Epidemiology of chronic kidney disease in Europe

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Citation for published version (APA):
Brück, K. (2016). Epidemiology of chronic kidney disease in Europe.
CHAPTER 7:

Longitudinal association of body mass index and waist circumference with left ventricular mass in hypertensive predialysis chronic kidney disease patients

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Nephrology Dialysis & Transplantation. 2013 Nov;28 Suppl 4: iv136-45.
http://ndt.oxfordjournals.org/content/28/suppl_4/iv136.long
ABSTRACT

Background
This study aimed to investigate the association of both body mass index (BMI) and waist circumference (WC) with left ventricular mass (LVM) in hypertensive predialysis chronic kidney disease (CKD) patients.

Methods
From 2004 to 2005, 206 consecutive incident adult patients from the outpatient CKD clinics of two hospitals in Greece were included. Inclusion criteria were the presence of CKD and hypertension. BMI (kg/m²), WC (cm) and LVM (g) were assessed annually for 3 years.

Results
The mean age was 68.1 years, mean BMI 29.1 kg/m² and mean WC was 103.7 cm. The median LVM was 245.7 g (n = 179). In the cross-sectional data, linear regression models showed that WC [β = 1.2 (95% confidence interval (CI) 0.15; 2.3)], and not BMI [β = 2.1 (95% CI: -0.70; 4.8)], was significantly associated with LVM. After adjustment for age, sex, primary renal disease, smoking and history of cardiovascular disease, both BMI [β = 4.7 (95% CI: 2.0; 7.4)] and WC [β = 1.2 (95% CI: 0.14; 2.3)] were significantly associated with LVM. These associations were pronounced in CKD stage 1–3, but not in CKD stage 4–5. In the longitudinal analysis, linear mixed models adjusting for confounders showed that both an increase in BMI [β = 2.9 (95% CI: 0.74; 5.1)] and an increase in WC [β = 1.1 (95% CI: 0.28; 1.8)] were significantly associated with an increase in LVM.

Conclusions
In hypertensive predialysis CKD patients, both BMI and WC were associated with LVM in CKD stage 1–3, but not in CKD stage 4–5. In the longitudinal analysis, both an increase in BMI and WC were associated with an increase in LVM. Future studies should focus on mechanisms responsible for the associations between anthropometric variables and LVM.

INTRODUCTION
Cardiovascular events, mortality and the progression to endstage renal disease (ESRD) are major complications of chronic kidney disease (CKD) (1–3). Previous studies have shown that a patient with CKD is at higher risk of developing a cardiovascular event than reaching ESRD (4–6). Left ventricular hypertrophy (LVH), a common comorbidity in CKD patients and hypertensive patients (7–10), is a strong risk factor for cardiovascular events and mortality (11–14). Therefore, identification of modifiable risk factors for increased LV mass (LVM) to prevent LVH and its major consequences in CKD patients is needed, especially in those with hypertension as this is an important risk factor for increased LVM.

Obesity, a worldwide health problem, is a potential risk factor for an increase in LVM and for chronic diseases like CKD (15, 16). Once patients have acquired CKD, obesity adds to the increased risk of cardiovascular events (17). Studies in dialysis (18) and predialysis CKD patients (17, 19, 20) recently suggested that abdominal obesity is a better predictor for adverse events than body mass index (BMI). BMI does not distinguish between weight from muscle and fat, and this might obscure the relationship between BMI and outcome. In contrast, waist circumference (WC) detects abdominal obesity and visceral fat, which appear to be the most important fat deposits affecting cardiovascular risk (21). So far, to our knowledge, studies investigating both BMI and WC as risk factors for LVM in (hypertensive) predialysis CKD patients are lacking. Furthermore, longitudinal studies with LVM as an outcome are very limited in this patient group (22).

Therefore, this longitudinal study aimed to investigate the association of both BMI and WC with LVM in hypertensive predialysis CKD patients.

METHODS
Patients
From 2004 to 2005, 206 consecutive incident adult patients from the outpatient CKD clinics of two hospitals in Greece were included in this study. Prior to the study, inclusion patients were followed up for 3 months to confirm the presence of CKD. The study population included patients with hypertension only (93% of study population), getting a more homogenous patient population in which all had this important risk factor for increased LVM. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg or if they were using antihypertensive medication. Exclusion criteria were a history of malignancy with a ‘free of disease’ period of <5 years, and the presence or history of inflammation or a major cardiovascular event of <5 years, and the presence or history of inflammation or a major cardiovascular event, defined as stroke, myocardial infarction or acute ischaemic heart disease, during the last 3 months prior to study entry. The definition of CKD was based on the Clinical Practice Guidelines for Chronic Kidney Disease (Kidney Disease Outcomes Quality Initiative) (23). The study was approved by local ethical committees of the two hospitals, and patients participated after providing
We used linear regression analysis to test the association between BMI and WC with a p-value lower than 0.05 was considered as statistically significant.

Data collection at baseline and follow-up
At study entry, the patients underwent a detailed review of their medical history and careful clinical examination. BMI, WC and LVM were assessed annually for a period of 3 years. Additionally, baseline measurements, including demographic characteristics, primary renal disease, diabetic status, smoking habits, medication and blood pressure, were assessed. A full haematology and biochemical screen was performed and estimated glomerular filtration rate (eGFR) (mL/min/1.73 m²) was calculated by the CKD-EPI formula (24).

Independent variables
BMI was calculated by dividing body weight (kg) by height² (m²). BMI was used as a continuous variable and was categorized into normal weight (18.5-24.9 kg/m²), overweight (25-29.9 kg/m²), and obese (>30 kg/m²). WC was measured in centimeters with the patient erect and the tape horizontally placed just above the iliac crest.

Outcome variables
The primary outcome was LVM. The secondary outcomes were LVM corrected for height² (m²) and LVM corrected for body surface area. We chose the uncorrected LVM as the primary outcome, because the anthropometric variables (which are used to calculate the corrected LVM outcomes) were also used as independent variables.

LVM was assessed by 2D-mode echocardiographic screening and Doppler for valve flow, which were performed within one week and no longer than one month from study entry, by a single cardiologist from each hospital, who followed a predefined protocol for the recordings and measurements (25). Left ventricular end-diastolic diameter (LVEDD), interventricular septum (IVS) and posterior wall (PW) thickness were measured according to the Penn Convention (26). LVM was estimated in grams with the Devereux formula (LVM = 1.04 x ((LVEDD + PW + IVS)³ − LVEDD²) − 13.6 g) (27).

Statistical analysis
Data are presented as mean and standard deviation (for normally distributed data), median and interquartile range (for non-normally distributed data), or as frequency in percent. To compare the patient characteristics across BMI categories we used tests for trend of means (for normally distributed data), and medians (for non-normally distributed data), or as frequency in percent (for categorical variables). A two-tailed p-value lower than 0.05 was considered as statistically significant.

We used linear regression analysis to test the association between both BMI and WC with LVM. For each association (i.e. BMI with LVM and WC with LVM) three models were built. Model 1 was an unadjusted model and Model 2 was adjusted for variables fulfilling the criteria for confounding (28), i.e. age, sex, primary renal disease, smoking, and a history of CVD. Model 3 was adjusted for the confounders of model 2 plus eGFR, in order to examine to what extent the associations were mediated by eGFR.

Additionally, the following two analyses were performed to test whether an interaction existed between both BMI and WC with CKD stage, systolic blood pressure, pulse pressure and sex. First, the corresponding multiplicative terms were introduced into the linear regression models. Second, unadjusted and adjusted linear regression models were performed by CKD stage, by tertiles of systolic blood pressure groups, by tertiles of pulse pressure groups, and by sex.

Linear mixed models were used to analyze the association between both BMI and WC with LVM using 3 year follow-up data, thereby adjusting for multiple measurements in the same patient and for possible confounders. For both associations (i.e. change in BMI with change in LVM and change in WC with change in LVM) the same three models were built as described above. The analyses were performed within IBM SPSS Statistics 19 and SAS version 9.2.

RESULTS
Baseline characteristics
Table 1 shows the characteristics of the whole patient population (n=206) and for those with at least one follow-up measurement on LVM (n=107), overall and by BMI category. Of the 206 individuals, the mean age was 68.1 years, mean BMI was 29.1 kg/m² (sd=5.0), and mean WC was 103.7 cm (sd=12.6). The 179 patients having data available on LVM had a median LVM of 245.7 g (males 297.4 g; females 220.8 g), a median LVM corrected for height of 69 g/m² (males 70.4 g/m²; females 64.6 g/m²), and a median LVM corrected for body surface area of 137.6 g/m² (males 154.0 g/m²; females 122.5 g/m²). The proportion of females, the proportion of patients with a history of a cardiovascular disease and the proportion of patients using diuretics, aspirin and statins increased with increasing BMI (p<0.05). In addition, LVM (height corrected) decreased with increasing BMI (p<0.05). Remarkably, in this group of predialysis CKD patients with hypertension, the proportion of current smokers decreased, eGFR estimated by CKD-EPI and MDRD increased, and systolic blood pressure and LDL decreased with increasing BMI category (p<0.05). It should be noted that for the 107 persons with follow-up data on LVM, systolic blood pressure and LDL did not significantly change by BMI category.
### Table 1: Baseline characteristics of pre RRT chronic kidney disease patients with hypertension, by body mass index (BMI) categories for persons at baseline (n=206).

| All persons (N=207) | Baseline BMI (kg/m²) | p value |
|---------------------|----------------------|---------|
|                     | All                  | Normal 18.5-24.9 | Overweight 25-29.9 | Obesity >=30 |         |
| Number (%)          | 206 (100)            | 47 (22.8)        | 79 (38.3)         | 80 (38.8)    |         |
| Age, years (years)  | 68.1 (60.5-73.7)     | 65.0 (51.7-71)   | 68.5 (60.4-74.4)  | 70.4 (62.0-74.0) | 0.03 |
| Male, %             | 52.9                 | 72.3             | 60.8              | 33.8         | <0.001 |
| DM, %               | 32.0                 | 25.5             | 27.8              | 40.0         | 0.07   |

#### Smoking, %

|                     | Never | Ex-smoker | Current | Hx of CVD, % |
|---------------------|-------|-----------|---------|--------------|
| No                  | 58.3  | 36.2      | 62.0    | 67.5         |
| p value             | 0.002 |

#### Primary renal disease, %

|                     | Glomerulonephritis | Diabetic nephropathy | Hypertensive nephrosclerosis | Other | Unknown |
|---------------------|--------------------|----------------------|-----------------------------|-------|---------|
| No                  | 8.7                | 15.5                 | 17.0                        | 25.8  | 33      |
| p value             | 0.1                |

#### eGFR, ml/min/1.73m²

|                     | CKD-EPI | CKD stage 1 | CKD stage 2 | CKD stage 3 | CKD stage 4-5* |
|---------------------|---------|-------------|-------------|-------------|----------------|
| No                  | 42.3 (27.2-68.8) | 13.6 | 24.8 | 38.3 | 23.3 |
| p value             | 0.06 |

#### DM= diabetes mellitus, Hx of CVD= History of cardiovascular disease, eGFR= estimated glomerular filtration rate. *CKD stage 4-5 not on renal replacement therapy. Results of continuous variables are presented as mean (SD) or median (25th and 75th percentile).
### Table 1: for all persons at baseline (n=206). (continued)

| Antropometric measures, cm | All persons (N=206) | Normal (18.5-24.9) | Overweight (25-29.9) | Obesity (≥30) | p value |
|----------------------------|---------------------|---------------------|----------------------|----------------|---------|
| WC                         | 103.7 (12.6)        | 90.1 (7.3)          | 100.8 (7.1)          | 114.5 (9.8)    | <0.001  |
| Left ventricular mass (LVM)* |                     |                     |                      |                |         |
| LVM, g                     | 245.7 (192.7-331.5) | 228.4 (190.0-297.4) | 253.6 (191.6-341.1)  | 253.3 (209.1-339.2) | 0.09    |
| LVM height indexed, g/m²   | 69.0 (52.5-86.0)    | 60.1 (48.9-74.4)    | 68.6 (50.4-85.5)     | 75.7 (58.7-95.7) | 0.001   |
| LVM body surface area indexed, g/m² | 137.6 (105.5-172.2) | 138.7 (106.1-173.7) | 139.9 (105.4-181.7)  | 134.8 (104.6-169.6) | 0.79    |
| Blood pressure (BP), mmHg  |                     |                      |                      |                |         |
| Systolic BP                | 142.5 (18.3)        | 146.4 (21.6)        | 143.6 (17.5)         | 139.1 (6.5)    | 0.03    |
| Diastolic BP               | 81.2 (10.9)         | 82.5 (13.3)         | 81.3 (9.6)           | 80.5 (10.7)    | 0.31    |
| Pulse pressure             | 61.2 (16.6)         | 63.9 (19.2)         | 62.3 (16.9)          | 58.7 (14.5)    | 0.09    |
| Lipids, mg/dl              |                     |                      |                      |                |         |
| LDL                        | 128.4 (36.3)        | 134.9 (38.6)        | 132.0 (36.1)         | 120.9 (34.3)   | 0.04    |
| HDL                        | 51.9 (13.2)         | 54.0 (12.5)         | 54.0 (12.8)          | 48.7 (13.6)    | 0.03    |
| Inflammatory factors, mg/l |                     |                      |                      |                |         |
| C-reactive protein (CRP)   | 2.0 (0.9-5.0)       | 2.0 (0.6-4.0)       | 2.0 (1.0-6.0)        | 2.2 (0.6-5.0)  | 0.51    |
| Medications, %             | ACEi                | 39.8                | 34.0                 | 45.6           | 37.5    | 0.87    |
|                            | ARB                 | 26.2                | 21.3                 | 29.1           | 26.3    | 0.63    |
|                            | Diuretic            | 53.4                | 36.2                 | 39.2           | 57.5    | 0.03    |
|                            | Aspirin             | 17.0                | 6.4                  | 17.7           | 22.5    | 0.02    |
|                            | Statin              | 34.0                | 19.1                 | 39.2           | 37.5    | 0.06    |

*Data available for 179 persons. Results of continuous variables are presented as mean (SD) or median (25th and 75th percentile).

### Table 1: for persons with follow-up data on left ventricular mass (n=107). (continued)

| Antropometric measures, cm | Persons with follow-up data on left ventricular mass (n=107) | Baseline BMI (kg/m²) | Normal (18.5-24.9) | Overweight (25-29.9) | Obesity (≥30) | p value |
|----------------------------|-------------------------------------------------------------|---------------------|---------------------|----------------------|----------------|---------|
| WC                         | 106.9 (13.2)                                                | 107 (100)           | 20 (18.7)           | 34 (31.8)           | 53 (49.5)      | <0.001  |
| Left ventricular mass (LVM) |                                                             |                     |                      |                      |                |         |
| LVM, g                     | 244.5 (190.0-330.6)                                         | 219.6 (163.4-320.2) | 242.4 (173.3-335.0) | 250.2 (207.6-323.1) | 0.17    |
| LVM height indexed, g/m²   | 67.7 (50.8-86.0)                                            | 57.0 (47.7-75.4)    | 60.9 (45.2-81.9)    | 74.0 (58.3-94.4)    | 0.008   |
| LVM body surface area indexed, g/m² | 130.8 (102.6-167.7)                                      | 127.1 (105.8-187.2) | 128.8 (94.5-181.7)  | 132.4 (103.4-163.7) | 0.98    |
| Blood pressure (BP), mmHg  |                                                             |                      |                      |                      |                |         |
| Systolic BP                | 139.3 (17.3)                                                | 139.3 (17.3)        | 138.7 (17.8)        | 139.7 (16.8)       | 0.92    |
| Diastolic BP               | 79.1 (11.1)                                                 | 80.6 (12.2)         | 77.1 (10.3)         | 79.8 (11.2)        | 0.8     |
| Pulse pressure             | 60.2 (15.5)                                                 | 58.7 (15.4)         | 61.7 (16.9)         | 59.9 (14.8)        | 0.77    |
| Lipids, mg/dl              |                                                             |                      |                      |                      |                |         |
| LDL                        | 121.9 (32.3)                                                | 128.0 (36.8)        | 125.1 (30.4)        | 117.6 (31.7)       | 0.22    |
| HDL                        | 52.3 (14.9)                                                 | 55.4 (16.3)         | 55.7 (15.0)         | 48.9 (13.8)        | 0.1     |
| Inflammatory factors, mg/l |                                                             |                      |                      |                      |                |         |
| C-reactive protein (CRP)   | 1.0 (0.31-3.5)                                              | 0.95 (0.17-2.15)    | 1.0 (0.39-3.5)      | 1.13 (0.38-4.1)    | 0.53    |
| Medications, %             | ACEi                                                          | 39.3                | 25.0                 | 47.1              | 39.6    | 0.43    |
|                            | ARB                                                           | 27.1                | 20.0                 | 26.5              | 30.2    | 0.39    |
|                            | Diuretic                                                      | 59.8                | 40.0                 | 55.9              | 69.8    | 0.02    |
|                            | Aspirin                                                       | 18.7                | 5.0                  | 17.6              | 24.5    | 0.06    |
|                            | Statin                                                        | 35.5                | 25.0                 | 44.1              | 34.0    | 0.74    |

Results of continuous variables are presented as mean (SD) or median (25th and 75th percentile).
Figures 1a, 1b, and 1c show the mean BMI, mean WC and median LVM by CKD stage. BMI and WC were lowest in CKD stage 4-5, whereas LVM was highest in CKD stage 4-5.

Cross sectional associations
Figure 2 and Table 2 show the association between BMI and LVM and that between WC and LVM. In the unadjusted analysis (model 1), WC, and not BMI (as a continuous variable) was significantly associated with LVM. After adjustment for confounders (model 2), both BMI and WC were significantly associated with LVM. Additional adjustment for eGFR increased all betas to some extent (model 3). When analyzing the association between BMI as a categorical variable with LVM, patients who were overweight or obese had a significantly higher LVM compared to patients with normal weight, both in the unadjusted and adjusted analyses (Table 2). When adding interaction terms in the linear regression models, those of BMI with CKD stage, systolic blood pressure, pulse pressure and sex, and the interaction terms of WC with CKD stage, systolic blood pressure, pulse pressure and sex failed to reach statistical significance. Nevertheless, when performing linear regression models by CKD stage, the adjusted models showed that both BMI and WC were associated with LVM in CKD stage 1-3, but not in CKD stage 4-5 (Table 3), suggesting an interaction between BMI and CKD stage and between WC and CKD stage in the association with LVM. As CKD stage 4-5 contained fewer patients than CKD stage 1-2 and CKD stage 3, we performed these analyses also by eGFR in tertiles, and obtained similar results. After adjustment for age, smoking and history of cardiovascular disease, the association between both BMI and LVM and WC and LVM was more pronounced in males (beta=7.4; 95% confidence interval (ci): 2.2; 12.6 and beta=3.8; 95% ci: 0.81; 6.7 respectively) than in females (beta=2.13; 95% ci: .011;4.2 and beta=1.02; 95% ci: -.33; 2.7 respectively).

Longitudinal associations
Table 4 shows that in persons with BMI, WC and LVM measurements both at baseline and at 3 years (n=71), the mean BMI did not significantly change over 3 years, whereas the mean WC was significantly lower after 3 years and the median LVM significantly higher after 3 years. In 66.2% of this patient population with 3 year follow-up data, LVM had increased over 3 years with a median (25th-75th percentile) increase of 54.6 gram (27.3-75.6 gram).

Table 5 shows the associations between the change in BMI and the change in LVM as well as between the change in WC and the change in LVM. In the unadjusted analysis a change in BMI was not associated with a change in LVM. In contrast, an increase in WC was associated with an increase in LVM. After adjustment (model 2), both an increase in BMI and an increase in WC were associated with an increase in LVM. Additional adjustment for eGFR increased the effect to some extent (model 3).
Table 2: The association between body mass index and waist circumference with left ventricular mass using linear regression analysis in cross-sectional data.

|                      | Model 1: Unadj | Model 2: Adj* | Model 3: Adj** |
|----------------------|---------------|---------------|----------------|
| BMI continuous       |               |               |                |
| Normal               | 1             | I             | I              |
| Overweight           | (0.17, 1.5)   | (0.65, 2.1)   | (0.91, 2.3)    |
| Obesity              | 1.6           | 1.6           | 1.6            |
| WC                   | 1             | I             | I              |
| n=179                |               |               |                |
| Left ventricular mass (g) |               |               |                |
| Model 2: Adj*       |               |               |                |
| BMI continuous       |               |               |                |
| Normal               | 1             | I             | I              |
| Overweight           | 0.9           | 0.9           | 0.9            |
| Obesity              | 1.2           | 1.2           | 1.2            |
| WC                   | 1             | I             | I              |
| n=179                |               |               |                |
| Left ventricular mass (g/m²) |               |               |                |
| Model 3: Adj**      |               |               |                |
| BMI continuous       |               |               |                |
| Normal               | 1             | I             | I              |
| Overweight           | 0.74          | 0.74          | 0.74           |
| Obesity              | 0.27          | 0.27          | 0.27           |
| WC                   | 1             | I             | I              |
| n=179                |               |               |                |
| Left ventricular mass height indexed (g/m²) |               |               |                |
| Model 2: Adj*       |               |               |                |
| BMI continuous       |               |               |                |
| Normal               | 1             | I             | I              |
| Overweight           | 1.4           | 1.4           | 1.4            |
| Obesity              | -0.18         | -0.18         | -0.18          |
| WC                   | 1             | I             | I              |
| n=179                |               |               |                |

* Model 2 adjusted for age, smoking, primary renal disease and history of cardiovascular disease.
** Model 3 adjusted for confounders of model 2 and eGFR.

Figure 2: Correlation between body mass index (left figure) and waist circumference (right figure) with left ventricular mass (n=206).
Table 3: The association between both body mass index and waist circumference with left ventricular mass, by CKD stage using linear regression analysis in cross sectional data.

| CKD stage | Left ventricular mass (g) |
|-----------|----------------------------|
|            | Model 1: Unadj | Model 2: Adj* |
| 1-2        | 1.3 (2.9; 5.5) | 1.3 (1.9; 6.1) |
| 3          | 4.2 (3.6; 4.9) | 2.3 (1.0; 3.5) |
| 4          | 4.7 (6.7; 4.3) | 3.6 (2.1; 11.3) |

*Data based on 71 persons who had BMI, WC and LVM measurements both at baseline and at 3 years. # Parametric paired t-test (for BMI and WC) and the Wilcoxon matched-pair signed-rank test (for LVM) were used.

Table 4: Mean BMI, mean waist circumference and median left ventricular mass at baseline and at 3 years follow-up (n=71*).

|            | Baseline | At 3 years follow-up | Baseline vs. 3 year follow-up p-value # |
|------------|----------|-----------------------|------------------------------------------|
| BMI, kg/m² | 30.6 (5.4) | 30.4 (5.6) | 0.99                                      |
| WC, cm     | 107.9 (12.5) | 105.2 (14.1) | 0.006                                     |
| LVM, g     | 227.3 (165.6; 294.2) | 253.7 (198.0; 333.7) | 0.002                                     |

Discussion

In this study of predialysis hypertensive CKD patients, we noted that WC, and not BMI, was significantly associated with LVM. However, after adjustment for confounders, both BMI and WC were associated with LVM. The results suggested that this association was pronounced in CKD stages 1-3 but not in CKD stages 4-5. In the longitudinal analysis, both an increase in BMI and an increase in WC were associated with an increase in LVM. The identification of these anthropometric variables as risk factors for LVM is essential for the prevention of LVH and its major consequences like cardiovascular mortality, especially in light of the current obesity epidemic.

Comparison of BMI and WC

Data from observational studies show that in predialysis CKD patients and dialysis patients measures of central obesity and visceral fat like WC and waist-to-hip ratio (WHR) may better predict adverse clinical outcomes including mortality than BMI. A likely explanation for this is that WC, and not BMI, mainly measures abdominal fat which reflects visceral fat, the most important fat deposit affecting cardiovascular risk. In line with this, other studies have shown that WC is highly correlated with both visceral fat (30, 31) and subcutaneous fat (31), whereas BMI is only highly correlated with subcutaneous fat (31). In contrast, WHR is highly correlated with visceral fat, and not with subcutaneous fat (31). Indeed, some studies found WHR to be a better predictor for adverse outcomes than both WC and BMI. Unfortunately, WHR was not available in our study.

After adjustment for potential confounders we found that both BMI and WC were significantly associated with LVM. These adjusted associations of both BMI and WC with LVM were, however, pronounced in CKD stages 1 to 3 but not in CKD stages 4-5. In patients with higher CKD stages in whom muscle wasting is common, a lower BMI and WC may not (only) reflect lower visceral fat (and lower CVD risk), but may also reflect lower muscle mass (and higher CVD risk). It should be noted that so far most studies in predialysis patients which have shown an association between anthropometric measures and adverse clinical outcomes like mortality or CVD, were performed in CKD stage 3 (17, 19), whereas little is known about these associations in CKD stage 4. The study by Kramer et al. (20) including patients with CKD stages 1 to 4 found no significant interaction between anthropometric variables and CKD stage in the association with all-cause mortality. In our study, we did not find any significant interaction terms either when adding interaction terms in the regression models. However, when analyzing the data by CKD stage, the results suggested an interaction between BMI and CKD stage and between WC and CKD stage in the association with LVM. With regard to the lower BMI in advanced CKD stages, it cannot be overemphasized that within CKD patients, obesity cannot be seen as a protective factor for adverse outcomes, as illustrated by a study of Honda et al. (32), in which low muscle mass at any level of fat mass was a strong predictor for mortality in CKD patients.

Longitudinal association of BMI and WC with LVM in hypertensive predialysis CKD patients

Studies with longitudinal data on LVM in patients with CKD are extremely scarce (22). A study by Eckhard (2009) showed that the LVMI did not significantly change over 3 years in patients with CKD stage 3 and 4 (33). In contrast, our study showed a significant increase of LVM in 3 years. To our knowledge studies examining the association between change in BMI and change in LVM or CVD are lacking. The study by Okumura (22) was the only one on factors associated with change in eGFR and LVM in CKD patients with hypertension. However, anthropometry was not assessed in this study. Interestingly, our study showed for the first time that an increase of BMI and an increase of WC were associated with an increase of LVM persisted after adjustment for potential confounders. This crucial
finding could help the prevention of LVH, and eventually its major consequences like cardiovascular mortality.

However, several longitudinal studies examined the association between anthropometric measures and CVD or mortality in this patient group (17, 19, 20). As mentioned before, these studies have shown that WC and WHR may better predictors for adverse outcomes than BMI.

**Potential mechanisms**

Traditionally, the association between obesity and LVM has been explained through hemodynamic changes. However, in our study the mean pulse pressure and mean systolic blood pressure were lower in the obese group in comparison to the normal weight group. This could indicate that, at least in pre dialysis CKD patients with hypertension, the association between obesity and LVM is more complex than simple hemodynamic effects. Numerous studies have shown that increased visceral and subcutaneous adiposity causes dysfunction of adipohormones and elevates systemic inflammatory cytokines (34). Adipohormones, such as adiponectin and leptin have a proliferative effect on smooth muscle cells and lead to increased vascular stiffness and LVH. On the other hand, cytokines secreted by the adipocytes such as hs-CRP and IL-6 lead to endothelial dysfunction which may also cause LVH (35). It should be noted however that in our study the median CRP was similar across the BMI groups, which suggests that the association between obesity and LVM may not be explained by CRP. However, it is of notice that there was an increasing use of statins and aspirin across the BMI groups (Table 1) and this might have influenced (decreased) the level of inflammation and therefore of CRP.

Identification of the mechanisms through which obesity influences LVM is essential for the prevention of LVH and its major consequences like cardiovascular events and mortality (11-14). The association between obesity and LVM indicates that obesity can be used as a modifiable risk factor in the reduction of CVD mortality. Rider et al. (36) proved that weight loss leads to a reduction in LVM in obese non-CKD persons. Nonetheless, future studies are needed to confirm this effect in CKD patients.

**Strengths and limitations**

The main strength of this study was the availability of longitudinal data on BMI, WC and LVM, the inclusion of patients from all CKD stages and use of the chronicity criterion. However, our study has some limitations. First, 2-D echocardiography was used despite the limitations of this technique for the quantification of LVM, mainly regarding geometric assumptions and the dependence on adequate endocardial and epicardial border definitions of the LV (37). Cardiac magnetic resonance imaging (CMRI) is considered to be the “gold standard” (37). However, CMRI is not widely available and quite costly, especially if applied in large numbers of patients and for a longitudinal follow-up. In order to minimize subjectivity and to limit variations in echocardiography performance and measurements, the 2-D echocardiographic screening was performed by a single cardiologist in each hospital, who followed a predefined protocol for the recordings, and the final reading and measurements for all echo studies were made by one cardiologist.

Furthermore, the echo study was performed within one week and no longer than one month from study entry, with the patient in steady state thus avoiding fluctuations in fluid volume. Second, cross sectional data are prone to selection bias. In contrast to the general population, we found in this pre-dialysis hypertensive CKD population that the proportion of current smokers decreased from the lowest to highest BMI category, that eGFR was progressively higher, and systolic blood pressure, and LDL were progressively lower from the lowest BMI category on. An explanation for the lower proportion of current smokers could be the medical consultation encouraging smoking cessation, and the lower proportion of males in the highest BMI category. An explanation for the progressively lower systolic blood pressure could be the higher use of diuretics and the better kidney function and for the lower LDL could be the higher use of statins from the lowest to the highest BMI categories, respectively. Furthermore, the highest eGFR in the highest BMI category may be the effect of obesity on kidney function through multiple mechanisms (e.g. hemodynamic effects, adipokines, inflammation). Third, although it is possible that BMI and WC cause LVM, in the cross sectional analyses it is not possible to distinguish causes and effects. Fourth, the study may suffer from confounding, as it was not possible to correct for confounders that were not measured or were unknown. Therefore, among others, in this observational study causality cannot be inferred.

**CONCLUSION**

Our results suggest that both BMI and WC were associated with LVM in hypertensive predialysis CKD patients, and this association was present in CKD stages 1-3, but not in CKD stages 4-5. Within the latter CKD stages the relationship is more complex due to the varied and multiple mechanisms by which uremia may influence LVM and peripheral muscle wasting. In the longitudinal analysis, both an increase of BMI and of WC was associated with an increase in LVM. Although traditionally the association between obesity and LVM has been explained mainly through hemodynamic changes, our results suggest that the increase in LVM may not exclusively be due to blood pressure. These results indicate that patients in the early stages of CKD should be advised to lose weight, if they are overweight or obese, and by this protect themselves from adverse cardiovascular events. Future studies should confirm these results and should focus on mechanisms responsible for the associations between anthropometric variables and LVM.
Acknowledgements

We would like to acknowledge our thanks to Dr. N. Kotzadamis and Dr. A. Kelesidis for kindly agreeing to use the data from the Department of Nephrology, General Hospital of Thessaloniki, Greece and to Dr. Y. Ververidis and Prof. D. Palesidis, Department of Nephrology, General Hospital of Veria, Greece for their advice and support to Dr. K. Ioannou's Thesis.

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12. The association between change in both body mass index and waist circumference and change in left ventricular mass, per year using linear mixed modelling.

Table 5: The association between change in both body mass index and waist circumference and change in left ventricular mass, per year using linear mixed modelling.

|                      | Left ventricular mass (g) |                      | Left ventricular mass height (cm) indexed (g/m²) |                      | Left ventricular mass body surface area indexed (g/m²) |
|----------------------|---------------------------|----------------------|-----------------------------------------------|----------------------|------------------------------------------------------|
|                      | Model 1: Unadj           | Model 2: Adj*        | Model 3: Adj**                                | Model 1: Unadj       | Model 2: Adj*                                       | Model 3: Adj**                                |
|                      | BMI, kg/m²               |                      |                                               |                      |                                                     |                                               |
|                      | 0.82                     | 2.9                  | 3.6                                            | 1.39                 | 0.61                                                 | 0.58                                          |
|                      | (-1.50; 3.16)            | (0.74; 5.1)          | (1.5; 5.7)                                    | (-0.43; 2.35)        | (-0.41; 1.6)                                        | (-0.44; 1.6)                                 |
|                      | WC, cm                    |                      |                                               |                      |                                                     |                                               |
|                      | 1.19                      | 1.1                  | 1.3                                            | 0.68                 | 0.28                                                 | 0.27                                          |
|                      | (0.39; 1.99)              | (0.28; 1.8)          | (0.52; 2.0)                                   | (0.31; 1.05)         | (-0.11; 0.67)                                       | (-0.12; 0.67)                                |

BMI= body mass index, WC= waist circumference.
*Model 2: adjusted for age, sex, primary renal disease, smoking, and history of cardiovascular disease.
**Model 3: adjusted for confounders of model 2 + eGFR.
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