



Feb 16, 2020

Markers of endothelial dysfunction and arterial stiffness in patients with early-stage autosomal dominant polycystic kidney disease: a meta-analysis

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ABSTRACT

Autosomal dominant polycystic kidney disease (ADPKD) represents the most prevalent life-threatening monogenetic hereditary kidney disease. Hypertension occurs early in the course of the disease and is linked to progressive decline of glomerular filtration rate, as well as with higher cardiovascular morbidity. Experimental studies support that both polycystin 1 and 2 are expressed in the cilia of endothelial and vascular smooth muscle cells, serving as mechanoreceptors that sense shear stress. Loss of polycystins may lead to reduced nitric oxide production, promoting vasoconstriction, renal hypoxia and functional decline. Several observational studies have recently evaluated endothelial damage in ADPKD patients by using surrogate markers, although no firm consensus exists about endothelial dysfunction and arterial stiffness in early-stage patients with preserved renal function. Therefore, a meta-analysis is planned in order to accumulate current literature evidence in the field and compare makers of endothelial dysfunction and arterial stiffness among early-stage ADPKD patients with preserved renal function and healthy controls.

- 1 Review title: Markers of endothelial dysfunction and arterial stiffness in patients with early-stage autosomal dominant polycystic kidney disease: a meta-analysis
- 2 Review question: To assess whether autosomal dominant polycystic kidney disease (ADPKD) is linked to endothelial dysfunction and arterial stiffness during its early stages by comparing the outcomes of noninvasive techniques and plasma biomarkers among patients with early-stage ADPKD and healthy controls. Population: Patients with preserved renal function Exposure: ADPKD Comparator: Healthy controls Outcomes: flow-mediated dilatation, pulse wave velocity, augmentation index, carotid intima-media thickness and carotid systolic blood pressure, plasma levels of asymmetric dimethylarginine and homocysteine Study type: Observational studies
- 3 Searches: Medline, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, Clinicaltrials.gov databases and Google Scholar databases will be searched from inception. The following key-terms will be applied: "autosomal polycystic kidney disease, ADPKD, endothelial, vascular, dysfunction, damage, stiffness, sclerosis, arteriosclerosis, FMD, flow-mediated dilatation, PWV, pulse wave velocity, Aix, augmentation index, carotid intima media, CIMT, homocysteine, ADMA, asymmetric dimethylarginine". No date or language restrictions will be applied.
- 4 Condition or domain being studied: Autosomal dominant polycystic kidney disease (ADPKD) represents the most prevalent life-threatening monogenetic hereditary kidney disease. Hypertension occurs early in the course of the disease and is linked to progressive decline of glomerular filtration rate, as well as with higher cardiovascular morbidity. Recent research interest has focused on the potential role of endothelial dysfunction in the pathophysiology and progression of ADPKD. Experimental studies support that both polycystin 1 and 2 are expressed in the cilia of endothelial and vascular smooth muscle cells, serving as mechanoreceptors that sense shear stress. Loss of polycystins may lead to reduced nitric oxide production, promoting vasoconstriction, renal hypoxia and functional decline. Several observational studies have recently evaluated endothelial damage in ADPKD patients by using surrogate markers, although no firm consensus exists about endothelial dysfunction and arterial stiffness in early-stage patients with preserved renal function.
- 5 Participants/population: Inclusion criteria: ADPKD patients with preserved renal function defined as an estimated glomerular filtration rate ≥ 60 ml/min/1.73 m². Exclusion criteria: Impaired renal function, history of coronary artery disease, severe heart failure or any major cardiovascular disease.

- 6 Types of study to be included: All types of observational studies (prospective/retrospective cohort, case-control, cross-sectional) will be considered eligible. Conference proceedings/abstracts that will be recognized through database search will be also evaluated for potential eligibility. Case reports, small case series (<10 patients), review articles, letters to the editor, animal and in vitro studies will be excluded.
- 7 Main outcomes: Values of flow-mediated dilatation, pulse wave velocity, augmentation index, carotid intima-media thickness and carotid systolic blood pressure, plasma asymmetric dimethylarginine and homocysteine among ADPKD patients and healthy controls.
- 8 Data extraction (selection and coding): The following data are planned to be extracted from each study: year of publication, study design, eligibility criteria, type of population, number of patients, median age, eGFR, systolic blood pressure, presence of hypertension and height-adjusted total kidney volume, as well as the outcomes of interest. Data collection will be performed independently by two reviewers.
- 9 Risk of bias (quality) assessment: The quality of the included studies will be assessed using the Risk Of Bias In Non-randomized Studies (ROBINS-I) tool, which evaluates the potential presence of bias in the domains of confounding, selection, classification, deviation from intended intervention, missing data, measurement and reporting of the outcomes. The quality of evidence will be evaluated with the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach, by taking into account study limitations, indirectness, imprecision, inconsistency and publication bias.
- 10 Strategy for data synthesis: A random-effects (DerSimonian-Laird) model will be used to provide pooled estimates of standardized mean differences and 95% confidence intervals. Small-sample adjustments will be made by obtaining new estimates using the Knap-Hartung method. The inter-study heterogeneity will be evaluated by the inconsistency index (I²), with values >50% indicating significant heterogeneity, while its impact on outcomes will be quantified by estimating the 95% prediction intervals. Publication bias will be assessed by the visual inspection of funnel plots and the trim-fill method. The credibility ceiling test will be performed by applying ceilings of 5% and 10%.
- 11 Analysis of subgroups or subsets: Sensitivity analysis will be conducted by separately pooling the results of patients without hypertension, as well as by examining only studies at low risk of bias.
- 12 Keywords: ADPKD, autosomal polycystic kidney disease, endothelial dysfunction, arterial stiffness, meta-analysis



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