The role of platelets and platelet-derived microvesicles in diabetic nephropathy.

Published: 08-05-2017
Last updated: 13-04-2024

To correlate platelet activity, PMV production and platelet and PMV RNA content to renal outcomes in diabetic nephropathy and to investigate the interaction between PMV and glomerular endothelial cells and podocytes.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Diabetic complications
Study type	Observational invasive

Summary

ID

NL-OMON47280

Source
ToetsingOnline

Brief title
PlaDNer

Condition

- Diabetic complications
- Nephropathies

Synonym
diabetic kidney injury, Diabetic nephropathy

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: NWO

Intervention

Keyword: diabetic nephropathy, microvesicles, miRNA, Platelets

Outcome measures

Primary outcome

The main parameter of this study is the content of mRNA and miRNA in platelets and PMVs.

Secondary outcome

Plasma and urinary microvesicles and inflammatory markers (e.g. TNF-alpha, il-6, il-8, il-1*), renal injury markers (e.g. Cystatin-C, nGAL), as well as platelet activity markers (platelet factor 4 and serotonin) and agonist-induced platelet aggregation (platelet count-based test) are secondary study parameters.

Study description

Background summary

Diabetic nephropathy (DN) is one of the complications of diabetes, which occurs in 20-40% of diabetic patients. Glomerular injury is the main hallmark of DN, resulting in glomerulosclerosis and albuminuria, which is stratified in normoalbuminuria (albumin-to-creatinin ratio (ACR) <30mg/g), microalbuminuria (ACR 30-300mg/g) and macroalbuminuria (ACR >300mg/g).
Patients with diabetes are at increased risk for cardiovascular disease. This risk is even more increased when renal insufficiency accompanies diabetes. Increased platelet activity is one element that leads to this increased risk. In diabetes, platelet activation is increased because of an altered balance between pro- and anti-coagulant mechanisms, mainly caused by endothelial injury. Also, platelets can be activated directly by high glucose levels.
Besides the importance of platelets in coagulation, mounting evidence shows that platelets are also involved in inflammation and repair. Platelets are involved in these processes by secreting a plethora of bioactive molecules either directly or via platelet-derived microvesicles (PMV). PMVs are buddings from the membrane or exosomes derived from intracellular granules. PMVs allows

communications between platelets and remote target cells. Recently, PMVs have emerged as important mediators of intercellular transfer of bioactive molecules, which appears to be crucial in normal physiology and under pathological circumstances. Moreover, PMV contain a multitude of platelet-derived effector molecules among which mRNAs and miRNAs. Platelet inherit (pre-)mRNA from the megakaryocyte, as well as abundant and a diverse array of miRNAs, which regulate de novo protein synthesis in both platelets and their recipient cells. Recent studies showed interactions between PMV and endothelial cells and macrophages, in both cases the protein expression was miRNA-mediated. Endothelial cells and macrophages are crucial cell types involved in DN development, therefore we suppose that PMV miRNAs are promising mediators in DN development.
In summary, platelet activity and PMV levels are increased in diabetes. However, the role of platelets and PMV in the progression of DN is currently unclear. We hypothesize that platelets act on injured glomerular endothelial cells and podocytes via microvesicles carrying mRNA and miRNA, resulting in pro-inflammatory and pro-fibrotic phenotype of these cells.

Study objective

To correlate platelet activity, PMV production and platelet and PMV RNA content to renal outcomes in diabetic nephropathy and to investigate the interaction between PMV and glomerular endothelial cells and podocytes.

Study design

The design of this study is an observational, case-control study.

Study burden and risks

Patients visit the outpatient clinic for diabetes regularly, to monitor their glucose control and health status. Blood and urine are routinely collected to measure the standard clinical parameters. Patients participating in this study only need to donate 2 extra vials (total of 18 mL) of blood to perform additional measurements for the study. The collection if this small amount of blood has minimal additional risk. The healthy volunteers do not have regular blood and urine collection, so the burden to participate in this study will be slightly higher in this group, however, the risk of these procedures is still minimal.

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

Type 2 diabetes
Age between 18-70 year

Exclusion criteria

Smoker
User of anti-platelet drugs
South-Asian or Sub-Sahara ethnicity

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:	Recruitment stopped
Start date (anticipated):	09-10-2018
Enrollment:	144
Type:	Actual

Ethics review

Approved WMO Date:	08-05-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-09-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-11-2018
Application type:	Amendment
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	NL59795.048.17