

## Kidney function estimate among subjects aged 18-59 years in Tubarão, Santa Catarina: A population-based study

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### ABSTRACT

**Introduction:** Among the increasing chronic degenerative diseases, chronic kidney disease (CKD) is a major public health challenge facing the 21<sup>st</sup> century. **Objectives:** To estimate the GFR by using the CKD-EPI formula among subjects aged 18-59 years, and to identify factors associated with glomerular filtration rate (GFR). **Methods:** A cross-sectional population-based study was conducted on adults between November 2011 and March 2012. We collected sociodemographic, anthropometric, clinical, and laboratory tests to build a database. The Pearson's chi-square test was used to assess the association between variables, and the Student's *t*-test was used for mean comparison at 95% confidence level. **Results:** A cohort of 371 adults was surveyed (63.8% women; 86.3% Whites). The mean age was 40.4 years (SD ± 12.3). Of the total, 76.8% had normal GFR; 21.8% showed a slight decline, 1.1% a moderate decline, and 0.3% a significant decline in GFR. There were significant differences related to age and obesity, because the greater the age or the higher the body mass index, the lower the GFR of participants. Individuals with systemic hypertension showed a tendency towards a reduction in GFR compared to non-hypertensive population ( $p < 0.06$ ). **Conclusion:** This study concluded that the vast majority of the surveyed subjects had normal GFR levels, and that only 1.4% (95% CI: 0.3 - 2.4) had moderate or severe dysfunction.

**Keywords:** creatinine; glomerular filtration rate; kidney function tests; renal insufficiency.

### INTRODUCTION

We have seen changes in the morbidity and mortality profile of the world population in recent decades, with a significant increase in chronic diseases, including chronic kidney disease (CKD), which remains a public health challenge in world, due to its economic and social implications.<sup>1,2</sup>

CKD is a silent disease in most cases, although diagnosis is easy with clinical history and inexpensive laboratory tests. However, in the absence of early detection, the disease has a progressive course that sometimes leads to complete loss of kidney function, which may cause death.<sup>3</sup>

To properly measure kidney function is important not only to make the diagnosis and proceed to treatment of renal diseases, but, among other applications, to administer adequate doses of drugs, define prognosis, interpret possible uremic symptoms and make decisions regarding the onset of renal replacement therapy.<sup>3,4</sup> It is based on these observations that laboratory tests are recommended, and these should ideally be low-cost and widely available in most laboratories.<sup>5,6</sup>

In everyday clinical practice, qualitative assessment of the kidney's excretory capacity is usually carried out by measuring plasma creatinine concentration.<sup>7</sup> This is because of the

method's simplicity, compared to the difficulties inherent to the technique of endogenous creatinine clearance with 24-hour urine collection - a more accurate method, but more laborious execution and subject to errors.<sup>8,9</sup>

However, normal plasma creatinine (PCr) values is not synonymous with normal renal function, and several studies have shown that a significant portion of individuals, despite having normal PCr values may have impaired kidney function.<sup>10,11</sup> Burmeister *et al.* found that up to 15% of individuals with normal PCr values had renal function levels below 60 ml/Min.<sup>8</sup>

Formulas for estimating GFR have been created and published in order to overcome some of the limitations encountered in establishing the glomerular filtration rate (GFR) by measuring plasma creatinine. These formulas use demographic and clinical variables known as surrogates for the physiological factors that were not measured and that impact the level of serum creatinine. The most commonly used formulas are the Cockcroft and Gault (CG), Modification of Diet in Renal Disease (MDRD), and more recently, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).<sup>12</sup>

The CG formula was the first of these equations to gain acceptance and to estimate creatinine clearance; however, it systematically overestimates GFR because creatinine tubular secretion and weight gain due to obesity or fluid overload are not taken into account.<sup>13</sup>

The MDRD equation to estimate GFR was originally developed based on the Modification of Diet in Renal Disease in CKD patients study data and did not include healthy individuals. In its original version, the MDRD equation requires establishing serum albumin and nitrogen urea.<sup>14</sup> Currently, the abbreviated MDRD formula with "four variables" has been recommended, for its performance is as good as that of the original one.<sup>14</sup> GFR calculated from the MDRD equation and the actual GFR are very close to results < 60 mL/min/1.73m<sup>2</sup>, while the true GFR exceeds the estimated rate by a small value when the GFR is > 60 mL/min/1.73m<sup>2</sup>.<sup>14,15</sup>

The Chronic Kidney Disease Epidemiology Collaboration group recently developed, from a cohort that included patients with and without CKD, a new equation which is a variation of the MDRD formula. The equation, called CKD-EPI, uses the same four variables of the MDRD equation, but in comparison, it has better performance and better risk prediction. Higher accuracy and lower bias associated with the CKD-EPI equation, particularly for GFR in ranges > 60 mL/min/1.73 m<sup>2</sup>, of the MDRD study are of routine clinical use.<sup>15,16</sup>

The aim of this study was to estimate renal function from GFR calculations made by the CKD-EPI formula in adults from a population sample from Tubarão (SC), and to pinpoint factors that may alter normal GFR values.

## METHODS

This study is linked to the ESATU project (Health Study of Adults from Tubarão), a partnership between the Center for Clinical Research of the Our Lady of Conception Hospital, University of Southern Santa Catarina and Department of Health of the city of Tubarão. This study received financial aid from the Support to Research and Innovation Foundation of the State of Santa Catarina (FAPESC) and was approved by Ethics Committee of UNISUL under protocol # 11.130.4.01.III.

Tubarão is a coastal town in the southern portion of Santa Catarina state. The resident population is made up of 97,235 people, 51.5% are females. We chose the minimum age of 18 years (when adults come of age in Brazil) to 59, which corresponded to 66.7% of the population, since in Brazil people 60 years of age and older are considered elderly. In addition, a previous study was published with the elderly of this town.<sup>17</sup>

We did a cross-sectional study that evaluated individuals between 18 and 59 years of age, living in Tubarão, SC. Considering that the adult population of Tubarão was of 64,849 people (2010 census), we used the estimated prevalence of 10.8% of chronic kidney disease,<sup>1</sup> with a significance level

of 5% and margin of error of 1%, resulting in a minimum sample of 138 individuals for a 95% confidence level.

The study included all participants from the ESATU study who underwent laboratory determinations of serum creatinine and who agreed to participate by signing the Term of Consent.

Participants were selected from simple random sampling, according to the numbers of homes registered in each of the 250 micro areas of the city, recorded in 27 family health strategy units (ESF). Each micro-area has a community health worker to make periodic home visits, and the coverage rate is estimated at about 90% of the resident population.

Data collection took place on Saturday mornings, on the premises of Our Lady of Conception Hospital, in pre-scheduled appointments of randomly selected participants. The patients were asked to fast for 12 hours, and to avoid drinking alcohol within 72 hours prior to the appointment.

The participant was interviewed so that we could collect demographic and socioeconomic data (age, gender, skin color, marital status, and educational level), behavioral data (physical activity, alcohol use, and cigarette) and clinical condition (hypertension, diabetes, dyslipidemia, obese).

We considered as smokers those individuals who smoked 100 or more cigarettes during his life. We used the CAGE questionnaire for those adults who reported drinking alcohol currently or in the past.

To measure physical activity we used the International Physical Activity Questionnaire - short version. We considered physically active those individuals who performed at least 30 minutes of physical activity five days a week or more, and  $\geq 150$  minutes of weekly physical activity was the cutoff point.

To define obesity among the adults studied, we used the cutoff point for the body mass index (BMI) proposed by the World Health Organization (WHO) - individuals with  $\text{BMI} \geq 30 \text{ kg/m}^2$  are considered obese at any age (general obesity).

To assess systolic and diastolic blood pressure levels, we used the criteria proposed by the Brazilian Society of Cardiology in its Hypertension Guidelines of 2010, which consists of checking three blood pressure measurements within one-minute intervals between measurements, with the patient seated. Patients with mean blood pressure values  $\geq 140/90$  mmHg or those using antihypertensive medications were considered hypertensive.

*Diabetes mellitus* diagnose was based on the medical history of diabetes and/or use of hypoglycemic agents, and by serum determination of blood glucose  $\geq 126$  mg/dl.

We collected 10 ml of peripheral venous blood for serum creatinine and fasting blood sugar levels, done by a technically skilled professional.

Kidney function was assessed by serum creatinine and GFR estimated by the CKD-EPI formula ( $\text{GFR} = 141 \times \text{min}(\text{SCR}/\kappa \text{ of } 1)^\alpha \times \text{max}(\text{SCR}/\kappa \text{ of } 1)^{-1.209} \times 0.993 \times 1.018^{\text{Age}} [\text{if female}] \times 1,159 [\text{if black}]$ ).

GFR was found to be normal or abnormal when the calculated values were seen to be above or below  $60 \text{ ml/min/1.73 m}^2$ . This criterion was used to classify individuals into two groups: with normal GFR ( $> 60 \text{ ml/min/1.73 m}^2$ ) and abnormal GFR ( $< 60 \text{ ml/min/1.73 m}^2$ ); and into the five stages of kidney dysfunction according to the chronic kidney disease guide:<sup>18,19</sup> Normal kidney function:  $> 90 \text{ ml/min/1.73 m}^2$ ; Mild kidney damage:  $60\text{-}89 \text{ ml/min/1.73 m}^2$ ; Moderate kidney impairment:  $30\text{-}59 \text{ ml/min/1.73 m}^2$ ; Severe kidney damage:  $15\text{-}29 \text{ ml/min/1.73 m}^2$ ; Kidney failure:  $< 15 \text{ ml/min/1.73 m}^2$ .

We entered the data in the EpiData software, version 3.1 (EpiData Association, Odense, Denmark) and statistical analysis was performed with the Statistical Software Product and Service Solutions (SPSS) version 20.0 (SPSS Statistics, Chicago, Illinois, USA). The qualitative variables were described in absolute and relative numbers. For associations between variables we applied the Fisher's exact test for categorical variables and the Student *t*-test for comparison of mean

values in the normal distribution of quantitative variables. The confidence interval was set at 95%.

## RESULTS

Three hundred and seventy one adults were studied in a population-based study of the city of Tubarão. Of these, 237 were women (63.8%). Most of the adults were white (86.3%) and their mean age was 40.4 years (SD = 12.3).

Table 1 shows the sociodemographic variables and their comparison among participants with normal or decreased GFR.

Individuals with reduced GFR had higher mean age ( $52.4 \pm 6.3$  years) than those with normal GFR ( $40.3 \pm 12.3$  years) ( $p = 0.028$ ). Table 2 depicts the clinical variables and comparisons among participants with normal or decreased GFR.

There was a significant difference as far as obesity was concerned, and the higher the BMI the lower the GFR in adults. In addition, individuals with hypertension diagnosis tended to have lower GFR compared to their non-hypertensive counterparts ( $p < 0.06$ ).

Table 3 depicts the sample distribution as to the classification of the GFR estimated by the CKD-EPI.

Figure 1 shows the prevalence of individuals with GFR < 60 ml/min calculated by different formulas in the literature.

We found that MDRD overestimated GFR as compared to the other formulas.

## DISCUSSION

In the present study we found a prevalence of 1.4% of subjects with GFR < 60 ml/min. Matsushita *et al.*<sup>20</sup> found a prevalence of 14.3%; however, there was a large proportion of elderly individuals in the sample, and old age is related to renal disorder and causes a higher percentage of GFR < 60.

There was no significant difference in GFR < 60 ml/min with respect to age, obesity; and we found a trend towards hypertension in the study population.

Studies have shown that advanced age is directly related to decreased GFR. Kidney function tends to

**TABLE 1** COMPARISON BETWEEN VARIABLES OF PATIENTS WITH GFR < 60ML/MIN AND GFR > 60 ML/MIN. (N = 371)

Variables	Total n (%)	TGF > 60 n (%)	TGF < 60 n (%)	<i>p</i> * value
<b>Gender</b>				
Male	134 (36.1)	3 (2.2)	131 (97.8)	0.252
Female	237 (63.9)	2 (0.8)	235 (99.2)	
<b>Age in years</b>				
18-39	151 (40.7)	-	151 (100.0)	0.146
40-49	111 (29.9)	2 (1.8)	109 (98.2)	
50-59	109 (29.4)	3 (2.8)	106 (97.2)	
<b>Married</b>				
Yes	256 (69.0)	4 (1.6)	252 (98.4)	0.507
No	115 (31.0)	1 (0.9)	114 (99.1)	
<b>Race</b>				
Caucasians	320 (86.3)	4 (1.2)	316 (98.8)	0.525
Non-Caucasians	51 (13.7)	1 (2.0)	50 (98.0)	
<b>Schooling</b>				
> 8 years	188 (50.7)	2 (1.1)	186 (98.9)	0.487
≤ 8 years	183 (49.3)	3 (1.6)	180 (98.4)	

decrease with increasing age, being an independent factor of the aforementioned comorbidities, confirming data in the literature,<sup>21-23</sup> that can be explained by the physiological and structural changes that occur in the renal system. In addition, epidemiological evidence shows that the prevalence of hypertension increases with idade.<sup>9,20</sup>

Regarding anthropometric indicators, patients considered obese had altered glomerular filtration rates when compared to otherwise normal individuals. It is quite settled in the literature that obesity is a major risk factor for glomerular hyperfiltration and progression to chronic kidney disease.<sup>6,24</sup>

The studied subjects who had hypertension diagnosed tended to have decreased GFR, a fact proven by Zhang *et al.*,<sup>25</sup> who pointed out that the main factors associated with kidney damage were: hypertension, diabetes and cardiovascular diseases.

Although the literature shows an association between *diabetes mellitus* and kidney damage, this study did not find statistical significance in this parameter, possibly due to the small number of individuals with DM in the sample. Some studies

**TABLE 2** COMPARISONS BETWEEN VARIABLES OF PATIENTS WITH GFR < 60 ML/MIN AND GFR > 60 ML/MIN. (N = 371)

Variables	Total n (%)	TFG < 60 n (%)	TFG > 60 n (%)	<i>p</i> * value
<b>DM</b>				
Yes	22 (5.9)	0 (0.0)	22 (6.0)	0.735
No	349 (94.1)	5 (100.0)	344 (94.0)	
<b>Obesity</b>				
Yes	100 (27.0)	4 (80.0)	96 (26.2)	0.020
No	271 (73.0)	1 (20.0)	270 (73.8)	
<b>Dyslipidemia</b>				
Yes	240 (65.0)	5 (100.0)	235 (64.6)	0.115
No	131 (35.0)	0 (0.0)	129 (35.4)	
<b>Hypertension</b>				
Yes	137 (37.3)	4 (80.0)	133 (36.7)	0.067
No	230 (62.7)	1 (20.0)	229 (63.3)	
<b>Sedentary lifestyle</b>				
Yes	225 (60.6)	4 (20.0)	221 (60.4)	0.347
No	146 (39.4)	1 (80.0)	145 (39.6)	
<b>Smoking</b>				
Yes	116 (31.3)	3 (60.0)	113 (30.9)	0.179
No	255 (68.7)	2 (40.0)	253 (69.1)	
<b>Alcoholism</b>				
Yes	31 (8.4)	1 (20.0)	30 (8.2)	0.343
No	340 (91.6)	4 (80.0)	336 (91.8)	

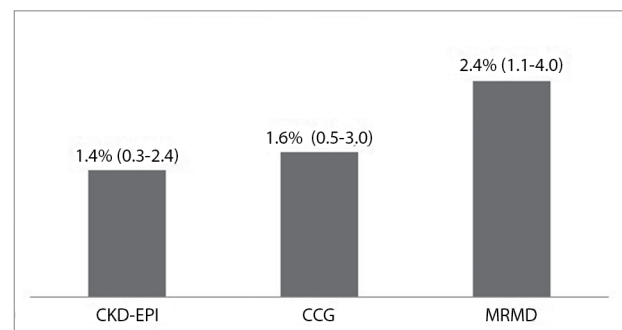
involving only diabetic patients showed high prevalence of GFR < 60 and association between diabetes and kidney injury.<sup>26,27</sup>

In this study there was no significant difference in renal function as far as gender is concerned, which corroborates data found in the literature.<sup>1,2,28</sup>

In the study there was no statistically significant difference between race and renal function. Similar data has been reported by Levey *et al.*;<sup>15</sup> however, authors such as Peralta *et al.*<sup>29</sup> pointed out that

**TABLE 3** DISTRIBUTION AND CLASSIFICATION OF THE GLOMERULAR FILTRATION RATE ESTIMATED BY THE CKD-EPI FORMULA, BASED ON THE CHRONIC KIDNEY DISEASE GUIDE

Classification	n (%)	IC 95%
Normal glomerular filtration rate (> 90 ml/min)	285 (76.8)	72,5-81,1
Slight reduction in the glomerular filtration rate (90-60 ml/min)	81 (21.8)	17,5-26,1
Moderate reduction in the glomerular filtration rate (59-30 ml/min)	4 (1.1)	0,3-2,4
Severe reduction in the glomerular filtration rate (< 30 ml/min)	1 (0.3)	0,0-0,8

**Figure 1.** Prevalence of patients with TFG < 60 ml/min/m<sup>2</sup> calculated by different formulas. (n = 371).

African-descendants had higher rates of decline in renal function regardless of sociodemographic or traditional risk factors.

As for the habits adopted by the sample, this studied showed no positive association between smoking and alcoholism and decreased GFR; however, it is well documented that smoking is a risk factor associated with decline in kidney function.<sup>30</sup>

The major criticism over the CKD-EPI paradigm and using the MDRD equation is that the underestimation of GFR measured by the MDRD leads to false positive diagnoses, as per depicted on Figure 1. When calculated by the MDRD, the prevalence of abnormal GFR was above 70% when compared to other formulas. This fact overestimates the risks and therefore increases healthcare costs.<sup>31</sup>

Although GFR < 60 ml/min prevalence rates were calculated by all formulas, we chose to use the CKD-EPI formula for comparative analyzes of

individuals from the ESATU study due to the results found in this study and in several papers.<sup>2,18,32</sup>

We concede to the methodological limitations in this study. For instance, we found no elements to differentiate between transient decrease in glomerular filtration rate and incipient CKD. Because it is a population sample, mainly involving healthy people and young adults, the prevalence of hypertension and DM was low; consequently, there was a low prevalence of CKD. The ESATU study limited the sample to individuals between 18 and 59 years of age, because the ESITU<sup>17</sup> study had already been carried out for individuals aged 60 years or more. Thus, this resulted in lower prevalence of CKD, as evidence shows that older age is directly related to TFG.

Data does not enable us to infer that the 1.4% individuals found with GFR < 60 ml/min/1.73 mm<sup>2</sup> have CKD or not, since the CKD definition proposed by the K/DOQI and endorsed by the National Kidney Foundation/Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) and Kidney Disease: Improving Global Outcomes (KDIGO) takes into account the presence of kidney damage (especially persistent proteinuria) with or without decreased GFR for a period of three months or more. Data on lifestyle (such as smoking, alcohol use, diet, physical activity) were self-reported by respondents, which can lead to low accuracy information. Another limiting factor is that the CKD-EPI formula is relatively recent, with only a few studies in other populations.

## CONCLUSIONS

We concluded that most individuals in the sample had normal GFR and that only 1.4% had moderate or severe degree of dysfunction. Older age and obesity were positively associated with decreased GFR and individuals with hypertension had a tendency towards reduced GFR.

The literature remains scarce as to studies involving the adult population with the new CKD-EPI formula. It is known that the CKD-EPI is not the best marker of renal function; it is, nonetheless, a good predictor of changes in GFR in the general population, it is of low cost and it must be used in clinical practice.

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