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Coronary endothelial dysfunction appears to be a manifestation of a systemic process: A report from the Women's Ischemia Syndrome Evaluation – Coronary Vascular Dysfunction (WISE-CVD) study

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Abstract

Background

Coronary microvascular dysfunction (CMD) is prevalent in symptomatic women with ischemia but no obstructive coronary artery disease (INOCA). Urine albumin-creatinine ratio (UACR) is a measure of renal microvascular endothelial dysfunction. Both are predictors of adverse cardiovascular events. It is unknown if CMD could be a manifestation of a systemic process. We evaluated the relationship between renal microvascular dysfunction and CMD as measured by invasive coronary function testing (CFT).

Methods and results

We measured urine albumin and creatinine to provide UACR in 152 women enrolled in the Women's Ischemia Syndrome Evaluation–Coronary Vascular Dysfunction (WISE-CVD) study (2008–2015) with suspected INOCA who underwent CFT. Invasive CFT measures of endothelial and non-endothelial dependent coronary microvascular function were obtained. Subjects were divided into those with detectable ($\geq$20 mg/g) and undetectable urine albumin (<20 mg/g). The group mean age was 54 ± 11 years, with a moderate cardiac risk factor burden including low diabetes prevalence, and a mean UACR of 12 ± 55 mg/g (range 9.5–322.7 mg/g). Overall, coronary endothelial-dependent variables (change in coronary blood flow and coronary diameter in response to cold pressor testing) had significant inverse correlations with log UACR (r = -0.17, p = 0.05; r = -0.18, p = 0.03, respectively).

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Conclusions

Among women with INOCA and relatively low risk factor including diabetes burden, renal microvascular dysfunction, measured by UACR, is related to coronary endothelial-dependent CMD. These results suggest that coronary endothelial-dependent function may be a manifestation of a systemic process. Enhancing efferent arteriolar vasodilatation in both coronary endothelial-dependent function and renal microvascular dysfunction pose potential targets for investigation and treatment.

Clinical trial registration

https://clinicaltrials.gov/ct2/show/NCT00832702.

Introduction

Prior work has determined that coronary microvascular dysfunction (CMD) is prevalent, associated with adverse clinical outcomes, poor quality of life and healthcare costs rivaling obstructive coronary disease in women with suspected ischemia with no obstructive CAD (INOCA)[1]. There are 3–4 million US patients with CMD, 100,000 new cases projected annually, and progression to heart failure with preserved ejection fraction (HFpEF) is most common, which is also more prevalent in women [1]. Further work suggests that CMD may be a manifestation of a systemic process. We have documented links between CMD and chronic kidney disease [2], and retinal microvascular dysfunction [3] in WISE women. Others have documented sex differences in retinal vascular [4] in hypertensive subjects, and brain small vessel changes in dementia [5] that are more adverse for women. Additionally, cross-sectional studies demonstrate a correlation between retinal microvascular changes and dementia, cognitive impairment, and brain imaging abnormalities [6]. These findings suggest the hypothesis that the rising burden of HFpEF and dementia that more often impact women may be due to a systemic microvascular dysfunction state.

Elevated urine albumin-creatinine ratio (UACR) is a measure of renal microvascular dysfunction [7], and has been suggested to be a marker of endothelial dysfunction [8, 9]. It has been studied extensively in patients with diabetes mellitus and is now recognized as an independent predictor of ischemic heart disease in asymptomatic as well symptomatic individuals without diabetes [10, 11]. Additionally UACR is an independent risk factor for clinical cardiovascular events including myocardial infarction (MI), stroke, cardiovascular death, and hospitalization for heart failure [12]. Furthermore younger, non diabetic and non hypertensive individuals also has shown correlation between UACR and subclinical vascular damage leading to cardiovascular diseases and death [13]. We investigated relations between two measures of microvascular dysfunction, CMD and UACR, to test the hypothesis that CMD is manifestation of a systemic process in women with suspected INOCA in the WISE—Coronary Vascular Dysfunction (CVD) Study.

Methods

Patient selection and procedures

The WISE-CVD study methods have been previously published [14]. Among the 369 women enrolled in WISE-CVD between 2008–2015, 244 had urine collected and measured for

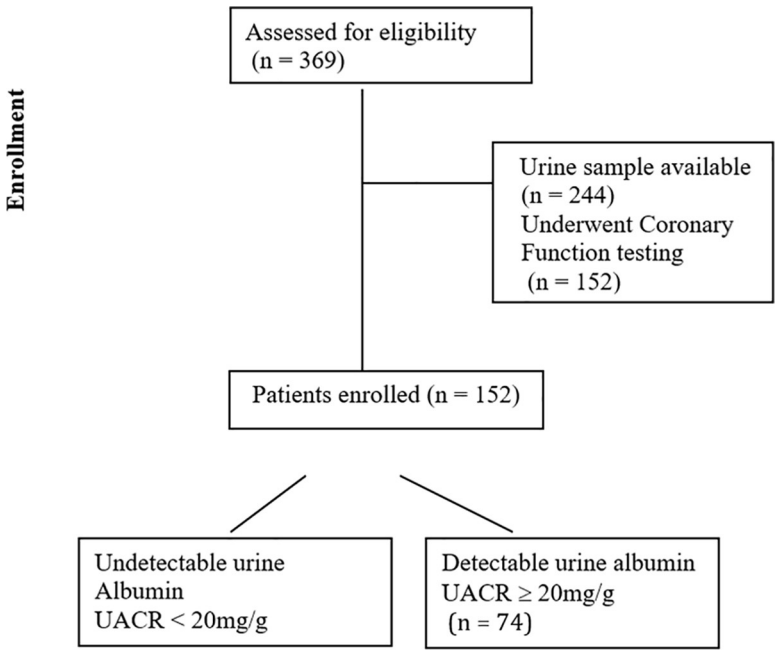

Fig 1. Flow chart for UACR CMD (WISE–CVD study).

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albumin and urine creatinine, and of those 152 (62%) had invasive coronary function testing (CFT) performed (Fig 1) and thus were included in the current study, as previously published [15]. Briefly, a doppler flow wire (FloWire® Volcano) was advanced through the diagnostic catheter and positioned in the proximal left anterior descending coronary artery. Intracoronary (IC) vasodilators and following parameters measured in response to IC adenosine (coronary flow reserve CFR normal $\geq$ 2.5), change in coronary blood flow in response to IC acetylcholine (ACH) (ΔCBF normal >50%), change in coronary diameter in response to acetylcholine (ΔACH normal > 5%), change in coronary diameter in response to cold pressor test (ΔCOP), and change in coronary diameter in response to nitroglycerin (ΔNTG) [15]. Institutional review boards at Cedars- Sinai Medical Center and the University of Florida, Gainesville each site approved the protocol, written and verbal informed consent was obtained from each subject, and data were monitored by an independent data safety monitoring committee.

Urine albumin (mg/g) and urine creatinine (g/dL) were measured via random spot urine samples using a commercial assay (Beckman Coulter Image® nephelometry). UACR was reported in mg/g, and in subjects with urine albumin in an undetectable range (<20 mg/g) UACR was reported as 0 mg/g. CFT was conducted as previously described [15]. Additionally, non-invasive cold pressor testing, an ice pack placed to the forehead (N = 75) or the left forearm (N = 77) for 2 minutes, was used as a non-pharmacological method for the evaluation of endothelial-dependent coronary microvascular function.

Statistical analysis

Pertinent baseline characteristics were tabulated and are reported. Continuous variables were summarized as mean ±SD. Categorical variables are presented as percentages. UACR was skewed so a log transformation was used for all analyses. Spearman correlations were used to evaluate associations of UACR and the CMD parameters, as well as subgroup relations (n = 138–152). The cohort was also divided into those with undetectable urine albumin (<20

mg/g) and detectable urine albumin (≥20 mg/g) based on the sex specific cut off point as shown in prior studies [16, 17]. Results that used the entire cohort and incorporated UACR used a value of 10 mg/g for those with undetectable levels. Fisher's exact test, student t test, and Wilcoxon rank sum test were performed as appropriate to evaluate for differences in baseline characteristics and CMD parameters between the two groups. Linear regression models included univariate predictors or variables of interest and used the outcomes of change in CFR, CBF, ACH, NTG, and COP adjusted for the explanatory variables of log UACR, systolic blood pressure (SBP), low density lipoprotein (LDL), body mass index (BMI), and indicators of whether the patient had statin or angiotensin converting enzyme inhibitor (ACE-I) or angiotensin renin blocker (ARB) use at baseline. The models were assessed mainly by analysis of residuals and comparing the change in parameter estimates when the subjects with undetectable UACR were added or removed. A Holm-Bonferroni adjustment was made to the p-values of the correlations as a group, and to the p-values from the regression model as another group [18]. A p-value of <0.05 was considered statistically significant for all analyses.

Results

Pertinent baseline characteristics are summarized in Table 1. Most subjects had a moderate level of cardiac risk factors, with a low prevalence of diabetes. Mean UACR was 24.66 ± 78.45 mg/g among those with detectable levels. Overall, 78/152 (51%) had urine albumin levels <20 mg/g, the lowest detectable range. To better understand the relationship between CMD and UACR, subjects were divided into two groups, those with detectable and undetectable urine albumin. Baseline characteristics and CMD parameters were compared between the group with detectable urine albumin and undetectable urine albumin. Those with and without detectable urine albumin had similar rates of self-reported diabetes (13% vs 8%, p = 0.42), hypertension (43% vs 31%, p = 0.17) and similar systolic blood pressure (Table 1). With regard to the invasive measures of CMD, those with detectable urine albumin had a statistically significantly lower ΔCBF (52.4±65.7 vs 86.3±101.3, p = 0.04) but no significant difference in the other invasive measures of CMD.

Overall, endothelial-dependent variables (change in coronary blood flow and coronary diameter in response to cold pressor testing) had inverse correlations with log UACR (Table 2), such that heavier proteinuria correlated with more abnormal coronary endothelial function. There were no significant correlations between UACR and non-endothelial coronary function. Despite an overall correlation between ΔCBF and ΔACH (r = 0.46, n = 138, p<0.0001) there was no significant relationship between UACR and ΔACH (r = -0.14, n = 152, p = 0.09) (Table 2) when the entire cohort was examined and used a value of 10 mg/g for those with undetectable levels.

Among those with detectable UACR (n = 74) there were no significant correlations between UACR and other patient variables, including age, weight, BMI, N-terminal pro-brain natriuretic peptide (NT-pro-BNP) or angina measured by the Seattle Angina Questionnaire (SAQ), however we observed a positive and significant correlation between log UACR and LVEDP (0.26, n = 69, p = 0.03). In multivariable regression modeling that included all 86 subjects with complete ΔCBF, UACR, SBP, LDL, ACEi/ARB, statin use and BMI data, all variables except ACEi/ARB were associated with ΔCBF, so ACEi/ARB was removed from the model. (Table 3). If only those 39 with detectable UACR are included in the model the associations are smaller and not significant. In regression models with ΔACH, ΔCOP, ΔNTG, and ΔCFR as outcomes, UACR did not contribute significantly to any model, however creatinine was a significant independent predictor of CFR (parameter estimate 0.83 per 1 unit creatinine, p = 0.0409).

Table 1. Baseline characteristics.

Characteristic (mean SD or %)	All subjects N = 152	UACR <20 mg/g, N = 78	UACR ≥20 mg/g, N = 74	p-value
Age (years)	54±11	54±11	53±11	0.861
BMI	30±8	30±8	31±9	0.705
Caucasian	72%	75%	69%	0.466**
Heart rate (bpm)	70±11	67±9	73±12	**0.0008**
SBP (mmHg)	126±18	124±17	129±19	0.106
DBP (mm Hg)	69±12	70±11	69±13	0.560
Dyslipidemia	12%	12%	12%	1.0**
NT-pro BNP	108.6±160.0	112.1±174.4	104.6±143.4	0.385*
GFR	91.7±17.6	90.3±16.7	93.1±18.5	0.342
Hemoglobin (g/dl)	13±2	13±3	13±1	0.309*
Serum creatinine (mg/dl)	0.8±0.2	0.8±0.2	0.7±0.1	0.235*
UACR (mg/g)	11.8±55.2, 0.1 (0.1, 576.2)	(undetectable) 0.1±0	24.1±77.5, 5 (1.1, 576.2)	By design
CFR	2.7±0.6	2.7±0.7	2.7±0.6	0.562
ΔCBF (%)	70.4±87.7	86.3±101.3	52.4±65.7	**0.039***
ΔACH (%)	-7±19.3	-4.8±18.6	-9.3±19.9	0.157
ΔCOP (%)	-3.4±18.6	-0.9±16.1	-6.1±20.8	0.093
ΔNTG (%)	7.8±20.1	9.7±18.5	5.7±21.5	0.221
History of Tobacco use	39%	45%	33%	0.176**
Diabetes	10%	8%	13%	0.417**
History of Hypertension	37%	31%	43%	0.166**
Family history of CAD	47%	45%	49%	0.617**
Statins	39%	33%	44%	0.232**
ACE-I/ARB	22%	20%	24%	0.554**
Full dose aspirin	12%	9%	15%	0.314**
Low dose aspirin	55%	58%	51%	0.409**

ΔACH = change in coronary diameter in response to intracoronary acetylcholine, BMI = body mass index, NT-pro BNP = brain natriuretic peptide, GFR = glomerular filtration rate, CAD = coronary artery disease, ΔCBF = change in coronary blood flow in response to intracoronary acetylcholine, CFR = coronary flow reserve in response to intracoronary adenosine, ΔCOP = change in coronary diameter in response to cold pressor test, DBP = diastolic blood pressure, HDL = high density lipoprotein, LDL = low density lipoprotein, LVEDP = left ventricular end diastolic pressure, ΔNTG = change in coronary diameter in response to intracoronary nitroglycerin, SBP = systolic blood pressure, UACR = urinary albumin creatinine ratio Test p-values were from t tests except

*indicates Wilcoxon rank sum test

**indicates Fisher's exact test.

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Discussion

Urine albumin-creatinine ratio (UACR) as a measure of renal microvascular endothelial dysfunction has not been previously evaluated in our novel population of women with suspected INOCA [19]. Mohandas et al in prior study showed that reduced renal dysfunction is associated with CMD using eGFR instead of UACR [2]. In addition prior studies, Sakamoto et al and Chade et al provided similar association between CFR and CKD however using eGFR in patients with underlying CKD, unlike our patient population [20, 21]. Our results provide evidence that renal endothelial dysfunction, as measured by UACR, has a direct relationship to coronary endothelial-dependent microvascular dysfunction, whereby greater renal proteinuria correlated with more abnormal endothelial function. Conversely UACR did not relate to non-endothelial coronary measures, however our results may also involve varying degrees of epicardial vasodilation/mild vasoconstriction throughout the coronary tree, and therefore may not be specific to the microcirculation. Multivariable regression modeling demonstrated that

Table 2. Spearman correlations between CMD variables and UACR.

Variable	Correlation Coefficient	P-value	Holm-Bonferroni adjusted p-value
CFR, N = 144	0.025	0.770	1.0
among CFR ≥ 2.5 (normal, N = 89)	-0.007	0.947	1.0
among CFR < 2.5 (abnormal, N = 55)	0.134	0.330	1.0
ΔCBF, N = 138	-0.171	**0.046**	**0.598**
among ΔCBF ≥ 50% (normal, N = 69)	-0.20	0.100	0.910
among ΔCBF < 50% (abnormal, N = 69)	-0.043	0.728	1.0
ΔACH, N = 152	-0.137	0.091	0.910
among ΔACH > 0 (Normal, N = 64)	-0.017	0.895	1.0
among ΔACH ≤ 0% (Abnormal, N = 88)	-0.258	**0.015**	**0.225**
ΔCOP, N = 146	-0.18	**0.029**	**0.406**
among ΔCOP > 0% (Normal, N = 69)	-0.033	0.785	1.0
among ΔCOP ≤ 0% (Abnormal, N = 77)	-0.204	0.075	0.825
ΔNTG, N = 151	-0.132	0.107	0.910
among ΔNTG > 20% (Normal, N = 45)	0.024	0.876	1.0
among ΔNTG ≤ 20% (Abnormal, N = 106)	-0.179	0.066	0.792

Abbreviations as prior.

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UACR was predictive of ΔCBF and was the second strongest predictor after LDL-cholesterol. These results support the hypothesis that coronary endothelial-dependent microvascular dysfunction may be a manifestation of a systemic process.

Prior studies examined the relationship between renal function and CMD and found it as a marker of CMD, when estimated glomerular filtration rate (eGFR) was reduced [22], however, there has been no studies identifying UACR with coronary endothelial-dependent microvascular dysfunction. The association between microalbuminuria and CMD has been hypothesized to be due to a shared pathogenic mechanism of subclinical damage of the vascular beds in both the renal and coronary arteries [23], Ludic et al studied the relationship between CKD and coronary endothelial dysfunction in diabetics vs non diabetic patients, and found coronary endothelial dysfunction correlated with renal dysfunction in type II diabetic patients [24]. Prior WISE study demonstrated that renal function (estimated GFR [eGFR]), was significantly correlated with CFR ($r = 0.22$, $p = 0.002$), which persisted even when adjusted for age, diabetes, hypertension, dyslipidemia, double product, BMI, severity of obstructive CAD, and hormone replacement therapy ($p = 0.0003$, model $R^2 = 0.18$) [2]. Other work has indicated that eGFR and UACR are markers of chronic kidney disease [25]. A study of diabetic patients (56% men) with no obstructive CAD was also consistent with the current results, demonstrating that endothelium-dependent vasoreactivity, measured by coronary artery diameter response to

Table 3. Multivariable regression independent predictors of ΔCBF among those with detectable UACR (N = 86).

Variable	Estimate (SE)	P-value	Holm-Bonferroni adjusted p-value
UACR	-11.53 (4.55)	0.013	0.052
SBP	-1.23 (0.54)	0.025	0.075
LDL	0.93 (0.29)	0.002	0.010
BMI	-2.41 (1.18)	0.044	0.088
Statin use	30.17 (19.05)	0.117	0.117

Abbreviations as prior.

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cold pressor, correlated with urinary albumin excretion rate ($r = -0.39$, $p = 0.0003$) [26]. Notably, only 14% of our study subjects were diabetic and all were women.

Multiple studies document that CMD carries an increased risk of adverse cardiovascular events [27, 28]. Data from several studies has established that microalbuminuria, which is measured by UACR, is an independent risk factor for clinical cardiovascular events including future stroke, myocardial infarction, cardiovascular death, and hospitalization for congestive heart failure [12] and an independent predictor of ischemic heart disease [10]. Moreover, ACE inhibition with the ACE-I ramipril in diabetes decreased the both adverse cardiovascular and renal outcomes [29]. As both UACR and CMD predict clinical adverse cardiovascular events, these results combined with the current results that link the two directly in our cohort, suggest that UACR may have prognostic and treatment implications in our novel population.

A potential explanation for this relationship between CMD and UACR is common risk factors contributing to endothelial dysfunction in both the coronary and renal microvasculature, including hypertension [30] and dyslipidemia [31]. Prior work in a study of 1567 subjects demonstrated major cardiac risk factors as independent correlates of urinary albumin excretion rate and prevalence of microalbuminuria in non-diabetic middle-aged men and women [32], suggesting that endothelial dysfunction is systemic [33]. Previous studies have found an association between kidney disease and microvascular dysfunction in the central nervous system [34], retina [35], and peripheral circulations [36]. Accordingly, albuminuria may represent a marker of global microvascular dysfunction, which includes renal and coronary endothelial dysfunction. This hypothesis opens the door to investigate future targets for treatment, for example ACE or ARB inhibitor therapy, long known to slow down renal dysfunction in diabetics with microalbuminuria [37–39]. A prior WISE clinical trial demonstrated improved CMD with quinapril which correlated with reduction in anginal symptoms [40]. In the LIFE study, subjects with a UACR greater than the median value at baseline, who were able to decrease their UACR to less than the median value at 1 year via use of losartan, had a reduced risk for cardiovascular mortality, stroke, and myocardial infarction compared with patients who were not able to decrease their UACR [41]. These studies suggest potential investigative areas for reduction of adverse events in CMD, as well as possibly prevention of HFpEF and dementia in women.

Limitations

There are several limitations in this study to consider. Our subjects, referred for clinically indicated coronary angiography, likely do not represent all women or patients not evaluated invasively, as evidenced by their modest risk factor profile. Analyses in higher risk populations such as obstructive CAD might demonstrate stronger findings. Our analysis is limited to 152 women, did not include reference control subjects, and only 74 (49%) had detectable urine albumin. Although we used multiple testing adjustments, our multiple correlation and linear regression models tested may over-estimate borderline relations–repeated analyses in larger sample sizes is needed. Urine albumin and urine creatinine were collected a single time at the first study visit; transient microalbuminuria can occur due to fever, recent exercise, elevation in blood pressure, infection, such that the amount of falsely increased urine albumin levels cannot be determined. Lastly, as mentioned this study was conducted in exclusively women, and therefore potentially not generalizable to men.

Conclusions

Among women with INOCA, renal microvascular dysfunction, measured by UACR, is related to coronary endothelial-dependent function. These results suggest that CMD may be a

manifestation of a systemic process. Further, because both UACR and coronary endothelial-dependent function predict clinical adverse cardiovascular events, these results may have prognostic and treatment implications. Enhancing efferent arteriolar vasodilatation in both coronary endothelial-dependent function and renal microvascular dysfunction pose potential targets for investigation and treatment.

Supporting information

S1 Data. Supporting information data set.
(CSV)

Author Contributions

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References

1. Bairey Merz CN, Pepine CJ, Walsh MN, Fleg JL. Ischemia and No Obstructive Coronary Artery Disease (INOCA): Developing Evidence-Based Therapies and Research Agenda for the Next Decade. Circulation. 2017; 135(11):1075–92. https://doi.org/10.1161/CIRCULATIONAHA.116.024534 PMID: 28289007
2. Mohandas R, Segal MS, Huo T, Handberg EM, Petersen JW, Johnson BD, et al. Renal Function and Coronary Microvascular Dysfunction in Women with Symptoms/Signs of Ischemia. PLoS ONE. 2015; 10(5):e0125374. https://doi.org/10.1371/journal.pone.0125374 PMID: 25951606
3. Handberg EM, Wen X, Klein R, Anderson RD, Pauly DF, Kelsey SF, et al. COULD RETINAL IMAGING PROVIDE A SIMPLE INEXPENSIVE NONINVASIVE INDEX FOR CORONARY MICROVASCULAR FUNCTION IN WOMEN WITH CHEST PAIN AND NONOBSTRUCTIVE CORONARY ARTERY DISEASE? AN ANCILLARY PILOT STUDY FROM THE NHLBI-SPONSORED WOMEN'S ISCHEMIA SYNDROME EVALUATION (WISE-ARIC). Journal of the American College of Cardiology. 2011; 57(14 Supplement):E1145.
4. Hubbard LD, Brothers RJ, King WN, Clegg LX, Klein R, Cooper LS, et al. Methods for evaluation of retinal microvascular abnormalities associated with hypertension/sclerosis in the Atherosclerosis Risk in Communities Study. Ophthalmology. 1999; 106(12):2269–80. https://doi.org/10.1016/s0161-6420(99)90525-0 PMID: 10599656

5. Warren MW, Weiner MF, Rossetti HC, McColl R, Peshock R, King KS. Cognitive impact of lacunar infarcts and white matter hyperintensity volume. Dementia and geriatric cognitive disorders extra. 2015; 5(1):170–5. https://doi.org/10.1159/000370109 PMID: 26034488

6. Heringa SM, Bouvy WH, van den Berg E, Moll AC, Kappelle LJ, Biessels GJ. Associations between retinal microvascular changes and dementia, cognitive functioning, and brain imaging abnormalities: a systematic review. Journal of cerebral blood flow and metabolism: official journal of the International Society of Cerebral Blood Flow and Metabolism. 2013; 33(7):983–95.

7. Charytan DM, Shelbert HR, Di Carli MF. Coronary microvascular function in early chronic kidney disease. Circulation Cardiovascular imaging. 2010; 3(6):663–71. https://doi.org/10.1161/CIRCIMAGING.110.957761 PMID: 20851872

8. Kuusisto J, Mykkanen L, Pyorala K, Laakso M. Hyperinsulinemic microalbuminuria. A new risk indicator for coronary heart disease. Circulation. 1995; 91(3):831–7. https://doi.org/10.1161/01.cir.91.3.831 PMID: 7828312

9. Stehouwer CD, Nauta JJ, Zeldenrust GC, Hackeng WH, Donker AJ, den Ottolander GJ. Urinary albumin excretion, cardiovascular disease, and endothelial dysfunction in non-insulin-dependent diabetes mellitus. Lancet (London, England). 1992; 340(8815):319–23.

10. Borch-Johnsen K, Feldt-Rasmussen B, Strandgaard S, Schroll M, Jensen JS. Urinary albumin excretion. An independent predictor of ischemic heart disease. Arteriosclerosis, thrombosis, and vascular biology. 1999; 19(8):1992–7. https://doi.org/10.1161/01.atv.19.8.1992 PMID: 10446083

11. Naha S, Naha K, Pandit VR, Balasubramanian R. Association of microalbuminuria with ischemic heart disease in non-diabetic Asian-Indians: A case control study. Avicenna Journal of Medicine. 2015; 5 (1):6–10. https://doi.org/10.4103/2231-0770.148501 PMID: 25625083

12. Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. Jama. 2001; 286 (4):421–6. https://doi.org/10.1001/jama.286.4.421 PMID: 11466120

13. Arnlöv J, Evans JC, Meigs JB, Wang TJ, Fox CS, Levy D, et al. Low-grade albuminuria and incidence of cardiovascular disease events in nonhypertensive and nondiabetic individuals: the Framingham Heart Study. Circulation. 2005; 112(7):969–75. https://doi.org/10.1161/CIRCULATIONAHA.105.538132 PMID: 16087792

14. Thomson LE, Wei J, Agarwal M, Haft-Baradaran A, Shufelt C, Mehta PK, et al. Cardiac magnetic resonance myocardial perfusion reserve index is reduced in women with coronary microvascular dysfunction. A National Heart, Lung, and Blood Institute-sponsored study from the Women's Ischemia Syndrome Evaluation. Circulation Cardiovascular imaging. 2015; 8(4):e002481. https://doi.org/10.1161/CIRCIMAGING.114.002481 PMID: 25801710

15. Wei J, Mehta PK, Johnson BD, Samuels B, Kar S, Anderson RD, et al. Safety of coronary reactivity testing in women with no obstructive coronary artery disease: results from the NHLBI-sponsored WISE (Women's Ischemia Syndrome Evaluation) study. JACC Cardiovasc Interv. 2012; 5(6):646–53. https://doi.org/10.1016/j.jcin.2012.01.023 PMID: 22721660

16. Mattix HJ, Hsu CY, Shaykevich S, Curhan G. Use of the albumin/creatinine ratio to detect microalbuminuria: implications of sex and race. J Am Soc Nephrol. 2002; 13(4):1034–9. https://doi.org/10.1681/ASN.V1341034 PMID: 11912263

17. Solomon SD, Lin J, Solomon CG, Jablonski KA, Rice MM, Steffes M, et al. Influence of albuminuria on cardiovascular risk in patients with stable coronary artery disease. Circulation. 2007; 116(23):2687–93. https://doi.org/10.1161/CIRCULATIONAHA.107.723270 PMID: 18025537

18. Holm S. A simple sequentially rejective multiple test procedure. Scandinavian Journal of Statistics. 1979; 6 (2):65–70.

19. Tsiachris D, Tsioufis C, Dimitriadis K, Syrseloudis D, Rousos D, Kasiakogias A, et al. Relation of impaired coronary microcirculation to increased urine albumin excretion in patients with systemic hypertension and no epicardial coronary arterial narrowing. Am J Cardiol. 2012; 109(7):1026–30. https://doi.org/10.1016/j.amjcard.2011.11.035 PMID: 22221953

20. Chade AR, Brosh D, Higano ST, Lennon RJ, Lerman LO, Lerman A. Mild renal insufficiency is associated with reduced coronary flow in patients with non-obstructive coronary artery disease. Kidney Int. 2006; 69(2):266–71. https://doi.org/10.1038/sj.ki.5000031 PMID: 16408115

21. Sakamoto N, Iwaya S, Owada T, Nakamura Y, Yamauchi H, Hoshino Y, et al. A reduction of coronary flow reserve is associated with chronic kidney disease and long-term cardio-cerebrovascular events in patients with non-obstructive coronary artery disease and vasospasm. Fukushima J Med Sci. 2012; 58 (2):136–43. https://doi.org/10.5387/fms.58.136 PMID: 23237869

22. Reis SE, Olson MB, Fried L, Reeser V, Mankad S, Pepine CJ, et al. Mild renal insufficiency is associated with angiographic coronary artery disease in women. Circulation. 2002; 105(24):2826–9. https://doi.org/10.1161/01.cir.0000021597.63026.65 PMID: 12070108

23. Weir MR. Microalbuminuria and cardiovascular disease. Clinical journal of the American Society of Nephrology: CJASN. 2007; 2(3):581–90. https://doi.org/10.2215/CJN.03190906 PMID: 17699466

24. Lo Iudice F, Galderisi M, D'Amore C, Savarese G, Marciano C, Casaretti L, et al., editors. Endothelial dysfunction as a link between renal and coronary microvascular dysfunction in type II diabetic patients with normal coronary arteries: a transthoracic echocardiographic doppler study. EUROPEAN HEART JOURNAL; 2013: OXFORD UNIV PRESS GREAT CLARENDON ST, OXFORD OX2 6DP, ENGLAND.

25. Vassalotti JA, Stevens LA, Levey AS. Testing for chronic kidney disease: a position statement from the National Kidney Foundation. American journal of kidney diseases: the official journal of the National Kidney Foundation. 2007; 50(2):169–80.

26. Cosson E, Pham I, Valensi P, Paries J, Attali JR, Nitenberg A. Impaired coronary endothelium-dependent vasodilation is associated with microalbuminuria in patients with type 2 diabetes and angiographically normal coronary arteries. Diabetes care. 2006; 29(1):107–12. https://doi.org/10.2337/diacare.29.1.107 PMID: 16373905

27. Johnson BD, Shaw LJ, Buchthal SD, Bairey Merz CN, Kim HW, Scott KN, et al. Prognosis in women with myocardial ischemia in the absence of obstructive coronary disease: results from the National Institutes of Health-National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE). Circulation. 2004; 109(24):2993–9. https://doi.org/10.1161/01.CIR.0000130642.79868.B2 PMID: 15197152

28. Shaw LJ, Bugiardini R, Merz CNB. Women and Ischemic Heart Disease: Evolving Knowledge. Journal of the American College of Cardiology. 2009; 54(17):1561–75. https://doi.org/10.1016/j.jacc.2009.04.098 PMID: 19833255

29. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. Lancet (London, England). 2000; 355(9200):253–9.

30. Agrawal B, Berger A, Wolf K, Luft FC. Microalbuminuria screening by reagent strip predicts cardiovascular risk in hypertension. Journal of hypertension. 1996; 14(2):223–8. https://doi.org/10.1097/00004872-199602000-00011 PMID: 8728300

31. Niskanen L, Turpeinen A, Penttila I, Uusitupa MI. Hyperglycemia and compositional lipoprotein abnormalities as predictors of cardiovascular mortality in type 2 diabetes: a 15-year follow-up from the time of diagnosis. Diabetes care. 1998; 21(11):1861–9. https://doi.org/10.2337/diacare.21.11.1861 PMID: 9802734

32. Cirillo M, Senigalliesi L, Laurenzi M, Alfieri R, Stamler J, Stamler R, et al. Microalbuminuria in nondiabetic adults: relation of blood pressure, body mass index, plasma cholesterol levels, and smoking: The Gubbio Population Study. Archives of internal medicine. 1998; 158(17):1933–9. https://doi.org/10.1001/archinte.158.17.1933 PMID: 9759691

33. Lerman A, Zeiher AM. Endothelial function: cardiac events. Circulation. 2005; 111(3):363–8. https://doi.org/10.1161/01.CIR.0000153339.27064.14 PMID: 15668353

34. Kobayashi M, Hirawa N, Yatsu K, Kobayashi Y, Yamamoto Y, Saka S, et al. Relationship between silent brain infarction and chronic kidney disease. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association—European Renal Association. 2009; 24(1):201–7.

35. Ooi QL, Tow FKN-FH, Deva R, Alias MA, Kawasaki R, Wong TY, et al. The Microvasculature in Chronic Kidney Disease. Clinical journal of the American Society of Nephrology: CJASN. 2011; 6(8):1872–8. https://doi.org/10.2215/CJN.10291110 PMID: 21784828

36. Anderson TJ, Uehata A, Gerhard MD, Meredith IT, Knab S, Delagrange D, et al. Close relation of endothelial function in the human coronary and peripheral circulations. J Am Coll Cardiol. 1995; 26(5):1235–41. https://doi.org/10.1016/0735-1097(95)00327-4 PMID: 7594037

37. Atkins RC, Briganti EM, Lewis JB, Hunsicker LG, Braden G, Champion de Crespigny PJ, et al. Proteinuria reduction and progression to renal failure in patients with type 2 diabetes mellitus and overt nephropathy. American journal of kidney diseases: the official journal of the National Kidney Foundation. 2005; 45(2):281–7.

38. de Zeeuw D, Remuzzi G, Parving HH, Keane WF, Zhang Z, Shahinfar S, et al. Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: lessons from RENAAL. Kidney international. 2004; 65(6):2309–20. https://doi.org/10.1111/j.1523-1755.2004.00653.x PMID: 15149345

39. Viberti G, Wheeldon NM. Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus: a blood pressure-independent effect. Circulation. 2002; 106(6):672–8. https://doi.org/10.1161/01.cir.0000024416.33113.0a PMID: 12163426

40. Pauly DF, Johnson BD, Anderson RD, Handberg EM, Smith KM, Cooper-DeHoff RM, et al. In women with symptoms of cardiac ischemia, nonobstructive coronary arteries, and microvascular dysfunction, angiotensin-converting enzyme inhibition is associated with improved microvascular function: A double-

blind randomized study from the National Heart, Lung and Blood Institute Women's Ischemia Syndrome Evaluation (WISE). American heart journal. 2011; 162(4):678–84. https://doi.org/10.1016/j.ahj.2011.07.011 PMID: 21982660

41. Wachtell K, Ibsen H, Olsen MH, Borch-Johnsen K, Lindholm LH, Mogensen CE, et al. Albuminuria and cardiovascular risk in hypertensive patients with left ventricular hypertrophy: the LIFE study. Annals of internal medicine. 2003; 139(11):901–6. https://doi.org/10.7326/0003-4819-139-11-200312020-00008 PMID: 14644892