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# Creatinine or cystatin C – which is a better index of renal function in morbid obesity?

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## ABSTRACT

**Purpose:** The most important index of renal function is estimated glomerular filtration rate (eGFR) which can be calculated from creatinine or cystatin C concentration in serum. There is uncertainty, which formula is best suited to assess renal function in morbidly obese patients. The aim of this study was to evaluate eGFR in patients with morbid obesity using formulas: Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), Grubb, Le Bricon, Hoek, Larsson, and to compare the obtained results.

**Material and Methods:** In 40 morbidly obese patients, serum concentration of cystatin C and creatinine were assayed. Values of eGFR were calculated using the above-mentioned formulas.

**Results:** The mean value of eGFR ranged from 85.9 to 111.1 ml/min/1.73m$^2$, depending on the formula. The biggest difference between the obtained values was 29% (Grubb vs. Hoek $p<0.01$). After calculation of eGFR from creatinine concentration (MDRD), 7 patients were qualified to the 2nd and 3rd stage of chronic renal disease, while application of Hoek's formula, based on cystatin C concentration, allotted 27 patients to 2nd and 3rd stage of chronic renal disease. Le Bricon formula gave eGFR values, that correlated best with albuminuria.

**Conclusion:** eGFR calculated using Le Bricon formula based on the cystatin C concentration was significantly lower than eGFR calculated from creatinine concentration and was more closely associated with albuminuria. Relying only on creatinine concentration to estimate glomerular filtration rate can lead to underestimation of renal malfunction in obese patients.

**Key words:** Morbid obesity, glomerular filtration, creatinine, cystatin C

## INTRODUCTION

Obesity is a constantly growing health issue worldwide [1]. Obese patients have increased risk of metabolic syndrome [2] and kidney function impairment [3]. Hypertension and type 2 diabetes are etiologic factors of 70% cases of end-stage renal disease, while the obesity is the main risk factor for these disorders [4]. Even in apparently healthy men, a correlation between body mass index and renal diseases was observed [5]. Glomerular filtration rate (GFR) is the basic determinant of kidney function. Clearance of exogenous substances is the most precise, however, difficult and expensive method of evaluating GFR [6]. In practice, creatinine clearance is usually assessed. A number of formulas based on the concentration of creatinine in serum have been proposed: Cockcroft-Gault [7], Modification of Diet in Renal Disease (MDRD) [8] and group Collaboration formula (CKD-EPI) [9].

Aforementioned formulas are not suitable for quickly increasing renal malfunction and are inadequate for patients without chronic renal disease [6]. Using body mass as a

determinant of muscle mass in Cockcroft-Gault's formula leads to overestimation of GFR in patients with oedema, overweight and obesity. Those equations are also inadequate for evaluation of GFR >60 ml/min [10].

Besides creatinine, eGFR can also be calculated from cystatin C concentration. Cystatin C is a polypeptide produced constantly in the same volume by all nucleated cells of the body. Because of its low molecular mass, it is easily filtrated by kidneys and it was suggested superior to creatinine for glomerular filtration assessment. Cystatin C was shown to be unaffected by age, gender or muscle mass [11]. Many authors proposed formulas based on cystatin C concentrations for estimating GFR: Grubb et al. [12], Larsson et al. [13], Le Bricon et al. [14] and Hoek et al. [15].

The aim of this study was to evaluate eGFR in patients with morbid obesity using formulas based on creatinine and cystatin C and to compare the obtained results.

## MATERIALS AND METHODS

We studied 40 morbidly obese patients awaiting bariatric surgery in the 1st Department of General and Endocrinological Surgery, Medical University of Bialystok, Poland. The study protocol was approved by the local Bioethics Committee (approval Nr: R-I-002/371/2010). Informed written consent was obtained from all patients. Patients with previously diagnosed renal disease, signs of acute inflammation or history of malignancy were excluded from the study.

Venous blood samples from all of the patients were drawn before treatment. All blood samples were allowed to clot before centrifugation. Sera were removed, aliquoted and stored at -80° C until assayed. Serum concentration of cystatin C was measured using enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, Abingdon, England) according to the manufacturer's instructions. The serum samples were diluted 30-fold for the determination of cystatin C. Serum cystatin C was assessed using ELISA immunoenzymatic assay from R&D with MiniBOS Dia-Sorin analyzer. Measurements were performed twice. The intra-assay coefficient of variation (CV%) of cystatin C is reported by the manufacturer to be 3.1 % at a mean concentration of 29.9 ng/ml, standard deviation (SD)=0.92. In the literature, the units of cystatin C concentration have uniformly been mg/l, and for this reason we decided to use these units in the present study. Serum creatinine was measured using kinetic method by Jaffe with picric acid on the Abbott Architect i8000 analyzer. 24-hour urine sample was collected for albumin measurement.

Estimated GFR was calculated according to MDRD [8], CKD-EPI [9], Grubb et al. [12], Larsson et al. [13], Le Bricon et al. [14] and Hoek et al. [15] formulas.

MDRD formula containing four variables (serum creatinine, age, race and gender):

$eGFR = 175 \times [Cr]^{-1.154} \times age^{-0.203} \times 1.212$ (if black) x 0.742 (if female)

[Cr] – creatinine concentration [8]

CKD-EPI formula contains variables for creatinine concentration in serum, age, gender and race (*Tab. 1*).

Grubb et al. [12] analysed the relation of the concentration of cystatin C assessed using immunoturbidimetric method and GFR was obtained from iohexol clearance in 536 patients. The authors developed formula:

$eGFR = 84.69 \times CysC^{-1.680}$ (x1.384 if children<14 years old); CysC - cystatin C concentration.

Larsson et al. [13], after the examination of 100 patients, compared GFR obtained from iohexol clearance with cystatin C and creatinine concentration. They reached better correlation of GFR with cystatin C (r=0.91) than with creatinine (r=0.84). For cystatin C concentration obtained by turbidimetric method they proposed the formula:

$eGFR = 99.43 \times CysC^{-1.5837}$; CysC - concentration of cystatin C.

Unlike all other methods used in our paper, formula of Larsson et al. [13] gives results in ml/min and not in ml/min/1.73m$^2$.

Among 25 patients after renal transplantation, Le Bricon et al. [14] compared GFR obtained from $^{51}$Cr-EDTA clearance with cystatin C concentration obtained by nephelometric method and creatinine concentration. They developed a formula:

$eGFR = 78/CysC + 4$; CysC - concentration of cystatin C.

Among 123 patients, mostly with kidney diseases and type 2 diabetes, Hoek et al. [15] compared GFR obtained from iothalamate clearance with creatinine clearance obtained from Cockcroft-Gault's formula and with cystatin C concentration obtained by nephelometric method. They proved correlation between GFR and cystatin C concentration (r=0.873) and Cockcroft-Gault's formula (r=0.876). More precise estimation of GFR was reached after application of formula:

$eGFR = -4.32 + 80.35 \times 1/CysC$; CysC - concentration of cystatin C,

than after using Cockcroft-Gault's formula.

The data were analysed using nonparametric tests. For visual representation we used median, range between 25 and 75 percentile, minimal and maximal values. Kruskal-Wallis ANOVA, Mann-Whitney and Spearmann's tests were applied. $P < 0.05$ was assumed as statistically significant. Statistical analysis was conducted using Statistica 10.0.

***Table 1.*** **CKD-EPI formula for Caucasian population based on creatinine concentration (Cr) in serum [9].**

| Gender | Creatinine concentration | Formula |
|---|---|---|
| Woman | ≤ 0.7 | GFR = 144 x $(Cr/0.7)^{-0.329}$ x $(0.993)^{age}$ |
| | > 0.7 | GFR = 144 x $(Cr/0.7)^{-1.209}$ x $(0.993)^{age}$ |
| Man | ≤ 0.9 | GFR = 141 x $(Cr/0.9)^{-0.411}$ x $(0.993)^{age}$ |
| | > 0.9 | GFR = 141 x $(Cr/0.9)^{-1.209}$ x $(0.993)^{age}$ |

## RESULTS

The studied group consisted of 16 men and 24 women (40% and 60%) at average age of 44.2 years. The average weight and body mass index (BMI) were 135.6 kg and 47.9 kg/m$^2$, respectively. The results of anthropometric measurements, mean concentrations of creatinine and cystatin C, creatinine clearance and the average values of other parameters are shown in *Tab. 2*. All of the patients were Caucasians. Measurements of cystatin C gave the coefficient of variation (CV%) between 0.22 and 6.26% (average 2.63 ± 1.88%).

The mean value of eGFR in morbidly obese patients ranged from 85.9 to 111.1 ml/min/1.73m$^2$, depending on used formula (*Fig. 1*). This variation reached 29% (Grubb vs. Hoek). The application of the formulas with serum cystatin C, leads to the results that differ from eGFR derived from serum creatinine (*Tab. 3*). Larsson's formula yielded the highest absolute values of eGFR, however, these data are expressed in ml/min. Considering only the results of eGFR expressed in ml/min/1.73m$^2$, the highest values were obtained using Grubb's formula, while the lowest - after applying Hoek's formula. None of the patients had eGFR lower than 60 ml/min/1.73 m$^2$ as calculated from creatinine concentration, whereas formulas based on cystatin C led to determination of eGFR <60 ml/min/1.73m$^2$ even in 6 patients (14%).

We demonstrated, that application of different estimating equations can lead to substantial differences in

***Figure 1.*** **Estimated GFR (eGFR) calculated using formulas based on creatinine (CKD-EPI and MDRD) or cystatin C (Grubb, Le Bricon, Hoek and Larsson) serum concentrations. The values of Larsson's formula are calculated in ml/min, and not in ml/min/1.73m$^2$.**

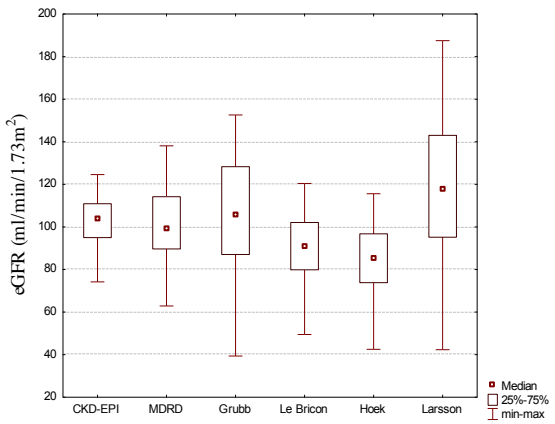


***Table 2.*** **Study group parameters (mean ± standard deviation).**

| | Value |
|---|---|
| Age (years) | 44.2 ± 10.9 |
| Height (cm) | 168.9 ± 10.4 |
| Weight (kg) | 135.6 ± 23.6 |
| BMI (kg/m$^2$) | 47.9 ± 6.7 |
| Creatinine (µmol/l) | 68.1 ± 10.6 |
| Cystatin C (mg/l) | 0.947 ± 0.243 |
| Creatinine clearance (ml/min) | 147 ± 31 |
| Glucose (mmol/l) | 6.33 ± 1.44 |
| Cholesterol (mmol/l) | 5.24 ± 1.01 |
| Triglycerides (mmol/l) | 1.79 ± 0.81 |
| HDL (mmol/l) | 1.21 ± 0.33 |
| LDL (mmol/l) | 3.29 ± 0.94 |
| Haemoglobin (mmol/l) | 8.75 ± 0.87 |
| Haematocrit (mmol/l) | 0.429 ± 0.044 |

***Table 3.*** **The level of statistical significance of differences between eGFR obtained using different formulas.**

| | | p value |
|---|---|---|
| MDRD | CKD-EPI | ns |
| | Grubb | ns |
| | LeBricon | p < 0.05 |
| | Hoek | p < 0.01 |
| | Larsson | p < 0.05 |
| CKD-EPI | Grubb | ns |
| | LeBricon | p < 0.01 |
| | Hoek | p < 0.001 |
| | Larsson | p < 0.05 |
| Grubb | LeBricon | p < 0.05 |
| | Hoek | p < 0.01 |
| | Larsson | ns |
| Le Bricon | Hoek | ns |
| | Larsson | p < 0.001 |
| Hoek | Larsson | p < 0.001 |

*ns – non significant*

***Table 4.*** **Number of patients categorized by stage of renal disease [16]. Formulas: CKD-EPI and MDRD are based on creatinine concentration, whereas Grubb's, Le Bricon's, Hoek's and Larsson's – on cystatin C concentration.**

| Formula | | Stage of renal disease (eGFR) 2 (60-89 ml/min/1.73m$^2$) | 3 (30-59 ml/min/1.73m$^2$) |
|---|---|---|---|
| Creatinine-based | MDRD | 7 | 0 |
| | CKD-EPI | 5 | 0 |
| Cystatin C - based | Grubb | 6 | 6 |
| | Le Bricon | 17 | 2 |
| | Hoek | 21 | 6 |
| | Larsson* | 4 | 2 |

** the values of Larsson's formula are calculated in ml/min, and not in ml/min/1.73m$^2$*

the classification of individual patients to stage 2 and 3 of kidney disease according to National Kidney Foundation classification [16] (*Tab. 4*). Estimation based on Hoek's formula led to allocating to stage 2 four times more patients than CKD-EPI formula, and three times, compared to the MDRD formula. Among 6 patients with stage 3 kidney disease according to Hoek's formula there was 1, who was allocated to stage 1 as calculated using CKD-EPI equation.

There was a positive correlation between BMI and cystatin C concentration (r=0.68). No associations were found between concentrations of either creatinine or cystatin C and waist/hip ratio, fasting glucose or C-reactive protein (CRP). Albuminuria had the strongest association with eGFR calculated using Le Bricon formula.

## DISCUSSION

It this study, we demonstrated substantial differences in estimated GFR in patients with morbid obesity depending on the formula used. There were considerable discrepancies between the values of eGFR based on creatinine as compared to those calculated from cystatin C concentration. The latter classified larger numbers of morbidly obese subjects to stage 2 and 3 of kidney disease.

There has been an on-going debate for quite some time what is the gold standard for determination of renal function in morbidly obese subjects. Creatinine concentration depends on muscle mass, which is relatively diminished in patients with BMI > 40 kg/m$^2$. On the other hand, in large population-based studies, cystatin C is shown to be associated with BMI [17, 18]. The nature of this association remains unclear. However, an independent strong correlation between cystatin C concentration and end-stage renal disease was demonstrated in morbidly obese patients [19]. Also studies assessing the relation between cystatin C, creatinine concentration and GFR obtained from exogenous clearance showed that concentration of cystatin C had closer relation with GFR than concentration of creatinine [20-22]. This finding was supported by meta-analysis suggesting the superiority of cystatin C concentration comparing with creatinine [3].

Wetmore et al. [23] compared values of eGFR obtained from formulas of Cockcroft-Gault, MDRD and two equations based on concentration of cystatin C. In order to calculate eGFR from the concentration of cystatin C, they applied Grubb's and Larsson's formulas. Using MDRD formula, they recognized less cases of chronic renal disease than after application of other formulas. It remains compatible with our researches. As shown in Tab. 4, less cases of 2nd and 3rd stage of renal diseases were recognized after applying formulas based on creatinine concentration than after using equations based on cystatin C concentration. Estimating GFR by CKD-EPI and MDRD formulas allowed to recognize 2nd and 3rd stage of chronic renal disease in 5 (CKD-EPI) and 7 (MDRD) patients. Applying formulas based on cystatin C concentration allowed to recognize 2nd and 3rd stage of chronic renal disease in 6 (Larsson), 12 (Grubb), 19 (Le Bricon) and 27 (Hoek) patients. Applying formulas based on creatinine concentration in obese patients may lead to delayed diagnosis of renal disease.

Among several estimating equations based on cystatin C concentration, Hoek's formula was reported to correlate the most closely with eGFR obtained from exogenous chemicals clearance [24].

Results presented above were obtained in general population. Publications comparing equations to calculate eGFR from creatinine and cystatin C in obese patients are often equivocal [25]. Although cystatin C concentration is independent of age, gender or muscle mass [11], it was suggested to depend on factors other than glomerular filtration, e.g. BMI, CRP and proteinuria [18]. Other researchers questioned those results suggesting their clinical insignificance [26]. Furthermore, closer correlation of creatinine than cystatin C with non-renal factors was indicated [27]. Friedman et al. [25] observed that creatinine concentration in serum is directly proportional to the height and inversely proportional to the adipose tissue mass and suggested superiority of cystatin C in evaluating renal functions in obese patients. Neither Cockcroft-Gault's nor MDRD formulas were found reliable in obese subjects [28].

One of the misleading issues concerning evaluation of eGFR is its calculation per body surface area (BSA) [29]. One of the most common formula to calculate body surface area (BSA) is DuBois' formula: BSA = weight (kg)$^{0.425}$ x height (cm)$^{0.725}$ x 0.007184 [30]. However, BSA of obese patients is out of proportion with lean body mass and volume of nephrons [31]. According to Delanaye et al. [29], in obese patients, adjustment of GFR to BSA leads to significant decrease in obtained GFR in comparison to its real values. Chagnac et al. [31] suggest applying GFR's absolute values. In our study, only Larsson's formula is expressed in ml/min. Applying this formula led to the highest average eGFR's values in comparison to formulas based on cystatin C and creatinine concentration. However, our results of eGFR calculated according to Larsson's equation had the largest dispersion among all formulas (44-188 ml/min).

Lack of comparison of eGFR based on serum creatinine and serum cystatin C concentrations to GFR obtained from exogenous clearance is the limitation of our study. However, such comparison was made by authors of all mentioned formulas and our aim was to evaluate variation between eGFR calculated on the basis of data easily available in everyday practice – creatinine and cystatin C serum concentrations.

## CONCLUSIONS

In the present study, we clearly demonstrated that applying different formulas to evaluate eGFR in morbidly obese patients results in substantial variation of renal function estimates. Those values may vary even by up to 29%. Equations based on creatinine concentration may lead to underestimation of renal disease incidence in morbidly obese subjects. Applying formulas based on cystatin C concentration, especially Hoek's formula, led to the recognition of 5 times more cases of 2nd and 3rd stage of chronic renal disease (GFR <90 ml/min/1.73m$^2$). We suggest, that cystatin C could be routinely used to assess renal function in morbidly obese subjects, especially when applying Le Bricon formula. Unfortunately, so far there is no agreement to the method of cystatin C determination. In our experience, ELISA is an effective and reliable option.

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