Heparan sulphate glycosaminoglycans in the glomerular filtration barrier

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The main objective of the study is to investigate the effect of a heparan sulphate glycosaminoglycan deficiency on the glomerular filtration barrier in humans. This main objective is approached through the secondary objectives of assessing whether a...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Chromosomal abnormalities, gene alterations and gene variants
Study type	Observational non invasive

Summary

ID

NL-OMON42338

Source
ToetsingOnline

Brief title
HS GAG in the glomerular filtration barrier

Condition

- Chromosomal abnormalities, gene alterations and gene variants

Synonym
Multiple osteochondromas

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Glomerular filtration barrier, Glycocalyx, Heparan sulfate glycosaminoglycans

Outcome measures

Primary outcome

The main study parameters are the differences in proportion of subjects with

micro-albuminuria, urinary albumin/creatinine ratio, and the difference in

perfused boundary region between patients and controls.

Secondary outcome

N/A

Study description

Background summary

Heparan sulphate (HS) glycosaminoglycans (GAG) have long been considered essential in glomerular filtration.(1) In the glomerular filtration barrier (GFB), they are present in both the glomerular basement membrane as the glomerular endothelial glycocalyx. In various proteinuric renal diseases, a decrease in HS-GAG expression was observed in the glomerular filtration barrier.(2) Also, in vitro experiments showed that removal of HS-GAG from the glycocalyx results in increased permeability to albumin.(3) Several animal models have been used to address the question whether loss of HS-GAG results in loss of glomerular permselectivity. Both mouse(4-7) and zebrafish (own results, in preparation for submission) do not exhibit loss of glomerular permselectivity. This study aims to investigate the effect of a HS-GAG deficiency in humans on the glomerular filtration barrier by studying the occurrence of micro-albuminuria and structural changes to the microvascular endothelium.

Reference List

(1) Kanwar YS, Linker A, Farquhar MG. Increased permeability of the glomerular basement membrane to ferritin after removal of glycosaminoglycans (heparan sulfate) by enzyme digestion. J Cell Biol 1980 Aug;86(2):688-93.
(2) van den Born J, van den Heuvel LP, Bakker MA, Veerkamp JH, Assmann KJ, Weening JJ, et al. Distribution of GBM heparan sulfate proteoglycan core

protein and side chains in human glomerular diseases. Kidney Int 1993 Feb;43(2):454-63.
(3) Singh A, Satchell SC, Neal CR, McKenzie EA, Tooke JE, Mathieson PW. Glomerular endothelial glycocalyx constitutes a barrier to protein permeability. J Am Soc Nephrol 2007 Nov;18(11):2885-93.
(4) Chen S, Wassenhove-McCarthy DJ, Yamaguchi Y, Holzman LB, van Kuppevelt TH, Jenniskens GJ, et al. Loss of heparan sulfate glycosaminoglycan assembly in podocytes does not lead to proteinuria. Kidney Int 2008 Aug;74(3):289-99.
(5) Sugar T, Wassenhove-McCarthy DJ, Esko JD, van Kuppevelt TH, Holzman L, McCarthy KJ. Podocyte-specific deletion of NDST1, a key enzyme in the sulfation of heparan sulfate glycosaminoglycans, leads to abnormalities in podocyte organization in vivo. Kidney Int 2014 Feb;85(2):307-18.
(6) Harvey SJ, Jarad G, Cunningham J, Rops AL, van d, V, Berden JH, et al. Disruption of glomerular basement membrane charge through podocyte-specific mutation of agrin does not alter glomerular permselectivity. Am J Pathol 2007 Jul;171(1):139-52.
(7) Goldberg S, Harvey SJ, Cunningham J, Tryggvason K, Miner JH. Glomerular filtration is normal in the absence of both agrin and perlecan-heparan sulfate from the glomerular basement membrane. Nephrol Dial Transplant 2009 Jul;24(7):2044-51.

Study objective

The main objective of the study is to investigate the effect of a heparan sulphate glycosaminoglycan deficiency on the glomerular filtration barrier in humans. This main objective is approached through the secondary objectives of assessing whether a HS-GAG deficiency results in micro-albuminuria and/or a reduced thickness of the microvascular glycocalyx.

Study design

The study is designed as a cross sectional, observational study.

Study burden and risks

Volunteers are requested to visit the Leiden University Medical Center once. Before visiting, they are asked to fill out one questionnaire. Participating HME-MO patients are asked for permission to view their mutation status. During the visit, volunteers are asked to deliver two urine samples. Also, a non-invasive technique is used to assess the microcirculation by placing a small camera under the tongue. This procedure is painless and takes 5-10 minutes. To perform this analysis, participants are asked to fast for at least two hours prior to the site visit. It is further described in the 'Methods' section of the research protocol. The overall risk of participating in this study is negligible. The main burden of participation consists of the site

visit and the two hour fasting period. A travel reimbursement and token of gratitude (VVV bon) is given to participants. Other than these incentives, no benefit is obtained through participating in this 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

Subjects should be over 18 years of age and capacitated.

Exclusion criteria

No confirmed mutation status in either the EXT1 or EXT2 gene

Study design

Design

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

Primary purpose: Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	03-09-2015
Enrollment:	80
Type:	Actual

Ethics review

Approved WMO

Date:	14-07-2015
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	NL53340.058.15