The development of diabetes-associated macrovascular disease in humanized mice

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1) Determine whether humanized mice develop enhanced restenosis upon vascular injury after reconstitution with human PBMCs derived from T2DM subjects with or without macrovascular disease.2) Determine what mechanism(s) induces deranged vascular...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Coronary artery disorders
Study type	Observational non invasive

Summary

ID

NL-OMON36433

Source
ToetsingOnline

Brief title
Humanized mice for studying diabetes-associated cardiovascular disease

Condition

- Coronary artery disorders
- Diabetic complications
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
atherosclerosis, cardiovascular disease

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen

Source(s) of monetary or material Support: Diabetes Fonds

Intervention

Keyword: Atherosclerosis, Cardiovascular disease, Progenitor cells, Type 2 diabetes

Outcome measures

Primary outcome

From the peripheral blood obtained PBMCs will be isolated using Ficoll density gradient centrifugation. Isolated cells will then be subjected to:

1) Flowcytometric analyses: These phenotypic analyses allows quantification circulating endothelial and smooth muscle progenitor cells (EPCs and SMPCs, respectively) in the peripheral blood of diabetic and non-diabetic subjects and correlate frequencies of these specific cell subsets to the presence of cardiovascular disease.

2) Injury to the arterial wall triggers smooth muscle cell proliferation, migration and matrix secretion. The resultant intimal hyperplasia is a common histological finding in restenosis after balloon angioplasty and other arterial occlusive diseases. We will induce arterial injury in human arterial grafts which have first been transplanted into the abdominal aorta of immunodeficient mice.

The results from these in vivo experiments will reveal whether the humanized model reflects the clinical situation of the individuals providing the tissues. T2DM is expected to impair endothelial and medial smooth muscle cell function

in the vascular wall and this may in turn influence the response of vascular progenitor cells upon vascular damage. Therefore, mice reconstituted with cells/tissues obtained from T2DM subjects likely develop more severe restenosis than mice transplanted with cells/tissues derived from non-diabetic controls.
In order to analyze whether exposure of PBMCs and arterial grafts derived from non-diabetic individuals to a T2DM environment influences their behaviour in response to vascular injury we will adapt our humanized mouse model by developing a humanized mouse model which has a diabetic background. We will transfer non-diabetic PBMCs to both non-diabetic and T2DM immunodeficient recipient mice that receives an arterial transplant. After arterial injury, the severity of restenosis will be determined. The results from these experiments will reveal whether vascular progenitor cells derived from non-diabetic individuals will adapt to a diabetic phenotype in vivo and whether this adaptation is permanent or reversible.

Secondary outcome

n.a

Study description

Background summary

Individuals with Type 2 diabetes mellitus (T2DM) have increased rates of cardiovascular disease including peripheral artery disease (PAD) and coronary artery disease (CAD) as well as restenosis after previous intervention. Development of cardiovascular disease in diabetic patients remains a major source of morbidity and mortality. A common approach for the prevention and treatment of cardiovascular disease in diabetes relies on the understanding of its complex pathophysiology. As yet, the underlying molecular mechanisms of increased cardiovascular disease in T2DM are still unclear but may involve

aberrant vascular progenitor cell function. Vascular progenitor cells include endothelial progenitor cells (EPCs) and smooth muscle progenitor cells (SMPCs).

We have recently started to recruit and include patients (METc 2008/335) whereby blood is collected for in vitro experiments. These experiments will determine differences in EPC and SMPC availability in the peripheral blood of T2DM patients with and without CAD or PAD (i.e. atherosclerosis in carotid artery and/or lower extremities) as well as in age- and sex-matched non-diabetic control subjects. Moreover, the molecular and functional differences in EPCs and SMPCs between these groups will be determined.

Since our goals imply translation of the obtained results towards the human T2DM patient, we propose to use human cells and arteries (from T2DM and non-diabetic controls with and without arterial disease) in a mouse host environment (i.e. the use of humanized mice). Such a model system enables studies on human cells that interact with the human vascular wall in vivo, but thereby also allowing interventions and analyses that are not feasible in the living human body.

Study objective

1) Determine whether humanized mice develop enhanced restenosis upon vascular injury after reconstitution with human PBMCs derived from T2DM subjects with or without macrovascular disease.

2) Determine what mechanism(s) induces deranged vascular progenitor cell frequency and function and whether this is permanent or reversible.

These objectives will reveal causal relationships between deranged vascular progenitor cell frequency and behaviour in individuals with T2DM and the relative risk to develop macrovascular disease. In addition, we will determine at which stage of the T2DM disease process vascular progenitor cells develop their aberrant phenotype, and whether these adaptations are permanent once induced, or whether they can be reversed.

Study design

In the current study, 4 different groups of patients will be included:

1) T2DM, no CAD (without PAD)
2) T2DM, with CAD (with or without PAD)
3) no T2DM, no CAD (without PAD)
4) no T2DM, with CAD (with or without PAD)

Arterial grafts are preferentially derived from side-branches of the left internal mammary artery (LIMA) or mesenteric arteries because of similarities

in size of these arteries and the mouse aorta. PBMCs and arterial tissue (LIMA) from groups 2 (T2DM) and 4 (non-diabetic) will be obtained from patients in need of bypass surgery because of CAD. Mesenteric material and blood from groups 1 and 3 will be available from patients requiring abdominal surgery. In addition, arterial material becoming available during reconstructive surgery will be used. Arterial material which would normally be disposed of, will be kept in sterile saline for our studies. Blood will be collected for standard pre-operative laboratory analysis, 5 extra tubes of blood (in total 50ml) will be collected for our studies. The peripheral blood will be collected in 4x 10ml EDTA vacutainer tubes (K3E 15% 0.12ml) and 1x SST vacutainer tube.

Study burden and risks

The nature of the research is such that participation entails no inherent risk for the subject. The extent of the burden is relatively low, donation of 50 ml peripheral blood and arterial material which is normally removed during surgery and would otherwise be disposed of as biological waste. Participants of the study will not have immediate benefit from the outcome of the study.

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

Patients eligible for participation are diagnosed with T2DM (duration 10-15 yrs) and divided into diabetic patients with CAD or without cardiovascular disease. Patients eligible for participation in the various control groups are patients without a history of T2DM but with CAD, respectively. In addition, healthy individuals who have neither a history of diabetes, cardiovascular disease, inflammatory or autoimmune disease, nor obesity nor any other chronic disease are will be included. Definition of CAD: Coronary artery disease (CAD) CAD is defined as previous myocardial infarction, resting ECG indicative of past MI, positive ECG at exercise stress test, echocardiography stress-test positive for inducible ischemia, evidence of significant coronary artery stenose on angiography with or without typical chest pain. Participants allocated to the different groups will be matched for: - gender - age - smoking - BMI - arterial hypertension - HbA1c (diabetics) - lipid profile

Exclusion criteria

Predefined exclusion criteria for T2DM include diagnosis of T1DM and presence of any of the following (self-reported) medical conditions: - auto-immune diseases - acute or chonic infection - age >80yrs - hemodialysis - immunosuppression - any other unrelated disease. Exclusion criteria for non-diabetics include: - diagnosis of T1DM or T2DM - auto-immune diseases - acute or chonic infection - age >80yrs - hemodialysis - immunosuppression - any other unrelated disease .

Study design

Design

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

Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-07-2011
Enrollment:	128
Type:	Actual

Ethics review

Approved WMO

Date:	21-01-2011
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	NL32431.042.10