Regulation of LPL in patients with the metabolic syndrome

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1) To asses heparin-induced LPL release curves in patients with the Mets 2) To determine differences in gene expression of LPL, GPIHB1 and ANGPTL4 in muscle and adipose tissue of patients with the MetS compared to health controls3) To determine...

Ethical review	Approved WMO
Status	Pending
Health condition type	Coronary artery disorders
Study type	Observational invasive

Summary

ID

NL-OMON34217

Source
ToetsingOnline

Brief title
LPL and MetS

Condition

- Coronary artery disorders
- Lipid metabolism disorders

Synonym
fat in blood, high cholesterol

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: GPIHBP1, LPL, Metabolic syndrome, Triglycerides

Outcome measures

Primary outcome

Differences between cases and controls for:

Plasma cholesterol, triglycerides, LDLc, HDLc, apoAI, apoB, apoCII, apoE,

apoCIII, ApoAV and ANGPLT 3 and 4

mRNA expression and protein concentration of LPL, GPIHBP1 and ANGPTL4 in

adipose tissue

mRNA expression and protein concentration of LPL, GPIHBP1 and ANGPTL4 in muscle

tissue

Histological examination of adipose tissue using antibodies against LPL,

GPIHBP1 and ANGPTL4.

Histological examination of muscle tissue using antibodies against LPL, GPIHBP1

and ANGPTL4

Secondary outcome

not applicable

Study description

Background summary

Recently, elevated plasma triglycerides (TG) have been shown to be an independent risk factor for cardiovascular disease (CVD). However the etiology of hypertriglyceridemia is complex and poorly understood. It is well known that lipoprotein lipase (LPL) plays a crucial role in hydrolysis of triglyceride-rich lipoproteins. More recently a new endothelial cell protein, glycosylphosphatidylinositol-anchored high density lipoprotein*binding protein

1 (GPIHBP1) has been identified as a platform for LPL binding at the endothelial cell surface. LPL action requires GPIHBP1 but is also modulated by several plasma proteins including ApoCII, ApoCIII, ApoAV and ANGPTL4. To date, the interaction between these proteins and GPIHBP1 and LPL in humans is largely unknown.
Hypertriglyceridemia is a common feature in patients with the metabolic syndrome (MetS) but the underlying mechanism is not completely understood. We propose that impaired LPL action is contributing significantly to the hypertriglyceridemic state often observed in patients with MetS.
In the current study we aim to improve our understanding of how LPL action is impaired in these patients. We will study tissue concentrations of LPL and GPIHBP1 and release kinetics of LPL in patients with the Mets. LPL resides in different compartments which may affect the time span of LPL release. LPL, bound to GPIHBP1 at the endothelial cell surface will be directly involved in TG hydrolysis and will be quickly released after a heparin bolus. We are also interested in testing that LPL localized in the subendothelial space will not be readily available for lipolysis and will have slower release kinetics in patients with MetS as it was found in a patient with GPIHBP1 deficiency. Thus a heparin-induced LPL release curve will reflect GPIHBP1 function and will provide valuable information on LPL action in vivo. We hope that detailed insights into the molecular mechanisms involved in LPL action may reveal novel targets for future treatment therapy focused on increasing LPL action and thus improving TG homeostasis and reduce CVD risk.n the current study we aim to test the hypothesis that LPL function is impaired in patients with the metabolic syndrome compared to healthy controls.

Study objective

1) To asses heparin-induced LPL release curves in patients with the Mets
2) To determine differences in gene expression of LPL, GPIHB1 and ANGPTL4 in muscle and adipose tissue of patients with the MetS compared to health controls
3) To determine differences in expression of LPL, GPIHB1 and ANGPTL4 in muscle and adipose tissue of patients with the MetS compared to health controls

Study design

This study will be a cross-sectional, case-control study

Study burden and risks

Patients and controls will visit the AMC in Amsterdam on 2 separate occasions for a time period of 30 minutes and 2 hours respectively. Subjects should fast overnight prior to both visits. During the screenings visit 12 millilitres of blood will be drawn of which no side effects are to be expected. Patients on lipid lowering drugs will be asked to discontinue treatment 4 weeks prior to the study visit. Discontinuation of lipid lowering medication for 4 weeks in

these patients is not expected to increase risk for CVD substantially.
A fat and muscle biopsy will be performed. The risks of these procedures are overall minimal. There can be some mild discomfort or pressure during the needle insertion and afterwards the area may feel tender or bruised. There is a slight risk of infection and there is also a minor risk of bruising or slight bleeding for several days. In our experience, fat and muscle biopsy are overall well tolerated and leave if any, minimal scarring.
During the heparin LPL test a drip will be placed which carries the risk of developing hematoma and pain. Theoretically administration of heparin carries the risk of bleeding, including the formation of hematoma at the place of injection, thrombocytopenia, reversible hair loss, collapse and vascular cramps. Since we administer 50 Units/kg we do not expect any complications. In fact, the heparin-LPL test has been performed in our hospital for more than 5 years. We have not witnessed any adverse event following a single heparin bolus. Due to the rapid half life of heparin, all anticoagulant effect will have disappeared within 2 hours following heparin administration.
During the study visit blood will be drawn for the assessment of lipids, glucose, insulin, adiponectin, ANGPTL4, apoC-III, apoA-V and LPL activity and mass and additional blood will be drawn for storage. Since the total volume of blood withdrawn during the study visit is less than 100 ml, no side effects are to be expected.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patient with metabolic syndrome will have to meet at least three of the following criteria (HTG will be a mandatory criteria).
o Central obesity; WC > 94 cm in male and > 80 cm in female
o Elevated plasma triglycerides 2.0-6.0 mmol/L
o Fasting plasma glucose (FPG) < 5.6 mmol/L

Exclusion criteria

* BMI >32
* Cardiovascular disease
* Current use of the following medications: Heparin, or other blood diluting medication
* Hepatic dysfunction
* End stage renal disease
* History of bleeding or recent surgical intervention

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL
Recruitment status: Pending

Start date (anticipated):	01-08-2010
Enrollment:	60
Type:	Anticipated

Ethics review

Approved WMO
Application type: First submission

Review commission: METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL32700.018.10