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Role of cystatin C and beta-2microglobulin in the diagnosis of type 2 diabetic nephropathy

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Contributions: BH, principal author of the study, conception, realization and publication of the work; AN, scientific orientation and overall supervision of the research project; MI, supervision of the collection, processing and analysis of biological samples; DR and BH, methodology and data analysis; MN and DM, selection and clinical evaluation of patients.

Conflict of interest: the authors declare that they have no conflicts of interest related to this study.

Ethics approval and informed consent: the study was approved by the University Hospital Ethics Committee (N°15/2018, 08/11/2024) and all participants in the present study gave written informed consent. The participants' confidential information (first name, last name, age, gender, height, weight, medical history and prescribed treatment regimen (oral antidiabetic agents, insulin therapy, or a combination of both) was recorded on a pre-established questionnaire.

Availability of data and materials: all data generated or analyzed during this study are included in this published article.

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Abstract

Nephropathy is one of the most frequent microvascular complications of diabetes. It generates the most reserved prognosis since it increases the risk of end-stage renal failure. Despite microalbuminuria remains the gold test for the early detection of Diabetic Nephropathy (DN), the dosage of this parameter is insufficient to predict DN risks due to certain limitations. Therefore, there is a paradigm shift towards new biomarkers that may predict the risk of DN early and prevent the onset of end-stage renal disease. This study aims to compare the variation patterns of cystatin C (cys C) and beta-2 microglobulin (β2-M) with estimated Glomerular Filtration Rate (eGFR) for the early detection of DN in patients with type 2 diabetes (T2D), to assess the Albumin to Creatinine Ratio (ACR) and to search for risk factors for DN. A descriptive cross-sectional study was conducted on 368 diabetic patients and 90 no diabetic subjects in the hospital. The statistical analysis was performed using SPSS 22 software. The prevalence of nephropathy was 41.29% in a predominantly women cohort with a mean age of 59 years. Correlation analyses and diagnostic performance evaluation using Receiver Operating Characteristic (ROC) curves, referencing a creatinine-based on eGFR threshold of <60 mL/min/1.73 m², demonstrated that cys C and ß2-M biomarkers exhibit superior sensitivity and specificity compared to the ACR for detecting impaired renal function. The results of this study demonstrated that serum cys C and ß2-M could be reported as effective early markers of diabetic nephropathy prediction.

Introduction

According to several relevant studies, diabetes is associated with 40% of new cases of end-stage chronic renal failure and it is considered as the main cause.[1] Diabetic kidney disease includes typical Diabetic Nephropathy (DN) and other forms of kidney damage.[2]

DN is known as Kimmelstiel-Wilson syndrome, nodular diabetic glomerulosclerosis or inter-capillary glomerulonephritis. It is a growing pathology with serious human and socio-economic consequences. Indeed, each successive stage of this nephropathy is associated with a high risk of cardiovascular events.

For this reason, systematic screening and appropriate management are required to limit the renal and cardiovascular complications associated with diabetes.[3] It is recommended to start the screening for DN after the T2D diagnosis because approximately 7% of patients suffer from microalbuminuria due to the clinical treatments for several years. For type 1 diabetes, screening should begin five years after the diagnosis.[1]

According to the American Diabetes Association (ADA) and French Kidney Federation, the fundamental markers for the detection and monitoring of chronic kidney disease in patients suffering from diabetes are the Urinary Albumin Excretion (UAE) rate and the estimation of Glomerular Filtration Rate (eGFR).[3] Although albuminuria measurement is an essential element in the diagnosis of DN, some patients may present a decrease in glomerular filtration rate estimated by the Modified Diet in Renal Disease (MDRD) without associated microalbuminuria.

To overcome these controversies, it would be logical to measure biomarkers of renal function that can optimize the early detection strategies for the prevention and treatment of DN. To correctly qualify the potential markers of renal damage in T2D it is useful to classify them according to the renal structure affected by the pathological process.

On this basis, many markers of glomerular damage have been distinguished including transferrin, immunoglobulin G (IgG), ceruloplasmin, cystatin C (cys C) or nephrin. In addition, many markers of tubular damage such as neutrophil-associated lipocalin gelatinase (NGAL), alpha-1-microglobulin, kidney injury molecule-1 (KIM-1) and beta-2 microglobulin (ß2-M) were reported.[4]

Cys C has been proposed as an alternative endogenous serum biomarker for the estimation of renal function. Cys C is a protein that is freely filtered at the glomerulus level and almost entirely reabsorbed and catabolized by epithelial cells of the proximal tubules. Its synthesis is constant and never affected by muscle mass, diet, age or inflammatory conditions.[5] Like ß2-M, which is a key component of the adaptive immune system, it is also freely filtered at the glomerulus level and then entirely reabsorbed and metabolized by the epithelial cells of the proximal tubules. Its level increases in case of kidney dysfunction.[6]

Therefore, it is essential to identify a reliable, unambiguous, reproducible and simple marker to detect kidney damage. The heterogeneity and the complexity of the physiopathological mechanisms of DN, its prevalence throughout the world, and the renal and cardiovascular risk to which diabetics are exposed prompted us to carry out this study on a population in the Batna region to: i) compare the interest and the effectiveness of the dosage of cys C and ß2-M in the diagnosis of type 2 DN compared to the calculation of eGFR using the MDRD equation, and to the classic dosage of microalbuminuria; ii) determine the risk factors for type 2 diabetic nephropathy in the studied population.

Materials and Methods

In the present descriptive and analytical cross-sectional study, 368 diabetic patients including 152 with nephropathy and 216 without nephropathy and 90 healthy subjects were recruited between September 2018 and October 2020. These individuals were directed by the outpatient diabetes center to the laboratory located for standard biological testing.

The inclusion criteria in this study are: both sexes, age > 35 years, and diagnosis of type 2 diabetes with and without nephropathy (according to ADA criteria). Subjects with a history of diabetes type 1 or suffering from other nephropathies, lymphoma, auto-immune diseases, hypothyroidism and urinary infections were excluded.

The study was approved by the University Hospital Ethics Committee (N°15/2018, 08/11/2024) and all participants in the present study gave written informed consent. The participants' confidential information (first name, last name, age, gender, height, weight, medical history and prescribed treatment regimen (oral antidiabetic agents, insulin therapy, or a combination of both) was recorded on a pre-established questionnaire.

With regard to Body Mass Index (BMI), its values were determined using the following mathematical expression:

$$BMI = \text{weight (kg)} / \text{height (m}^2\text{)}$$

both height and weight were measured by the attending physician during the consultation for each patient.

Strict 12-hour fasting blood samples were collected between 8 a.m. and 9 a.m. for the analysis of blood glucose, lipid parameters, creatinine and uric acid, cys C and ß2-M and the assessment of the urinary albumin excretion rate on a morning urine sample to assess the albumin to creatinine ratio (ACR). Glycemic balance was assessed by glycated hemoglobin (HbA1c); eGFR was estimated using the abbreviated MDRD equation:

eGFR = 186 × (serum creatinine)-1.154 × (age)- 0.203 × (0.742 if woman)

The dosages of glycemia, creatinine, uric acid, lipid profile, cys C (turbidimetric immune test on latex particles), high-sensitivity C-reactive protein (hs-CRP) were carried out on Integra 400 analyzer (Roche, Meylan, France), Vitamin D (chemiluminescence: principle of competition) on E411 analyzer (Roche, Meylan, France), ß2-M (immunoturbidimetric) on AU 480 chemistry analyzer (Beckman Coulter, Brea, California, USA), HbA1c on Capillarys Flex (Sebia, Paris, France).

Based on the urinary ACR values, patients were divided into three groups, normal albuminuria (non-diabetic subjects), diabetics with nephropathy and diabetics without nephropathy.

The data were analyzed using BM SPSS version 22 software.
A range of statistical analyses was performed in this study. The chi-square test was applied to assess the associations between categorical variables. Comparisons of means between two independent groups (diabetic patients with nephropathy and those without) were conducted using the Student's t-test, while analysis of variance was utilized for comparisons involving more than two groups, specifically diabetic patients with nephropathy, diabetic patients without nephropathy, and non-diabetic controls. Pearson's correlation coefficient was employed to evaluate the strength of associations between continuous variables with normally distributed data.

The Receiver Operating Characteristic (ROC) curve (evaluation of the diagnostic performance of the studied biomarkers) and bivariate logistic regression were applied to measure the association between the occurrence of an event (DN) and the risk factors.

For all these tests p values < 0.05 were considered statistically significant

Results

The study cohort consisted of 368 patients with diabetes (157 men and 211 women) and 90 non-diabetic controls (31 men and 59 women), with mean ages of 59.0 ± 10.6 and 48.7 ± 10.3 years, respectively. The diabetic group had a mean disease duration of 10.1 ± 7.2 years. Treatment modalities included metformin in 51.4% of patients, while 68% received insulin therapy, either as monotherapy or in combination with oral antidiabetic agents.

The average BMI of this study was in the overweight range 34.8% *vs* 48.9%, of all diabetics, 13% have nephropathy, 12.5% have retinopathy and 55% are hypertensive, with an average length of 8.25±3.56 years.

In the present study, diabetic nephropathy was observed in 40.4% of men patients compared to 28.1% of women patients. Of those affected, 41.53% were aged between 68 and 78 years. Disease duration analysis revealed that 38.88% of patients with nephropathy had less than 10 years of diabetes progression, while 45.52% had diabetes for over 10 years. Furthermore, 45.1% of patients with nephropathy exhibited concomitant diabetic retinopathy, and nephropathy was present in 43.34% of hypertensive diabetic individuals.

Diabetic Patients with Nephropathy

Glycemic Profile: Elevated fasting plasma glucose and HbA1c levels.
Lipid profile: Marked dyslipidemia characterized by significant increases in LDL-cholesterol and triglycerides, a reduction in HDL-cholesterol, and a pronounced elevation of lipoprotein(a).
Renal function : Presence of microalbuminuria progressing to overt proteinuria; increased serum creatinine and reduced eGFR. Elevated levels of cys C and β2-M.
Inflammatory Marker: Significantly increased hs-CRP.

Diabetic Patients without Nephropathy
Glycemic Profile :Better-controlled fasting glucose and HbA1c values, which may still be mildly elevated compared to normative ranges.

Lipid profile : Moderate dyslipidemia, with mild elevations in LDL-cholesterol.
Renal function: Preserved renal function with absent microalbuminuria; normal serum creatinine; cys C and β2M.
Inflammatory marker : Mildly elevated hs-CRP.

Non-Diabetic Subjects
Glycemic profile : Normoglycemia.
Lipid profile : Normal lipid parameters.
Renal function Normal renal function.
Inflammatory marker: Low hs-CRP levels.

In diabetic patients with nephropathy, the glycemic profile is characterized by markedly elevated fasting plasma glucose and HbA1c levels, reflecting sustained and insufficient glycemic control. The lipid profile also reveals pronounced dyslipidemia, evidenced by significant increases in LDL-cholesterol and triglycerides, a reduction in HDL-cholesterol, and a notable elevation of lipoprotein(a). From a renal perspective, these patients exhibit progressive impairment, beginning with microalbuminuria, accompanied by increased serum creatinine and a decline in eGFR. This deterioration is further supported by elevated levels of cys C and β_2-M, both sensitive markers of renal dysfunction. Moreover, inflammatory markers indicate an enhanced systemic inflammatory state, as demonstrated by the significant elevation of high-sensitivity C-reactive protein (hs-CRP).
In diabetic patients without nephropathy, glycemic control appears overall more satisfactory. Fasting plasma glucose and HbA1c levels are better regulated, although they may remain slightly above established reference ranges. Their lipid profile shows a more moderate dyslipidemia, characterized mainly by a mild elevation in LDL-cholesterol, without the pronounced disturbances observed in patients with renal involvement. Renal function remains preserved in this group, as evidenced by the absence of microalbuminuria, normal serum creatinine levels, and cys C and ß2-M concentrations within physiological limits. From an inflammatory perspective, these patients nevertheless exhibit a moderate increase in high-sensitivity C-reactive protein (hs-CRP), suggesting the presence of a low-grade but clinically relevant inflammatory state.
However, in non-diabetic subjects, the glycemic profile remains strictly normal, reflecting an efficient regulation of glucose metabolism. Their lipid profile also falls within physiological ranges, with no detectable abnormalities in lipid fractions. Renal function is fully preserved, as indicated by normal biochemical parameters and the absence of any signs suggestive of glomerular or tubular

impairment. Finally, inflammatory markers demonstrate a minimal inflammatory state, as evidenced by the low concentrations of hs-CRP.

The biochemical profile of each subgroup of the study population is shown in Table 1.

The comparison of means between the variants (diabetic groups with nephropathy, without nephropathy and non-diabetic subjects) using the Student test showed that the average triglyceridemia in diabetics with nephropathy is higher than that of diabetics without nephropathy (1.61 g/L versus 1.37 g/L) (p=0.01). In addition, the average HDL cholesterol level in diabetics with nephropathy is lower than that of those without nephropathy (0.39 g/L versus 0.42 g/L) (p=0.01). Average HbA1c and ACR levels in DN are higher than that of Diabetics without nephropathy (DWN) (8.02 versus 7.36%) p=0.0001 and (115.08 versus 9.57 mg/g) of creatinine) p=0.0001, respectively.

Similarly, the average of ß2-M and cys C levels in DN are higher than that of DWN (3.11 versus 1.85 mg/L p=0.01; and (0.92 versus 0.86 mg/L) p=0.01, respectively.

While, the ANOVA test revealed a very significant difference between the three groups (p=0.0001) concerning: blood sugar, HbA1c, creatinine, GFR, triglyceride, HDL cholesterol, ACR, ß2-M and cys C.

The study of the correlation between cys C, ß2-M and the BMI and biochemical parameters revealed that eGFR was negatively and significantly correlated with cys C (r = -0.467; p=0.0001) (Figure 1).

On the other hand, cys C was also positively and significantly correlated with ß2-M (r =0.596; p=0.0001) (Figure 2) and creatinine (r =0.473; p=0.0001) (Figure 1).

Furthermore, the correlation coefficient between cys C and ACR (r =0.170; p=0.001) showed a positive linear relationship (Figure 3). ß2-M was also positively and significantly correlated with creatinine (r = 0.327; p=0.0001) (Figure 3) and significantly but negatively correlated with eGFR (r=-0.390, p=0.0001) (Figure 3), it was also positively and significantly correlated with ACR (r=-0.128, p=0.006).

ROC analysis was carried out to define the diagnostic profile of serum levels of cys C, ß2-M and ACR for the detection of a eGFR < 60 mL/min/1.73 m^2 in T2D subjects (with and without diabetic nephropathy).

This latter showed an area under curve (AUC) of cys C 0.846 (95% CI, 0.748-0.943) with a cutoff value of 1.205 (sensitivity 71% and specificity 94%; Figure 4).

On the other hand, the ß2-M level supported the diagnostic profile by showing an AUC of 0.776 (95% confidence interval - CI, 0.662-0.890) with a cutoff value of 2.39 (sensitivity 71% and specificity 87%). Finally, regarding the ACR, AUC of 0.650 (95% CI, 0.553–0.747) was observed,

with an optimal cutoff value of 28.35, yielding a sensitivity of 58.1% and a specificity of 70.4%. (Figure 4).

The curve demonstrated respective AUC of 0.84, 0.77, and 0.65. Optimal cutoff values were identified as 1.20 mg/L for cys C, 2.39 mg/L for β2-M, and 28.35 mg/g for the ACR, indicating superior diagnostic accuracy of cys C and β2-M compared to ACR in detecting reduced kidney function.

Discussion

The conducted study on the new biomarkers of T2D diabetic nephropathy within the population of Batna lasted two years (from 2018 to 2020). This descriptive cross-sectional study highlights the importance of establishing an epidemiological profile of diabetics with and without nephropathy and of deducing the risk factors for DN; it highlights the necessity and the interest of introducing and validating new biomarkers that could early detect renal damage in diabetics before a possible decline in GFR and/or an increase in UAE.

The bivariate study of the diabetic (with and without nephropathy) and non-diabetic subjects status, according to BMI, clinical history and biochemical profile revealed that in T2D non-modifiable demographic factors contribute to the observed epidemic trend.

These results are in good agreement with previous studies by Aksun *et al.*,[10] Jeon *et al.*,[14] Ben Dhia *et al.*,[11] Motawi *et al.*[12] and Argyropoulos *et al*.[7]

The comparsion between the averages of BMI and biological characteristics between the studied groups (diabetics with and without nephropathy and non-diabetic subjects) faithfully concords with the described characteristics in the literature concerning the profile of diabetics with nephropathy compared to diabetics without nephropathy, Specifically, glycemic imbalance, longer duration of diabetes, dyslipidemia characterized by hypertriglyceridemia and low HDL cholesterol levels, a higher ACR in diabetic patients with nephropathy compared to those without, and a lower eGFR in the nephropathy group were observed

Previous studies led to similar results with some disparities that could be explained by the dissimilarity between the studied groups (study type, sample size) as well as the inherent variability in assay techniques and modalities, and interpretation of the results. Mahfouz *et al.*,[8] Motawi *et*

al.,[12] Jeon *et al*.,[9] and Sapkota *et al*.[15] found the same biological profile in diabetics with and without nephropathy.

Based on the study of the correlation between cys C, ß2-M, BMI, and the other biochemical parameters in the present study, a correlation between cys C, GFR, creatinine and ACR and a correlation between ß2-M and eGFR, creatinine and ACR were observed. Many previous reports have proven the relationship between serum cystatin levels, creatinine, eGFR, and urinary albumin. This confirms that our results corroborate the results of several studies with a positive and significant correlation between cys C/ß2-M, cys C /creatinine, cys C/eGFR and cys C/ACR.[10,14,16]

The ROC analysis was carried out to define the diagnostic profile of the level of cys C and ß2-M and the ACR for the detection of a eGFR < 60 mL/min/1.73 m^2 in T2D subjects (with and without diabetic nephropathy).

The obtained findings confirm that cys C and serum ß2-M showed a higher predictive capacity for the detection of diabetic kidney disease in T2D than urinary albuminuria; these results agree with the meta-analysis of Arceo *et al*.[20] and many other studies indicating virtually identical AUC values, a cutoff value, especially those for cys C.[10,16-18]

Finally, the multifactorial analysis by binary logistic regression of risk factors (the Backward method) of diabetic nephropathy in our patients showed that glycemic imbalance and hypertriglyceridemia and the reduction in HDL cholesterol (less than 0.45 in women) multiply the risk of occurrence of diabetic nephropathy respectively by 2.84, 2.16, and 13.81. Our results do not agree with those of Bouattar in 2009 showing age, glycemic imbalance and retinopathy as risk factors in multivariate analysis.[20]

Conclusions

The results obtained in the present study suggest that cystatin C and beta 2 microglobulin as tubular and glomerular markers, respectively may be potential independent and reliable markers for the early detection of diabetic nephropathy. These biomarkers presented a performance in terms of ROC analysis compared to albuminuria. AUC sensitivity and specificity of cystatin C and beta-2 microglobulin were higher than that of microalbuminuria (ACR).

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Table 1. Biochemical profile of each subgroup of the studied population.

Variables	DN (n=152)	DWN (n=216)	NDS (n=90)	p	p1
Glucose (g/L)	2.48±1.13	1.81±0.68	0.91±0.14	0.001	0.45
HbA1C (%)	8.03±1.18	7.35±1.46	5.3±0.41	0.001	<0.0001
Creatinine (mg/L)	8.61±3.30	7.56±2.00	7.72±2.02	0.001	<0.0001
Uric acid (mg/L)	52.37±13.92	49.77±14.33	48.50±15.85	0.02	0.07
MDRD (mL/min/1.73 m^2)	93.81±28.63	99.91±27.13	115.32±30.12	0.001	
Cholesterol (g/L)	1.64±0.79	1.65±0.37	1.84±0.37	0.001	0.97
Triglycerids (g/L)	1.61±0.79	1.37±0.59	1.17±0.57	0.001	<0.001
HDL-cholesterol (g/L)	0.39±0.13	0.42±0.11	0.45±0.15	0.001	<0.01
LDL-cholesterol (g/L)	1.002±0.37	1.63±0.98	1.16±0.35	0.012	0.41
Apo A1(g/L)	1.25±0.22	1.29±0.19	1.05±0.19	0.001	0.16
ApoB(g/L)	0.87±0.26	1.50±0.74	0.89±0.16	0.001	0.30
Lp(a)(nmol/L)	44.46±45.69	52.58±51.59	42.45±36.84	ns	0.13
ACR (mg/g)	116.123±160.37	9.55±4.96	7.45±4.58	/	<0.0001
Albuminuria (mg/24H)	92.09±157.70	10.38±6.7	8.54±4.52	/	
Vitamin D (ng/mL)	20.59±14.53	17.95±13	23.91±13.21	Ns	
β2-M (mg/L)	1.85±0.61	1.52±0.16	1.31±0.40	0.001	<0.01
cys C (mg/L)	0.92±0.30	0.86±0.22	0.75±0.21	0.001	<0.02
hs-CRP (mg/L)	37.79±37.15	3.03±4.1	2.67±3.76	Ns	0.31

DN, Diabetics with nephropathy; DWN, Diabetics without nephropathy; NDS, Non-diabetic subjects p value, Between the three groups and p1 value, Between DN and DWN; HbA1c, glycated hemoglobin; MDRD, Modified diet in renal disease; HDL, high density lipoprotein; LDL, low

density lipoprotein; Lp a, lipoprotein a; ACR, albumin to creatinine ratio; β2-M, beta-2 microglobulin; cys C, cystatin C; hs-CRP, high sensivity C -reactive protein.

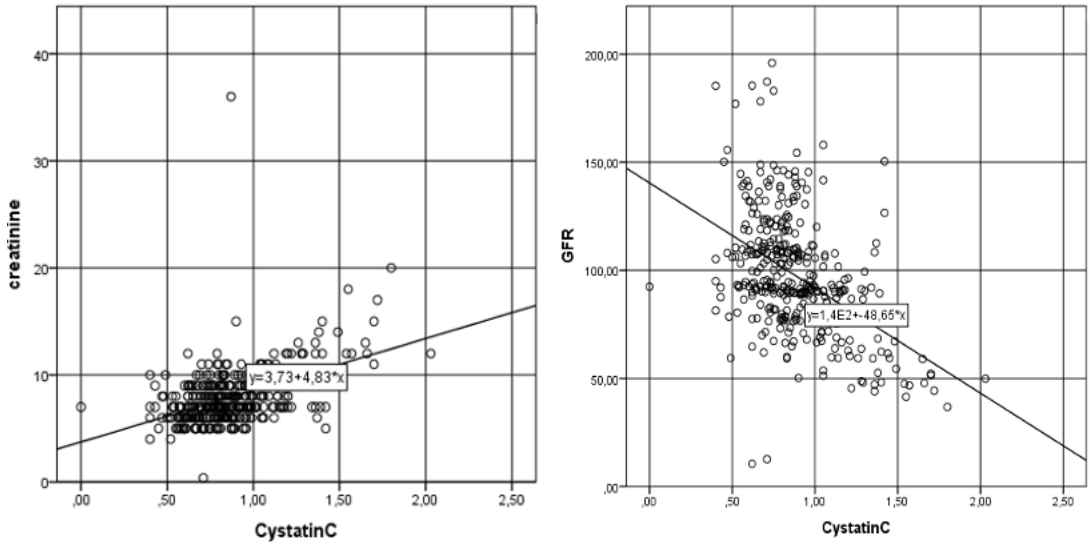

Figure 1. Correlation between cystatin C and creatinine (left r=0.473, p=0.0001 and cystatin C and glomerular filtration rate (eGFR) (right r=–0.473, p=0.0001).

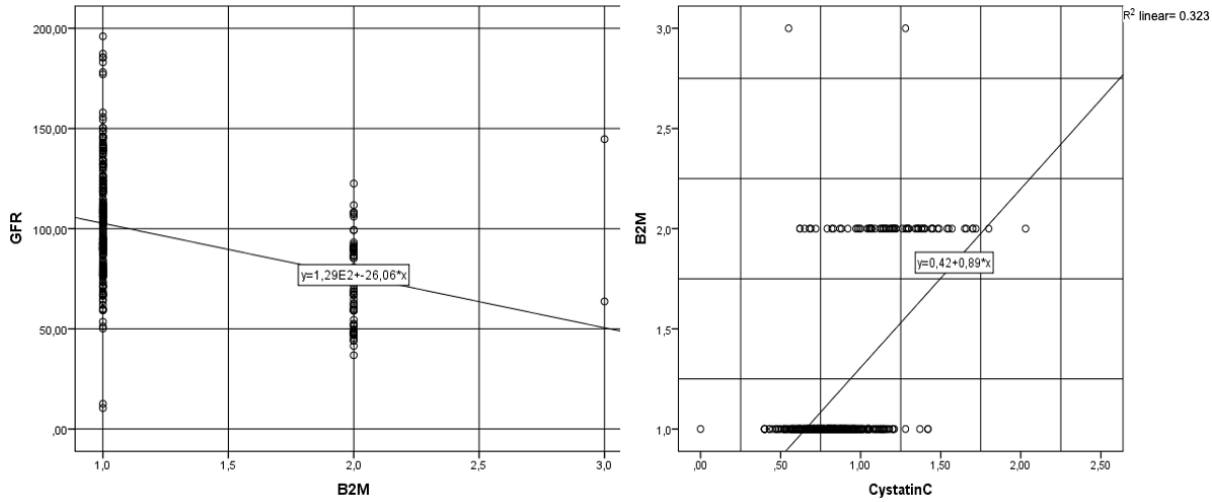

Figure 2. Correlation between beta-2 microglobulin (ß2-M) and glomerular filtration rate (eGFR) (on the left; r=-0.327, p=0.0001) and cystatin C (cys C) and ß2-M (on the right; r=0.596, p=0.0001)

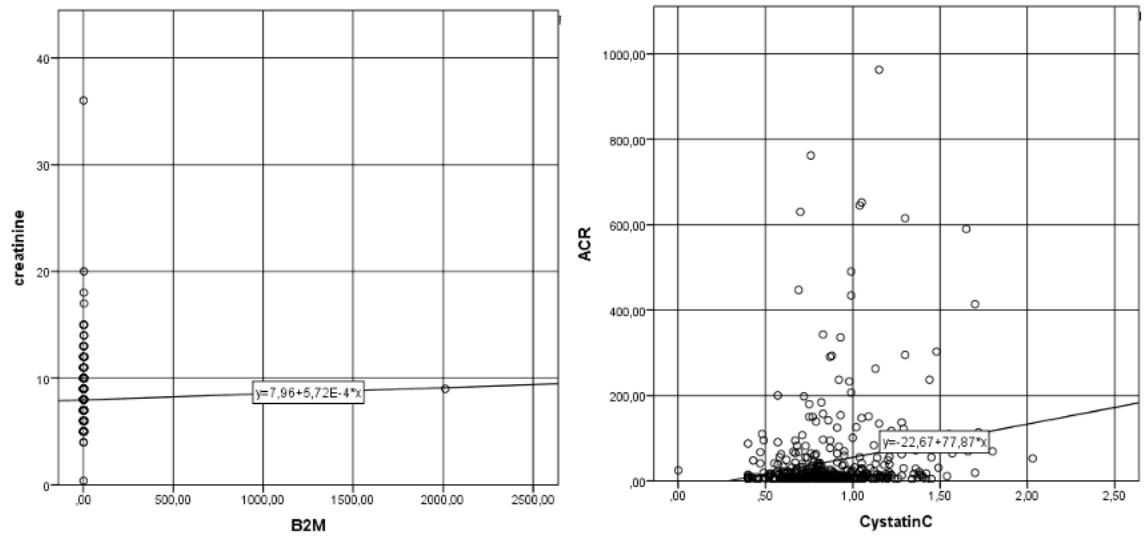

Figure 3. Correlation between beta-2 microglobulin (ß2-M) and creatinine (on the left; r=0.327, p=0.0001) and cystatin C (cys C) and albumin to creatinine ratio ACR (on the right; r=0.170, p=0.001).

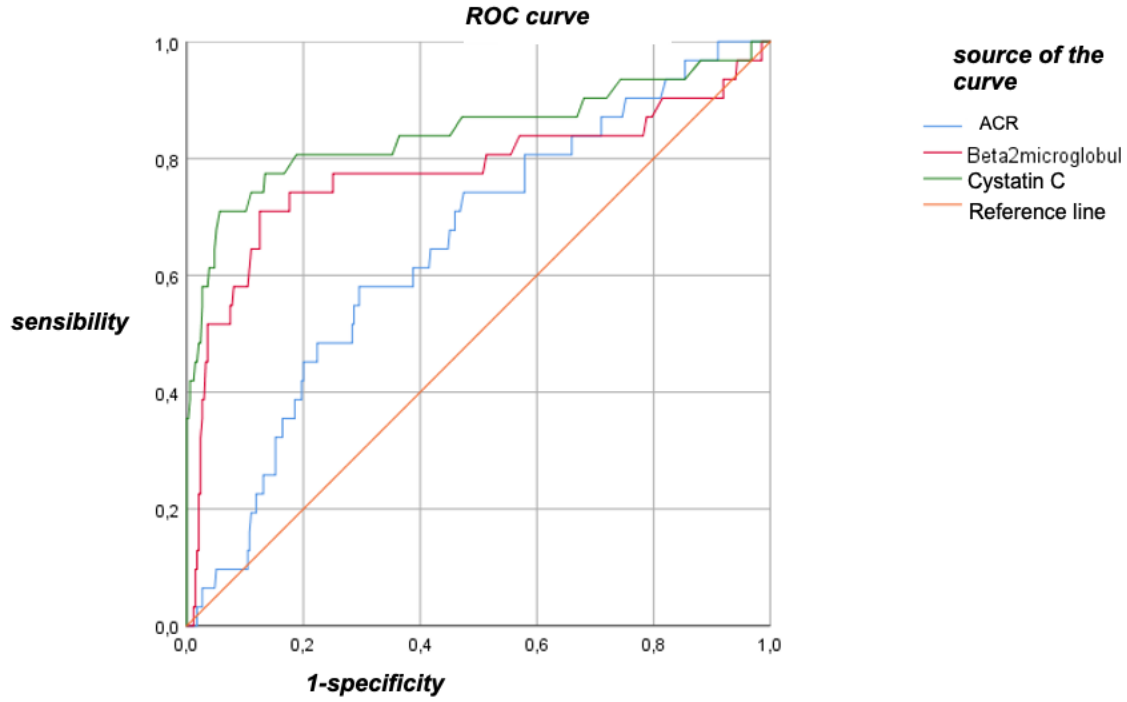

Figure 4. Receiver Operating Characteristic (ROC) curve analysis evaluating cystatin C (cys C), beta-2 microglobulin (β2-M) and albumin to creatinine ratio (ACR) against a Modified Diet in Renal Disease (MDRD)-calculated glomerular filtration rate (eGFR) <60 mL/min/1.73 m².