

## Prevalence of Cardiac Remodeling among Non-Dialysis Dependent Chronic Kidney Disease Outpatients in a Sample of the Iraqi Population: A Preliminary Study.

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Abstract:

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**Background:** Pressure overload, uremic toxins, and deteriorating renal function are the main causes of ventricular hypertrophy in chronic kidney disease, which increases with the severity of the condition.

**Aims:** The study aims to investigate the types and prevalence of cardiac remodeling among outpatients in Thi-Qar city who do not require dialysis and have chronic kidney disease stages (3, 4, and 5).

**Methods:** In a cross-sectional study, 51 non-dialysis CKD patients (stages 3-5) with estimated glomerular filtration rate (eGFR) less than 60 mL/min who were categorized according to Kidney Disease Improving Global Outcome guidelines were examined. The eGFR was calculated using the CKD-EPI Creatinine Equation. Interviews were used to get clinical and demographic data as well as comorbidities. Transthoracic echocardiography was also performed on each participant.

**Results:** The study included 25 men and 26 women who had been diagnosed with chronic kidney disease, predominantly in the fifth to sixth decades of life, where the BMI differed significantly, with the highest mean value observed in stage 3 group ( $30.95 \pm 5.51$  kg/m<sup>2</sup>;  $p = 0.005$ ). Participants' median duration of CKD was roughly one to two years, with a range of one to seven years. 39.21% of the subjects had uncontrolled diabetes, while 70.58% of the subjects had uncontrolled hypertension. At stage 3, 63.64% of participants showed cardiac remodeling, 62.96% at stage 4, and 76.92% at stage 5 CKD. The Cardiac Remodeling was more frequent in males versus females (76% vs. 57.69%).

**Conclusion:** According to this study, cardiac remodeling was common among CKD outpatients prior to dialysis and became more prevalent as the severity of the disease increased.

**Keywords:** Left Ventricular Hypertrophy, Cardiac Remodeling, Transthoracic Echocardiography.

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## انتشار إعادة تشكيل القلب بين مرضى الكلى المزمن غير المعتمدين على غسيل الكلى في عينة من السكان العراقيين: دراسة تمهيدية

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### الخلاصة:

**الخلفية** يزداد تضخم البطين الأيسر في مرض الكلى المزمن (CKD) بشكل متناسب مع شدة المرض. تُعزى هذه الزيادة بشكل أساسي إلى الضغط، وتراكم السموم اليوريمية، والتدهور المستمر في وظائف الكلى.

**الأهداف** هدفت هذه الدراسة إلى فحص مدى انتشار وأنواع إعادة تشكيل عضلة القلب لدى الأفراد المراجعين للعيادات الخارجية المصابين بمرض الكلى المزمن في المراحل 3، 4، و 5، والذين لم يبدووا بعد في برنامج الغسيل الكلوي بمدينة ذي قار.

**الطرق** أجريت دراسة مقطعية على 51 مريضاً غير معتمدين على الغسيل الكلوي (CKD المراحل 3-5)، والذين صُنِّفوا وفقاً لإرشادات KDIGO بمعدل ترشيح كبيبي مقدر أقل من 60 مل/دقيقة، باستخدام معادلة CKD-EPI للكرياتينين. تم جمع البيانات السريرية والديموغرافية والأمراض المصاحبة عبر المقابلات، وخضع جميع المشاركين لتخطيط صدى القلب عبر الصدر.

**النتائج** شملت العينة 25 ذكراً و26 أنثى، غالبيتهم في الخمسينات وذوي وزن زائد، بمتوسط مدة للمرض من 1-2 سنة. سُجِّلت نسب عالية من الأمراض المصاحبة غير المتحكم بها 70.58% ارتفاع ضغط دم، 39.21 سكري. بلغ معدل انتشار إعادة تشكيل عضلة القلب الإجمالي 66.67%. لوحظ ازدياد في الانتشار مع تقدم المراحل: 63.64% في المرحلة 3، 62.96% في المرحلة 4، و76.92% في المرحلة 5. وكان الانتشار أعلى لدى الذكور (76%) مقارنة بالإناث (57.69%).

**الاستنتاج** تُظهر هذه الدراسة أن إعادة تشكيل عضلة القلب هي ظاهرة شائعة بين مرضى الكلى المزمن المراجعين للعيادات الخارجية قبل مرحلة الغسيل الكلوي، وتصيح أكثر شيوعاً بشكل ملحوظ مع تفاقم وشدة المرض.

**الكلمات المفتاحية:** تضخم البطين الأيسر، إعادة تشكيل القلب، تخطيط صدى القلب عبر الصدر.

### Introduction:

The historically significant area of Thi-Qar City, which is about 180 kilometers from Basra in southern Iraq, is home to about 2 million people (1). Public health and the prevalence of chronic diseases are impacted by the region's current issues, which include limited access to healthcare, environmental stressors, and a 17% unemployment rate (2). According to the WHO, 55% of all deaths in Iraq are attributable to non-communicable diseases (NCDs), which include patients with; diabetes, cancer, heart disease, stroke, and chronic lung disease (3).

Unfortunately, there are limited resources available on the prevalence of CKD patients in Thiqr city and in Iraq in general. However, a 2021 study in Basra found a prevalence of 6.8% for CKD in this city (4). As we know, 10% of the global population suffers from CKD, and the incidence globally has an increasing rate, according to the Centers for Disease Control and Prevention (CDC)-Kidney Disease Surveillance System. Approximately one in every seven persons in the United States has CKD stages 1-5, with the overall crude prevalence of CKD being 13.9% from 2017 to March 2020 (5)(6). The renal



disease is linked to early death, disability, lower quality of life (QOL), and psychosocial problems. It also incurs high costs for governments, healthcare systems, patients, and their families (7). According to the Pan American Health Organization (PAHO), CKD was the eighth leading cause of death and disease burden in the Americas in 2019, ranking tenth for years of life lost (8). Regarding the epidemiology of cardiovascular diseases, CKD not only raises the incidence of these disorders but also seems to alter their presentation, with approximately 70% of deaths related to disease burden. It also impacts the epidemiology of arrhythmia and cardiomyopathy(9)(10). Recently, the term 'cardiac remodeling (CR)' has been recognized as a key process through which a failing heart attempts to manage increased wall tension, contributing to the progression of heart failure (HF) (11). Indeed, most deaths from CKD are caused by hypertension and related cardiovascular (CV) disorders, with left ventricular hypertrophy (LVH) being a typical end-organ sign of uncontrolled hypertension. Consequently, the connections between the kidney and heart have long been the focus of pathophysiological research (12)(13). Magnetic resonance imaging (MRI) or echocardiography (ECHO) are commonly used for comprehensive cardiac evaluations, but they are frequently underutilized in CKD patients. All emerging cardiac assessments are carried out early, before renal transplantation, to reduce the association between CKD and the progression of cardiac issues (14)(15). Our research represents the initial investigation in Iraq focused on examining the prevalence and classifications of cardiac remodeling in a limited cohort of outpatients with stage 3, 4, and 5 chronic kidney disease, who are not reliant on dialysis.

### Methods:

A cross-sectional observational research includes patients with CKD stages 3, 4, and 5 who are not on dialysis; all stages are classified according to Kidney Disease Improving Global Outcome (KDIGO) guidelines (16). The patient's GFR calculated by the CKD-EPI Creatinine Equation, an online calculator as recommended by the National Kidney Foundation (NKF) and the American Society of Nephrology (ASN) (17). Fifty-one outpatients from a private nephrology clinic in Thi-Qar city were recruited. Patients ranged in age from 18 to 75 years and had been diagnosed with CKD for more than 3 months. Demographic and clinical details were gathered through clinical interviews, including patient name, age, sex, BMI, BSA, and systolic and diastolic blood pressure. All patients categorised to controlled versus uncontrolled hypertension. Controlled hypertension defined as BP < 140/90 (18), documented along with comorbidities. blood samples were collected from all patients, approximately 6 ml of venous blood into a gel tube and an EDTA tube, then centrifuged for 20 minutes to obtain 2 mL of serum for measurement of serum urea and creatinine using the Cobas c111, and HbA1c using the Cobas E411. Controlled diabetes is defined as an HbA1c level of less than 7 (19).

**Measurements of Outcome:** For measure the incidence of cardiac remodeling, all participants underwent Transthoracic Echocardiography (TTE) with a 2D ultrasonography system (Philips Medical Systems, Netherlands) performed by a trained specialist echocardiographer at her private clinic blinded to CKD stage. Since all study participants are outpatients, data were reported in accordance with the guidelines of the American Society of Echocardiography (ASE) and the European Society of Cardiology (ESC) (20)(21). For measuring LVMI, an online



Omni calculator is used (22). TTE data, such as Left Ventricular End-Diastolic Diameter (LVEDD), Interventricular Septal Thickness in Diastole (IVSD), and Posterior Wall Thickness in Diastole (PWD), along with sex and BSA, were used in the Omni calculator to determine Left Ventricular Mass Index (LVMI) and Relative Wall Thickness (RWT), with ejection fraction percentage for all participants. Left ventricular geometry was categorized as usual (normal LVMI, normal RWT), concentric remodeling (normal LVMI, high RWT), eccentric LVH (high LVMI, normal RWT), or concentric LVH (high LVMI, high RWT). The reference range for LVH is LVMI > 115 g/m<sup>2</sup> in men and > 95 g/m<sup>2</sup> in women. Normal RWT is less than 0.45 (23). All study groups used the same instruments, protocols, and trained personnel to evaluate all variables in order to guarantee measurement comparability. Following a 5-minute rest period, a specialist at her private clinic performed echocardiograms in a quiet room for all enrolled participants. For a month, every patient's demographic, clinical, laboratory, and ECHO parameters were recorded within an hour.

**Inclusion and Exclusion criteria:** Patients with CKD who were between the ages of 18 and 75, had an estimated GFR of <60 mL/min, and were not dialysis dependent were chosen based on certain criteria. However, patients with asthma, a history of recent cardiac surgery in less than 6 months were excluded from the study.

#### **Ethical approval:**

This preliminary observational cross-sectional study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the College of Pharmacy, Mustansiriyah University, Iraq, under Approval No. 74, dated June 3, 2024. All adult participants (age 18-74 yrs) with written informed consent.

#### **Statistical analysis:**

The data from the current research were analyzed statistically using IBM SPSS version 27, including one-way ANOVA, the Chi-Square test, and the Kruskal-Wallis H test for data that did not follow normal distribution. Normality was checked with the Shapiro-Wilk test. Significance level less than 0.05.

#### **Results:**

**Table 1: Demographic data and Clinical characteristics.**

| Variable                               | CKD S-3                   | CKD S-4                   | CKD S-5                   | P-value          |
|--|---------------------------|---------------------------|---------------------------|------------------|
| Age (yrs) Mean ± S. D                  | 59.63 ± 11.5              | 59.18 ± 11.4              | 50.00 ± 16.9              | 0.096            |
| BMI kg/m <sup>2</sup> , Mean ± S. D    | 30.95 ± 5.51 <sup>a</sup> | 26.48 ± 4.34 <sup>b</sup> | 24.51 ± 4.74 <sup>b</sup> | <b>0.005</b>     |
| Duration of CKD median and range/month | 12 (3-84)                 | 12 (4-72)                 | 24 (3-72)                 | <b>0.044</b>     |
| Sex (No., %)                           | Male                      | 5(20)                     | 10 (40)                   | <b>&lt;0.001</b> |
|  | Female                    | 6 (23.08)                 | 17 (65.38)                |                  |
| Hypertension (No., %)                  | Controlled                | 4 (7.84)                  | 7 (13.72)                 | 0.425            |
|  | Uncontrolled              | 7 (13.72)                 | 20 (39.21)                |                  |
| Diabetic (No., %)                      | Controlled                | 6 (11.76)                 | 15 (29.41)                | <b>0.016</b>     |
|  | Uncontrolled              | 5 (9.8)                   | 12 (23.52)                |                  |



Normally distributed Age and body mass index (BMI) are expressed as mean  $\pm$  standard deviation (SD). The median and range of the duration of CKD were displayed (non-normally distributed). The variables of diabetes, hypertension, and sex were analyzed using the chi-square test, displayed as

percentages (%) and numbers (n). Bold text indicates a p-value  $< 0.05$ , which was deemed statistically significant. The same uppercase letter indicates no significant difference, while different uppercase letters indicate a statistically significant difference between stages.

**Table 2: ECHO parameters including Left Ventricular Mass Index ((LVMI)), Relative Wall Thickness (RWT), and Ejection Fraction (EF%) in patients with stages 3, 4, and 5 of chronic kidney disease.**

| Parameters                | CKD S-3<br>(mean $\pm$ SD)    | CKD S-4<br>(mean $\pm$ SD)    | CKD S-5<br>(mean $\pm$ SD)    | p. value     |
|---------------------------|-------------------------------|-------------------------------|-------------------------------|--------------|
| LVMI (gm/m <sup>2</sup> ) | 99.65 $\pm$ 20.6 <sup>b</sup> | 111.6 $\pm$ 29.1 <sup>b</sup> | 144.6 $\pm$ 43.1 <sup>a</sup> | <b>0.002</b> |
| RWT                       | 0.404 $\pm$ 0.07              | 0.425 $\pm$ 0.78              | 0.450 $\pm$ 0.06              | 0.320        |
| EF %                      | 0.615 $\pm$ 0.08              | 0.583 $\pm$ 0.10              | 0.581 $\pm$ 0.08              | 0.603        |

Data are expressed as mean  $\pm$  standard deviation (SD). The same uppercase letters above the numbers indicate no statistical significance, while different uppercase letters indicate a statistical significance at p-value  $< 0.05$  in bold.

**Table 3: Types of Cardiac Remodeling in Different CKD Stages.**

| Remodeling Type        | CKD S-3 |        | CKD S-4 |        | CKD S-5 |        | Chi square test<br>(P-value) |
|------------------------|---------|--------|---------|--------|---------|--------|------------------------------|
|                        | No.     | %      | No.     | %      | No.     | %      |                              |
| Non-remodeling         | 4       | 36.36  | 10      | 37.03  | 3       | 23.07  | 0.058                        |
| Concentric remodeling  | 4       | 36.36  | 2       | 7.4    | 0       | 0.00   | <b>&lt;0.001</b>             |
| Concentric hypertrophy | 1       | 9.09   | 13      | 48.14  | 8       | 61.53  | <b>&lt;0.001</b>             |
| Eccentric hypertrophy  | 2       | 18.18  | 2       | 7.4    | 2       | 15.38  | 0.07                         |
| Total                  | 11      | 100.00 | 27      | 100.00 | 13      | 100.00 |                              |

**Table 4: Types OF Cardiac Remodeling in Male versus female.**

| Categories             | Male |       | Female |       | Chi square test (P-value) |
|------------------------|------|-------|--------|-------|---------------------------|
|                        | No.  | %     | No.    | %     |                           |
| Non-remodeling         | 6    | 24.00 | 11     | 42.31 | <b>0.005**</b>            |
| Concentric Remodeling  | 4    | 16.00 | 2      | 7.69  |                           |
| Concentric Hypertrophy | 13   | 52.00 | 9      | 34.62 |                           |
| Eccentric Hypertrophy  | 2    | 8.00  | 4      | 15.38 |                           |

**Table 5: Overall Prevalence of Cardiac Remodeling in All Patients with CKD Across All Stages.**

| CKD Stages | Total No. | Remolding |       | Non-remodeling |       | Chi square Test<br>P-value |
|------------|-----------|-----------|-------|----------------|-------|----------------------------|
|            |           | No.       | %     | No.            | %     |                            |
| Stage 3    | 11        | 7         | 63.64 | 4              | 36.36 | 0.061                      |
| Stage 4    | 27        | 17        | 62.96 | 10             | 37.04 |                            |
| Stage 5    | 13        | 10        | 76.92 | 3              | 23.08 |                            |



## Discussion:

Cardiac remodeling in CKD patients is driven by several interacting factors, including uncontrolled hypertension, inflammatory toxins, and extracellular fluid overload. These mechanisms contribute substantially to ventricular hypertrophy, which accounts for more than 85% of cardiovascular risk in this population(24)(25)(26). This study is the first to explore in Thi-Qar city the prevalence of cardiac remodeling among a small group of outpatients with chronic kidney disease (CKD) not on dialysis. Patients classified according to the CKD-EPI formula, with an estimated glomerular filtration rate (GFR) below 60 ml/min, adjusted for body surface area (BSA), covering stages 3, 4, and 5 CKD. There were no notable differences between age groups of CKD patients, most of whom were in their fifties. These results align with CDC data showing that CKD affects about 34% of people over 65, compared to roughly 6% under 44, in the U.S. This variation is linked to age-related conditions like HT and DM (27). Forty percent of patients are men and 65.38 percent are women, indicating that women may be more likely to seek medical attention. The majority of patients are in stage 4 CKD. In addition, 40% of men have stage 5 CKD, compared to roughly 11% of women, suggesting that men may develop CKD more quickly. Our examination of the mean BMI at each stage shows a decrease as the illness progresses. This pattern is probably caused by metabolic alterations, inflammation, or weight-loss initiatives, which is consistent with Xiaonan H. Wang's research showing that CKD causes muscle loss (28).

Given the non-normal distribution of our CKD duration data, it is noteworthy that the median duration for stages 3 and 4 is comparable. Patients in stage 5, however, usually have a longer history of CKD. The significant variation in disease duration throughout all stages highlights the varied course of CKD and

the necessity of individualized treatment strategies (29). When comparing participants with well-controlled diabetes or hypertension to those with uncontrolled diabetes or hypertension, no discernible differences exist. This may be as consequences of differences in clinical care settings, and small sample size(30).

Heart failure, arrhythmias, and sudden cardiac arrest are among the cardiovascular risks associated with CKD worldwide. Furthermore, compared to the general population, the incidence of cardiovascular events was noticeably higher in advanced CKD stages 4 and 5 (31). An important pattern that the severity of the disease link to increased LVMI; in stage 5 CKD, the increase in left ventricular mass was greater than in stages 3 and 4. RWT and EF%, however, were constant across stages. These results may be related to CKD-related variables like hypertension, fluid overload, and uremic toxins (32), suggesting ventricular hypertrophy as an adaptive process rather than a decompensatory response aimed to preserve normal systolic.

Table 3 outlines the types of cardiac remodeling—concentric remodeling, concentric hypertrophy, and eccentric hypertrophy—based on estimated LVMI and RWT. It shows that concentric remodeling is more common in stages 3 and 4 of CKD, marked by an increased RWT without a notable rise in left ventricular mass (LVM). This pattern likely stems from an initial rise in systemic vascular resistance and mild hypertensive hypertrophy (33). However, LVMI and RWT rise as the disease progresses, and concentric hypertrophy is more prevalent in stages 4 and 5 CKD than in stage 3 CKD. Given that fluid overload, anemia, and fibrosis are linked to the progression of CKD, the prevalence of this type is reasonable (34). Additionally, the distribution of eccentric hypertrophy is roughly equal across the stages of CKD. Given that about 70.58% of patients



have uncontrolled hypertension, this could be due to comorbid conditions. Furthermore, the research's estimated BMI indicates that obesity is common in the early stages (35)(36). Interestingly, male patients are more likely to have concentric remodeling (16%) and concentric hypertrophy (52%), while female patients are more likely to have eccentric hypertrophy (15.38%) (Table 4). This is consistent with a Russian study that found 39.7% of men had concentric LVH and 79.2% of women had eccentric LVH (37). In addition, CR was present in 76% of males and 57.69% of females. This gender disparity may result from the protective effects of estrogen in women and the influence of testosterone in men, which is in line with an Italian study that found that men have a higher rate of CR (38). The incidence of CR is positively correlated with declining renal function, with about 60% of cases occurring in stages 4 and 3 and 76.92% in stage 5 CKD that is not dialysis dependent. This observation is consistent with the Paoletti et al. findings (38). Following all that has been mentioned, it is important to recognize that LVH alone is a documented risk factor for cardiac arrhythmias and heart failure (39). As a result, it is essential to identify and treat patients with LVH as soon as possible in order to reduce its effects on people with CKD, reduce associated comorbidities, and enhance general health outcomes.

#### Limitations of our study:

The study is preliminary in nature with limited statistical power and single private nephrology clinic, so multi-centers or clinic with a larger sample size is necessary to accurately measure the prevalence of cardiac remodeling in CKD patients and evaluate its influence on other risk factors.

#### Conclusion:

The majority of the CKD patients in this research were in their fifth decade of life. As the disease progressed, left ventricular

hypertrophy increased with progress of disease, reaching 76.92% in stage 5 but no significant difference between 3 stages. Males were present more frequently with concentrated hypertrophy, whereas females present commonly with eccentric hypertrophy. Furthermore, both forms of hypertrophy were more prevalent in stage 5 CKD, while concentric remodeling was more common in stage 3.

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