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The HUGE formula (hematocrit, urea and gender): association with cardiovascular risk

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Abstract. – OBJECTIVES: To evaluate the relationship between chronic renal failure (CFR) defined through HUGE (hematocrit, urea and gender) formula score and the patient's cardiovascular risk measured through cardiovascular disease antecedents such as ischemic cardiopathy, cerebrovascular disease and peripheral arterial disease.

DESIGN AND METHODS: The sample consisted of 2,831 subjects. Mean age was 51.2±14.7 years and 53.5% were female. Serum creatinine, urea, hematocrit and 24h proteinuria were analyzed. HUGE score was calculated from gender, urea and hematocrit. GFR was estimated from uncalibrated serum creatinine using the abbreviated Modification of Diet in Renal Disease equation (MDRD-4). UAE was measured in first morning urine sample.

RESULTS: Using HUGE formula 2.2% (n = 61) of subjects had CRF. Of them, 12 (19.7%) had cardiovascular disease history. Among patients without CRF (n = 2770), 194 subjects had history of previous cardiovascular diseases (0.07%; $p < 0.001$ Square Chi test). Using the MDRD-4 formula 4.0% of subjects (n = 113) had a GFR < 60 ml/min. Of them, 18 (15.9%) had cardiovascular disease history. Among patients without CRF (n = 2718), 188 subjects had history of previous cardiovascular diseases (0.07%; $p < 0.001$ Square Chi test). Odd's ratio for cardiovascular diseases using HUGE definition of CRF was 3.25 ($p = 0.001$, Mantel-Haenszel test). CFR was associated to higher pulse pressure (PP) and increased urinary albumin excretion.

CONCLUSIONS: A significant cardiovascular risk was associated to the diagnosis of CRF through HUGE formula. This relation was closer than the obtained using MDRD estimated GFR in spite of a bigger sample. HUGE formula seems to be a useful tool for diagnosing CRF and evaluate the cardiovascular risk of these patients.

Key Words:
Cardiovascular risk, Chronic kidney disease, HUGE formula.

Introduction

Recently, community-based longitudinal studies have demonstrated that chronic kidney disease (CKD) measured through estimated glomerular filtration (eGFR), is an independent cardiovascular risk factor for the composite study outcome, including myocardial infarction, fatal coronary heart disease, stroke, and death[1]. These results were confirmed recently in a Japanese population[2] and in a population with preexisting cardiovascular (CV) disease[3]. Moreover, CKD is a growing public health problem that currently affects over 20 million adults in the United States[4]. Globally, the increasing incidence and prevalence of CKD is associated with adverse health outcomes and high health-care costs[5].

The HUGE formula with data obtained from a general population, offers a readily available and inexpensive method for diagnosing CKD based on haematocrit plasma serum urea levels and gender[6]. It is more accurate than MDRD formulae to differentiate chronic renal failure (CRF) from eGFR < 60 ml/min/1.73 m^2. It has been tested in databases with a total of 125.373 subjects. It is particularly useful in persons aged over 70 years of age and it could overcome the disadvantages derived from the use of serum creatinine to calculate eGFR, since it reduces the diagnosis of CKD by a 10.46% in elderly people. In Spain, where it has been estimated a CRF prevalence using MDRD equation about 6.8% in general population (2.992.000 subjects)[7], the HUGE formula would cut this figure by more than 300.000 persons. More recently it has been demonstrated that it could define the prognosis of diabetic nephropathy patients[8].

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This study has tried to evaluate the relationship from HUGE formula score and the patient´s cardiovascular risk measured through cardiovascular disease antecedents such as ischemic cardiopathy, cerebrovascular disease and peripheral arterial disease.

Design and Methods

3,402 subjects between 25 and 79 years living in the area of Don Benito-Villanueva de la Serena (Badajoz, Spain) were randomly selected from the database of the Health Care System. Non-residents, institutionalized and deceased persons, disabled subjects, pregnant women, and people unable to give written informed consent were excluded. 2,833 ones were recruited and 2,831 were included in the survey (participation rate 82.7%). Mean age was 51.2±14.7 years, median 50 (RI 24), and 53.5% were female. A wide description of sample has been published elsewhere[9].

Serum creatinine, urea and haematocrit were analyzed after overnight fast. Urinary albumin excretion (UAE) was measured in first morning urine sample. Glomerular filtration rate (GFR) was estimated from uncalibrated serum creatinine using the abbreviated Modification of Diet in Renal Disease equation (MDRD-4) for every sex[10,11] and the CKD-EPI formula (adjusted also for gender)[12]. Only caucasian patients were included in the study. Patients were classified according to K/DOQI stages of chronic renal disease following the results of MDRD equation[13]. For statistical comparisons chronic renal failure (CRF) was defined as a GFR < 60 ml/min estimated by CKD-EPI formula. UAE was measured in first morning urine sample. Microalbuminuria was diagnosed when the albumin/creatinine ratio was greater than 22 in men or 31 mg/g in women[4]. Proteinuria was defined as an UAE higher than 300 mg/g. Blood pressure was measured with an electronic device (Omron 705®). Increased pulse pressure (PP) was defined as a PP ≥ 55 mmHg.

The HUGE formula score was also calculated for all subjects. This is a method for diagnosing CRF based on haematocrit, serum urea levels and gender. The mathematical expression of HUGE formula is:

$$L = 2.505458 - (0.264418 \times Hematocrit) + (0.118100 \times Urea) [+ 1.383960 \text{ if male}]$$

If L is lower than "0", it means that the individual does not have CRF. If L is > 0, it means that the individual have CRF[15].

Statistical Analysis

Results are expressed as mean ± 1 standard deviation. Kolmogorof-Lilliefors Test showed that urinary albumin excretion did not follow a normal distribution so these values were compared using Wilcoxon test for paired data. Other continuous values have been compared through paired Student "*t*" test. The square chi test was used for comparison of discrete data changes. Odd's ratio significance was analyzed using Mantel-Haenszel test. All statistical tests were two-sided. *p* values lower than 0.05 were considered as significant. Analysis was developed with the statistical package SPSS 13.0 (SPSS Inc., Chicago, IL, USA).

Results

Using HUGE formula 2.2% (n = 61) of subjects had CRF (95% CI: 0.015-0.032). There were not differences between men (2.2%; 95% CI: 0.015-0.030) and women (2.1%; 95% CI: 0.015-0.030). Of them, 12 (19.7%; 95% CI: 0.116-0.313) had cardiovascular disease history (data are shown in Table I). Among patients without CRF (n = 2770), 194 subjects had history of previous cardiovascular diseases (0.07%; 95% CI: 0.061-0.080, $p < 0.001$ Square Chi test). Using the MDRD-4 formula 4.0% of subjects (n = 113) had an eGFR < 60 ml/min (95% CI: 0.033-0.048). Of them, 18 (15.9%; 95% CI: 0.103-0.238) had cardiovascular disease history. Among patients without CRF (n = 2718), 188 subjects had history of previous cardiovascular diseases (0.07%; 95% CI: 0.060-0.079, $p < 0.001$ Square Chi test).

Odd's ratio for cardiovascular diseases using HUGE definition of CRF was 3.25 (IC95%, 1.70-6.22; with cardiovascular diseases 1.042; 95% CI: 1.007-1.078; without cardiovascular diseases, 0.356; 95% CI: 0.211-0.602, $p < 0.001$, Mantel-Haenszel test). For eGFR < 60 ml/min the Odd's ratio was 2.550 (IC 95% 1.508-4.311; with cardiovascular diseases 1.107, IC 95% 1.021-1.201; without cardiovascular diseases 0.434, IC 95% 0.278-0.678; $p = 0.001$, Mantel-Haenszel test) (Figure 1).

44.3% (95% CI: 0.325- 0.567) of patients with HUGE score > 0 showed increased PP (pulse pressure) vs. 30.0% (95% CI: 0.283-0.317) in those without CRF ($p = 0.017$, Square Chi test). Mean PP was 59.7±22.6 mmHg in CRF group vs. 50.5±17.1 mmHg in non CRF group ($p = 0.002$, Student's *t* test).

Table I. Cardiovascular disease history.

	HUGE < 0	HUGE > 0	p (χ^2 test)	Odds ratio
Acute myocardial infarction	38 (1.4%)	1 (1.6%)	0.860	1.20 (0.16-8.86)
Angor pectoris	56 (2.0%)	3 (4.9%)	0.118	2.50 (0.76-8.24)
Ictus	48 (1.7%)	2 (3.3%)	0.352	1.95 (0.46-8.23)
Peripheral arterial disease	95 (3.4%)	9 (14.8%)	< 0.001	4.87 (2.33-10.2)

Mean microalbuminuria was 19.3±39.7 mg/g in CRF group vs. 7.2±20.0 mg/g in non CRF group ($p < 0.001$, Wilcoxon test). Prevalence of microalbuminuria was 15.5% (95% CI: 0.084-0.269) for the CRF group and 4.4% for the other group (95% CI: 0.037-0.053) ($p < 0.001$ Square Chi test).

Discussion

HUGE formula was developed and validated to improve the diagnosis of CRF in general population using clinical and laboratory data that are obtained routinely in patients with CKD. So that it could be easily integrated into a laboratory information system or a clinical health record. Our data suggest that its results correlates with the individual patient´s cardiovascular risk evaluated through the cardiovascular disease history.

There has been rapidly growing interest in the relation between kidney disease and the risk of death and cardiovascular disease. With recognition that the presence of mild chronic kidney disease is of considerable importance, several studies have examined the association of different cutoff values of serum creatinine with the risks of death from any cause, death from cardiovascular causes, and cardiovascular events, and most of these studies have found increased risks with higher serum creatinine levels[15].

Nevertheless, creatinine is secreted by proximal tubular cells as well as filtered by the glomerulus; thus, the creatinine clearance exceeds the GFR. Moreover, tubular secretion of creatinine varies among and within individual persons, especially in those with a mild to-moderate reduction in the GFR[16]. Since serum creatinine levels are not linearly associated with GFR, the use of predictive equations has been proposed as a more accurate means of estimating the GFR, with the MDRD equation having better predictive ability in certain populations[17,18]. In this way, using the MDRD equation an independent, graded association was observed between a reduced estimated GFR and the risk of death, cardiovascular events, and hospitalization in a large, community based population[13]. Several reports suggest that an estimated GFR below 60 ml per minute per 1.73 m^2 is a risk factor for both new and recurrent cardiovascular disease in the general population and in people at increased risk for cardiovascular disease[19-21]. In these patients, death from cardiovascular disease is more common than progression to kidney failure[22]. Patients with an estimated GFR below 60 ml per minute per 1.73 m^2 are, therefore, considered to be in the high-risk group for cardiovascular diseases, and they should undergo intensive evaluation and treatment of risk factors for cardiovascular disease.

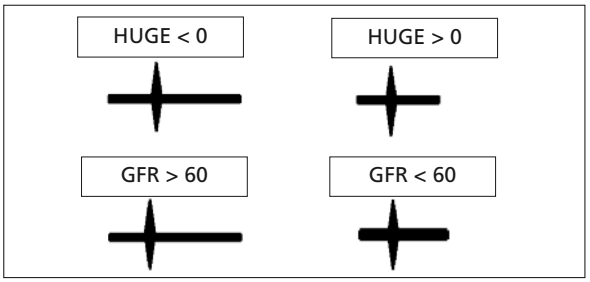

Figure 1. Odds ratio for cardiovascular diseases.

It should be noted that MDRD formula showed differences in the prediction of CRF when compared with the observed diagnosis using HUGE one (it near double the prevalence). In a large database of 125.373 outpatients, the differences in the prediction for CRI between the HUGE formula and the MDRD in the population older than 70 years rose to 10.46%. Nevertheless, in general population (the sample recruited in our study) the differences are more striking, since the prevalence of CRF is near doubled when MDRD estimated GFR is used to define CRF.

In older patients, PP is an indicator of large-artery stiffness and becomes a dominant factor predicting cardiovascular risk[23]. PP may be the most reliable blood pressure indicator when systolic hypertension is accompanied by normal or low diastolic blood pressure (DBP). This may have important implications because isolated

systolic hypertension is the most common type of hypertension among untreated adults > 50 years old[24]. The higher frequency of increased PP in the group with CRF defined by HUGE formula suggests again a more close relationship of the HUGE score with cardiovascular risk when compared with MDRD estimated GFR.

Viberti et al[25] coined the term microalbuminuria in 1982 to describe an increased urinary albumin excretion not detectable by the usual urinalysis but exceeding 20 μg/min. With this criterion, they differentiated patients with insulin-dependent diabetes mellitus into those with and those without microalbuminuria and suggested that patients with microalbuminuria might have a worse renal prognosis. Microalbuminuria in diabetic patients has been recognized not only as a predictor of progression of diabetic nephropathy but also as a powerful independent risk factor for cardiovascular disease[26]. Even in non diabetic hypertensive patients microalbuminuria has been shown to predict renal and cardiovascular events, and a continuous relation between urinary albumin excretion and cardiovascular, as well as non-cardiovascular, mortality has recently been found in a general population study[27,28]. The urinary albumin excretion in healthy subjects ranges between 5 and 20 mg/24 h[29]. Microalbuminuria has classically been defined as urinary albumin excretion from 30-300 mg/24 h or equivalent amounts when timed overnight or spot urine samples are used[30]. On spite of this cut off point for microalbuminuria definition the risk of coronary heart disease and death increased significantly by 70 and 50%, respectively, in patients with urinary albumin excretion values between 5 and 10 mg/min, and even by 100% for both outcomes in patients with urinary albumin excretion values higher than 10 mg/min[31]. Nevertheless, we have used the definition used by the 2007 European Guidelines for the Management of Arterial Hypertension[34]. One more time the higher prevalence and intensity of microalbuminuria in CRF patients (diagnosed by HUGE equation) suggest a close relationship between the results of this formula and cardiovascular risk.

Conclusions

A significant cardiovascular risk associated to the diagnosis of CRF through HUGE formula could be detected in spite of a very small sample of CRF patients. This relation was closer than the obtained using MDRD estimated GFR in spite of a bigger sample. HUGE formula seems to be a useful tool for diagnosing CRF and evaluate the cardiovascular risk of these patients.

Conflict of Interest

None.

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