) and ankle-brachial index (r = 0,40, p 0,03, score 4,84).

Conclusions: The reported data demonstrated that plasma levels of fibrinogen and D-dimers are independent predictors of a significant higher mortality risk in patients with diabetic polyvascular disease.

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KRÜPPEL-LIKE FACTOR 5 IS A KEY TRANSCRIPTION FACTOR OF ADIPOCYTE DIFFERENTIATION. Yumiko Oishi, Iciro Manabe, Kensuke Tsushima, Takayuki Shindo, Toshimasa Yamauchi, Kazuyuki Tobe, Takashi Kadowaki, Ryozo Nagai. *Department of Cardiovascular Medicine, University of Tokyo, Bunkyo, Tokyo, Japan, Department of Cardiovascular Medicine, Department of Clinical Bioinformatics, University of Tokyo, Bunkyo, Tokyo, Japan, Department of Metabolic Diseases, University of Tokyo, Bunkyo, Tokyo, Japan.*

Krüppel-like transcription factor5 (KLF5) is a zinc finger transcription factor that plays a pivotal role in pathogenesis of cardiovascular diseases, such as atherosclerosis and cardiac hypertrophy. Interestingly, KLF5 heterozygous knockout mice showed a significant reduction in the mass of white adipose tissue. In this study, we investigated the role of KLF5 in adipocyte differentiation. KLF5 was expressed during the early stages of adipocyte differentiation of 3T3L1 preadipocytes. Constitutive overexpression of the wild-type KLF5 resulted in enhanced adipocyte differentiation of 3T3L1, while the dominant negative KLF5 inhibited differentiation. Of particular note, KLF5 overexpression alone promoted spontaneous adipocyte differentiation of 3T3L1 without the humorous stimuli. Moreover, mouse embryonic fibroblasts (MEF) obtained from KLF5+/− embryos showed much reduced adipocyte differentiation. These data clearly indicate that KLF5 is required for adipocyte differentiation. Several transcription factors including C/EBP and PPAR-gamma have been shown to be involved in adipocyte differentiation. Therefore, we investigated the interplay between KLF5 and these factors. The dominant negative KLF5 inhibited expression of PPAR-gamma2, whereas wild-type KLF5 induced PPAR-gamma2 expression in 3T3L1, indicating that KLF5 resides upstream of PPAR-gamma2. In reporter assays, KLF5 and C/EBP cooperatively transactivated the PPAR-gamma2 promoter, suggesting that KLF5 directly controls the PPAR-gamma2 transcription. We also found that the KLF5 gene expression was controlled by C/EBP. Taken together, KLF5 is a key factor in the transcription factor network that orchestrates adipocyte differentiation. KLF5 may be involved in pathogenesis of vascular diseases by not only directly controlling function of SMCs, but also by mediating the interaction between adipocytes and blood vessels.

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CANDESARTAN TREATMENT RESTORES DIABETES-INDUCED CHANGES IN [CA2+]I TRANSIENTS OF CARDIOMYOCYTES. Semir Ozdemir, Mehmet Ugur, Hakan Gürdal[1], Belma Turan. *Departments of Biophysics, [1]Pharmacology and Clinical Pharmacology, Ankara University.*

Experimental diabetes is known to be associated with a cardiomyopathy, which occurs even in the absence of vascular complications. Slowing of cardiac muscle contractions and relaxations in association with altered kinetics of intracellular Ca2+ ([Ca2+]i) transients have been reported. The aim of this study was to investigate possible role of AT1 receptors in diabetes-induced changes in the kinetics of [Ca2+]i transients and contractile activity of cardiac muscle. Our results showed that treating diabetic rats with AT1 blocker candesartan-cilexetil (5 mg/kg/day for 4 weeks) restored altered kinetics of [Ca2+]i transients in cardiomyocytes, and altered kinetics of relaxation in papillary muscle. We also showed that incubation of cardiomyocytes from diabetic rats with a protein kinase C (PKC) inhibitor bisindolylmaleimide I (BIM) had a similar effect to candesartan treatment on [Ca2+]i transients. These results indicate that AT1 receptors may contribute to diabetes-induced alterations in [Ca2+]i transients and also to cardiac muscle contractions. This action of AT1 receptors may be linked to activity of PKC.

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TISSUE-SPECIFIC EFFECT OF FATTY ACIDS ON INSULIN SENSITIVITY: EVIDENCE THAT FATTY ACIDS, OLEATE AND PALMITATE, INDUCE MUSCLE INSULIN RESISTANCE BUT HAVE NO EFFECT ON HEPATIC INSULIN SENSITIVITY. Rafik Ragheb, Khosrow Adeli, George Fantus. *University of Toronto, Hospital for Sick Children and Hospital Health Network, Toronto, Ontario, Canada, Hosital for Sick Children, Toronto, Ontario, Canada, Mount Sinai Hospital, Toronto, Ontario, Canada.*

Introduction: The insulin signaling system is complex, and a common mechanism to explain the occurrence of acute and chronic insulin resistance is difficult to identify. There is a strong correlation between insulin resistance and the increased lipid availability in the tissue.

Rationale/hypothesis: Increased fatty acid flux has been suggested to be strongly associated with insulin resistant states such as obesity and type 2-diabetes, however the underlying mechanisms are currently unknown. Increased lipid is a primary factor in the activation of defined signaling mechanisms that reduces insulin action in muscle, adipose and liver cells. Our general objective is to define mechanisms through which fatty acids induce insulin resistance in muscle and liver models. We will investigate: (i) the molecular mechanisms by which oleate and palmitate as an example reduce the insulin sensitivity and eventually lead to insulin resistance development in both muscle and liver treated cells. (ii) dissecting the signaling components that participate in the development of insulin resistance by free fatty acids (FFAs). (iii) if there is an effect for FFAs upon insulin signaling in the liver, we will further study the effect of both FFAs and insulin on hepatic lipoprotein metabolism. One of the fundamental defects in insulin resistant patients is metabolic dyslipidemia found in large part due to enhanced VLDL (very low density lipoprotein) secretion by liver and hypertriglyceridemia.

Experimental Approach: To test our hypothesis, we will first investigate FFAs-induced insulin resistance in muscle cell line as well as primary hamster hepatocytes. Two FFAs will be used in the experiments to induce insulin resistance in this system. The mono-unsaturated FFA oleate (18:1n9) and the saturated FFA palmitate (16:0), which are among the