

Overall research theme:

## Studies of the relation between endothelial dysfunction, diabetes and atherosclerosis

Latest update:

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Characteristics of the research group:

This research group has activities within the fields of controlled clinical, clinical epidemiology and basic research. Activities in several fields is a deliberate decision aimed at improving the chance of allowing original combinations of methods and ideas to surface. Within basic research the group has for 4 years focused on endothelial dysfunction in diabetes. Basically this group studies endothelial function in healthy people exposed to interventions relevant to diabetes as well as diabetic patients exposed to interventions relevant to cardiovascular function. Lately we have taken up the technique of measuring proteins in the insulin signalling cascade in vascular tissue from subcutaneous fat biopsies.

Running projects: Titles and abstracts:

### **Effect of Anti-tumor necrosis factor alpha on endothelial function, insulin resistance and vascular insulin signaling in patients with type 2 diabetes**

Studies from this groups has demonstrated that infusion of tumor necrosis factor alpha inhibits insulin stimulated endothelial function. Tumor necrosis factor alpha is elevated in patients with type 2 diabetes and may be part of the explanation for insulin resistance. Therefore patients with type 2 diabetes are given a course of anti-tumor necrosis factor treatment (eterncept) and before/after endothelial function, insulin stimulated endothelial function, vascular insulin signaling and hyperinsulinaemic euglycemic clamp are studied. A control group serves as time-control.

### **Effect of ACE inhibition on endothelial function, insulin stimulated endothelial function, thrombocyte aggregation and plasminogen activator inhibitor**

Angiotensin Converting Enzyme (ACE) inhibition protects patients with diabetes against future cardiovascular events, but the reason is not well described. This study aims at elucidating some of the potential mechanisms. An ACE inhibitor can improve endothelial function and we will study whether this directly causes reduced thrombocyte aggregation after intraarterial infusion. We speculate that improved release of NO to the blood stream will influence thrombocytes and render them less prone to aggregation. We will further study how short term and long term ACE inhibition changes insulin stimulated endothelial function, plasminogen activator inhibitor concentration in blood as well as expression of protein and RNA in vascular tissue from a fat biopsy.

### **Effect of exercise and rapid acting oral hypoglycemic treatment on postprandial**

## **endothelial dysfunction in patients with type 2 diabetes**

Postprandial hyperglycemia is an independent risk factor for morbidity in patients with type 2 diabetes. Elevation in blood glucose following a meal or an OGTT causes transient endothelial dysfunction in healthy subjects an effect that is more pronounced in patients with type 2 diabetes. There is increasing indication that specific intervention against postprandial elevations in blood glucose may be relevant. Exercise and tight glucose control both reduce the atherosclerotic in patients with diabetes. We speculate that the beneficial effect of exercise and tight control may be partly mediated by reduction of postprandial hyperglycemia. Thus groups of patients with diabetes are exposed to no change, a vigorous exercise program for 8 weeks or tight glucose control. Before and after we measure endothelial function in the morning and 1,2 and 4 hours after an oral glucose load.

*Recent publications related to the projects described above:*

### Printed

1. Rask-Madsen C, Ihlemann N, Kober L, Torp-Pedersen C. Endothelial Function Is Insulin Resistant in Patients with Type 2 Diabetes and Ischemic Heart Disease. *DIABETES* 2000;49((Suppl 1)):1017.
2. Rask-Madsen C. Effect of insulin therapy on endothelial function and insulin-stimulated endothelial function in patients with type 2 diabetes and ischemic heart disease. PhD Thesis, University of Copenhagen, Denmark; 2002.
3. Ihlemann N, Stokholm KH, Eskildsen PC. Impaired vascular reactivity is present despite normal levels of von Willebrand factor in patients with uncomplicated Type 2 diabetes. *Diabet.Med.* 2002;19(6):476-481.
4. Madsen, C. R. and C. T. Torp-Pedersen (2002). "[Endothelial dysfunction in metabolic syndrome and the significance of exercise]." *Ugeskr Laeger* **164**(16): 2142-5.

### Submitted

1. Hermann T, Rask-Madsen C, Ihlemann N, Dominguez H, Jensen C, Storgaard H, Vaag A, Kober L, Torp-Pedersen C. Normal insulin-stimulated endothelial function and impaired insulin-stimulated muscle glucose uptake in young adults with low birth weight. *Diabetologia* 2002;Submitted.
2. Rask-Madsen C, Dominguez H, Ihlemann N, Hermann T, Kober L, Torp-Pedersen C. Tumor necrosis factor- $\alpha$  inhibits insulin's stimulating effect on glucose uptake and endothelium-dependent vasodilation in humans. Submitted to *Circulation*.
3. Ihlemann N, Hermann T, Rask-Madsen C, Dominguez H, Jensen C, Storgaard H, Vaag A, Kober L, Torp-Pedersen C. Tetrahydrobiopterin prevents endothelial dysfunction following an oral glucose test. Submitted to *Circulation*.
4. Ihlemann N, Hermann T, Rask-Madsen C, Dominguez H, Jensen C, Storgaard H, Vaag A, Kober L, Torp-Pedersen C. Endothelial function and insulin stimulated endothelial function in patients with ischemic heart disease. Submitted to *American Journal of Cardiology*.