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Research Article

Serum Cystatin C in Early Kidney Dysfunction in Prediabetic Participants of the Brazilian Longitudinal Study of Adult Health - ELSA-Brasil

Julia Ines F Branda[1,4], Bianca de Almeida-Pititto[2,4], Isabela Bensenor[3,4], Paulo A Lotufo[3,4] and Sandra Roberta G Ferreira[1,4]*

[1]*Department of Epidemiology, School of Public Health, University of São Paulo, São Paulo, Brazil*

[2]*Department of Preventive Medicine, Federal University of São Paulo, São Paulo, Brazil*

[3]*Department of Internal Medicine, Medical School, University of São Paulo, Brazil*

[4]*Center of Clinical and Epidemiological Research at University of São Paulo, São Paulo, Brazil*

***Corresponding Author:** Sandra Roberta G Ferreira, Department of Epidemiology, School of Public Health, University of São Paulo, São Paulo, Brazil.

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Abstract

Serum cystatin C (sCys C) was proposed as a marker of kidney function. In diabetic subjects, slight elevation of albuminuria indicates renal damage but it is unclear whether this begins in prediabetic stages. We investigated whether sCys C levels are already increased in prediabetes, contributing to early detection of kidney dysfunction. In a cross-sectional analysis of 947 participants of the Brazilian Longitudinal Study of Adult Health - ELSA, sCys C and estimated glomerular filtration rate (eGFR) were compared between normoglycemic and prediabetic subjects. Prediabetic subjects were stratified into 4 groups - G1, normal sCys C and normal albumin-to-creatinine ratio (ACR); G2, abnormal sCys C and normal ACR; G3, normal sCys C and abnormal ACR; G4, abnormal sCys C and ACR, and their eGFR compared. Prediabetic subjects had higher sCys C than normoglycemic ones [0.67 (0.41 - 0.95) vs 0.48 (0.31 - 0.81) mg/L, $p < 0.001$] and lower eGFR (96.3 ± 17.4 vs 100.6 ± 17.1 mL/min/1.73m2, $p < 0.001$). Normoglycemic hyperfiltrating subjects had lower sCys C than normofiltrating ones ($p = 0.035$). Considering prediabetic groups, eGFR gradually decreased from G1 to G4 (96.8 ± 17.4 vs 96.2 ± 16.9 vs 94.0 ± 17.2 vs 77.2 ± 25.4 mL/min/1.73m^2, p-trend = 0.06) and mean eGFR in G4 was lower than in G1 ($p = 0.017$). The finding of higher sCys C levels in prediabetic subjects suggests this determination could be a helpful marker for examining kidney function in early stages of dysglycemia when albuminuria is still within the normal range. The follow-up of participants should allow testing the role of sCys C as an early marker for renal dysfunction in prediabetes.

Keywords: *Prediabetes; Kidney Disease; Glomerular Filtration Rate; Cystatin C; Microalbuminuria*

Abbreviation

ACR: Albumin-to-Creatinine Ratio; A1c: Glycated Hemoglobin; BMI: Body Mass Index; BP: Blood Pressure; CKD: Chronic Kidney Disease; DALYs: Disability Adjusted Life Years; DKD: Diabetic Kidney Disease; eGFR: Estimated Glomerular Filtration Rate; ELSA-Brasil: Brazilian Longitudinal Study of Adult Health; HDL-c: High Density Lipoprotein Cholesterol; KDIGO: Kidney Disease Improving Global Outcomes; LDL-c: Low Density Lipoprotein Cholesterol; sCys C: Serum Cystatin C; SD: Standard Deviation; TSH: Thyroid Stimulating Hormone

Introduction

Reported prevalence rates of prediabetes are alarming worldwide and in some populations this condition could affect 7.7 to 56% of adults [1-3]. Such conditions of mild hyperglycemia (named impaired fasting glucose and impaired glucose tolerance [4]) have been associated with progression to overt diabetes, as reported in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) [5] and they already deleterious for tissues and organs. It was demonstrated that chronic kidney disease (CKD) occurs even in prediabetic stages and that its prevalence is increasing in some populations, ranging from 9.0 to 21.3% [6-8]. CKD is a major public health concern worldwide [9] and in US diabetes represents the main cause of incident cases of renal failure [10]. According to the Global Burden of Disease [11], diabetes and CKD were the eighth cause of Disability Adjusted Life Years (DALYs) worldwide and the seventh cause in Brazil.

Sustained hyperglycemia at prediabetic levels can trigger glomerular hyperfiltration and so can contribute to kidney damage [12,13]. Thus, early identification of individuals at risk seems important for preventive purposes. Diabetic kidney disease (DKD), as defined by reduced glomerular filtration rate (GFR) and/or presence of albuminuria, represents the main cause of CKD in patients who initiate renal replacement therapy [14]. Up to 40% of subjects with type 2 diabetes mellitus develop CKD which is associated with reduced quality of life and increased mortality [15].

Usually, incipient kidney dysfunction is detected by the presence of microalbuminuria [16,17]. However, type 2 diabetic subjects may have a reduced GFR before the occurrence of microalbuminuria [18]. This condition of non-albuminuric kidney disease can occur in up to one fifth of DKD [19] and such phenotype was also reported in prediabetic subjects [20]. Therefore, search for early markers of renal dysfunction in prediabetes seems of great interest.

Serum cystatin C (sCys C) is an endogenous marker of kidney function and recent studies have suggested that this may be a more sensitive marker for early kidney impairment [21]. Its determination overcomes limitations of serum creatinine, with accuracy to assess renal damage [22,23]. Cystatin C is not influenced by age, gender, protein intake and muscle mass [24,30], although some conditions, such as hyperthyroidism and obesity, can alter its levels [29]. Special groups such as the elderly with reduced muscle mass have particular benefit of using sCys C determination [24]. A recent study of a small sample of diabetic individuals found that sCys C was a more sensitive parameter than creatinine to detect nephropathy [25]. It is unclear how sCys C performs as an earlier marker for the detection of incipient diabetic nephropathy. When sCys C was examined in normal and microalbuminuric diabetic subjects, subtle alterations predicted the severity of albuminuria even in the normoalbuminuric stage [26]. As far as we know, whether alterations of sCys C represent an opportunity to prevent and/or delay DKD particularly in prediabetes is unclear.

We hypothesized that kidney damage can occur even without the elevation of albuminuria and that sCys C could be helpful as an early marker of renal dysfunction in prediabetic subjects. We investigated whether sCys C levels are increased in prediabetes, contributing to the detection of kidney dysfunction independently of albuminuria.

Methods

Study design and population

This is a cross-sectional analysis of baseline data from the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), a multicenter cohort study designed to identify new risk factors and determinants of diabetes and cardiovascular disease [27]. The study was approved by Ethics Committee and informed consent signed by all participants. The details of the study objectives and methods were previously reported [2,27]. Briefly, from August 2008 to December 2010, ELSA-Brasil included 15,105 employees aged 35 to 74 years from six capital cities of Brazil. A convenience sample of 998 normoglycemic and prediabetic participants aged between 35 to 54 years was selected from 5,061 participants of ELSA-Brasil in São Paulo center for a sub-study [28], in which the current study was conducted. Participants with

missing data regarding sCys C or estimated GFR (eGFR) were excluded. Estimated GFR < 45 mL/min/1.73m^2 and hypertension (blood pressure ≥ 140/90 mmHg or antihypertensive treatment) were exclusion criteria, as well as thyroid dysfunctions (TSH < 0.1 and ≥ 10 μUI/mL). It was previously shown that hypothyroidism tended to decrease while hyperthyroidism to increase sCys C levels [29,30]. Body mass index (BMI) ≥ 30 kg/m^2 was also excluded since obesity can affect sCys C production and overestimate eGFR when its circulating levels are employed [29,31]. One prediabetic participant with an outlier ACR value > 2,600 mg/g was excluded from the analyses, supposing that this could be due to another renal disease rather than the disturbance of glucose metabolism. A total of 51 participants were excluded.

Clinical and laboratory data

Interviews and anthropometric examinations were carried out by trained personnel using standardized questionnaires and measurements [32]. BMI was calculated as weight in kilograms divided by height in meters squared. Blood pressure (BP) was measured with Omron HEM 705CPINT device (Omron Co, Kyoto, Japan) after a 5-minute rest. Three measurements were taken at 1-min intervals and mean values were calculated. After overnight fasting, blood and urine samples were obtained for several determinations [33]. Participants underwent a 2-hour 75g oral glucose tolerance test. Aliquots of biological samples were frozen at -80°C for further determinations [34].

Plasma glucose was measured by the hexokinase method (ADVIA Chemistry; Siemens, Deerfield, Illinois, USA) and A1c using a high-pressure liquid chromatography (Bio-Rad Laboratories, Hercules, California, USA), according to the National Glycohemoglobin Standardization Program. GFR was estimated using the equations proposed by the Chronic Kidney Disease Epidemiology Collaboration (eGFR CKD-EPI) [35]. Albuminuria was determined in a 12h-overnight sample by nephelometry and was expressed as albumin-to-creatinine ratio (ACR). Serum cystatin C was measured using Human Cystatin C ELISA kit (Elabscience Biotechnology, Houston, Texas, USA). Intra-assay and inter-assay coefficients of variability range were 5.05 - 5.38% and 3.29 - 6.48%, respectively.

Definitions

Participants with BMI ≥ 30 kg/m^2 were considered obese. Prediabetes diagnosis was defined by fasting plasma glucose (100 - 125 mg/dL) or 2-hour post-load glucose (140 - 199 mg/dL) or hemoglobin A1c (5.7 - 6.4%) [4,27]. The following categories of eGFR CKD-EPI were considered: a) hyperfiltration when eGFR ≥ 125 mL/min/1.73m^2; b) normal eGFR for values ≥ 90 and < 125 mL/min/1.73m^2 and c) mildly decreased eGFR for values ≥ 60 and < 90 mL/min/1.73m^2, according to KDIGO 2012 [29]. Microalbuminuria was defined by values of ACR ≥ 30 mg/g creatinine [29]. Normal ranges of sCys C were 0.64 to 0.84 mg/L for men and 0.57 to 0.74 mg/L for women [36].

Prediabetics participants was divided into four groups combining levels of ACR and sCys C: group 1 (G1) had both normal sCys C and ACR; group 2 (G2) had abnormal sCys C and normal ACR; group 3 (G3) had normal sCys C and abnormal ACR; and group 4 (G4) had both abnormal sCys C and ACR.

Statistical analysis

Continuous variables with normal distribution were expressed as mean ± standard deviation (SD) and compared using Student *t* test. Non-normal distributed parametric variables (ACR and sCys C) were expressed as median and interquartile range and compared using Wilcoxon rank test. ANOVA or Kruskall-Wallis test was used to compare variables of more than two groups of participants, complemented with Tukey test, and p for trend was obtained. Sensitivity analyses excluding obese and hypertensive participants from comparisons were performed. Chi-squared test was used to compare frequencies and 95% confidence intervals (95%CI) were provided. Correlation was tested using Pearson coefficient. Significance level was set at a p-value of 0.05. Statistical analyses were performed using the R Project for Statistical Computing (R version 3.5.2).

Results

The mean age of 947 participants (520 women, 427 men) was 45.7 ± 4.9 years. Sixty percent referred white skin color and 40% non-white colors; among the latter participants 6% has Asian ancestry. The entire sample had normal mean values of systolic (117.0 ± 14.5

mmHg) and diastolic BP (75.0 ± 10.4 mmHg), eGFR 97.6 ± 17.4 mL/min/1.73m^2), ACR (10.8 ± 36.8 mg/g creatinine) and sCys C (0.75 ± 0.61 mg/L). Their mean eGFR, sCys C and AER were within normal ranges and no correlation was detected between these parameters. A total of 671 participants had prediabetes and 276 had normal glucose tolerance. In average, participants were slightly overweight and a higher proportion of physically active subjects were found in the normoglycemic group (42.0% versus 33.6%, p = 0.02).

Mean values of age, BMI, BP, lipids, serum creatinine and eGFR were higher in prediabetic than in normoglycemic participants (Table 1). Despite normal ACR values in both groups of participants, median was lower in prediabetic compared to the normoglycemic one [5.8 (4.5 - 7.5) versus 6.6 (5.5 - 8.1) mg/g, p < 0.01]. Median sCys C was higher in prediabetic than in normoglycemic participants [0.67 (0.41 - 0.95) versus 0.48 (0.31 - 0.81) mg/L, p < 0.01], but values were within the reference range. However, proportions of participants with elevated sCys C was higher among prediabetic participants than the in normoglycemic ones (39% versus 28%, p < 0.002). Medians of sCys C for men and for women did not differ [0.61 (0.38 - 0.92) versus 0.63 (0.37 - 0.89) mg/L, p = 0.562, respectively] and analyses were not stratified by sex.

	Normoglycemic N = 276	**Prediabetic N = 671**	**P-value**
Age (years)	44.7 (4.9)	46.1 (4.8)	< 0.001
Body mass index (kg/m^2)	25.3 (3.8)	26.7 (4.24)	< 0.001
Systolic blood pressure (mmHg)	111.4 (12.4)	118.8 (14.8)	< 0.001
Diastolic blood pressure (mmHg)	71.2 (9.5)	76.5 (10.4)	< 0.001
Fasting plasma glucose (mg/dL)	94.3 (3.7)	105.7 (7.0)	< 0.001
2-hour plasma glucose (mg/dL)	107.8 (18.0)	126.0 (27.4)	< 0.001
Glycated hemoglobin (%)	4.9 (0.4)	5.4 (0.5)	< 0.001
Total cholesterol (mg/dL)	202.2 (32.7)	212.3 (38.2)	< 0.001
HDL-cholesterol (mg/dL)	59.5 (13.2)	53.6 (13.0)	< 0.001
LDL-cholesterol (mg/dL)	122.3 (28.6)	131.4 (33.16)	< 0.001
Triglycerides (mg/dL)	102.1 (51.2)	139.0 (83.85)	< 0.001
Creatinine (mg/dL)	0.87 (0.16)	0.96 (0.19)	< 0.001
eGFR (mL/min/1.73m^2)	100.6 (17.1)	96.3 (17.4)	< 0.001
ACR (mg/g)*	6.6 (5.5 - 8.1)	5.8 (4.5 - 7.5)	< 0.001
Serum cystatin C (mg/L)*	0.48 (0.31 - 0.81)	0.67 (0.41 - 0.95)	< 0.001
Elevated ACR, n (%)	8 (3)	21 (3)	0.999
Elevated serum cystatin C, n (%)	77 (28)	259 (39)	0.002

Table 1: *Clinical data of prediabetic and normoglycemic participants.*
eGFR: Estimated Glomerular Filtration Rate; ACR: Albumin-Creatinine Ratio.
Data are expressed as frequency (%), mean (SD) or median (interquartile range).
*P-values obtained by chi-square, Student t or *Wilcoxon test.*

Comparisons between prediabetic and normoglycemic participants within eGFR category (mildly decreased, normal and increased eGFR) showed that median values of sCys C were always higher in prediabetic ones. Median ACR was within the normal range for the

three categories, although statistically higher values were observed in normoglycemic compared to prediabetic participants with normal or mildly decreased eGFR (Table 2). Considering the category of hyperfiltrating participants, normoglycemic group had a significantly higher BMI [26.2 ± 4.3 versus 25.0 ± 5.4 kg/m^2, p = 0.041] than prediabetic one.

	Mildly decreased eGFR (≥ 60 - < 90 mL/min/1.73 m^2) n = 330			Normal eGFR (≥ 90 - < 125 mL/min/1.73 m^2) n = 544			Increased eGFR (≥ 125 mL/min/1.73 m^2) n = 59		
	Normoglycemia N = 88	Prediabetes N = 242	P-value	Normoglycemia N = 163	Prediabetes N = 381	P-value	Normoglycemia N = 24	Prediabetes N = 35	P-value
Cystatin C, mg/L	0.54 (0.29-0.80)	0.66 (0.39-0.96)	0.004	0.53 (0.34-0.82)	0.68 (0.43-0.95)	0.003	0.37 (0.27-0.48)	0.62 (0.30-0.85)	0.031
ACR, mg/g	6.22 (5.07-7.25)	5.65 (4.38-7.17)	0.042	6.89 (5.79-8.30)	5.91 (4.62-7.69)	< 0.001	7.04 (6.03-8.02)	6.67 (5.20-7.65)	0.371

Table 2: *Median (interquartile interval) of renal function parameters of participants grouped according to estimated glomerular filtration rate (eGFR) categories and presence of prediabetes. ACR: Albumin-Creatinine Ratio. Wilcoxon test used.*

Figure 1 depicts sCys C values in normoglycemic and prediabetic participants according to their eGFR category. Only normoglycemic participants with hyperfiltration were associated with a significant reduction in sCys C (p = 0.035). Median sCys C was unchanged across categories of eGFR in prediabetic participants (p > 0.05).

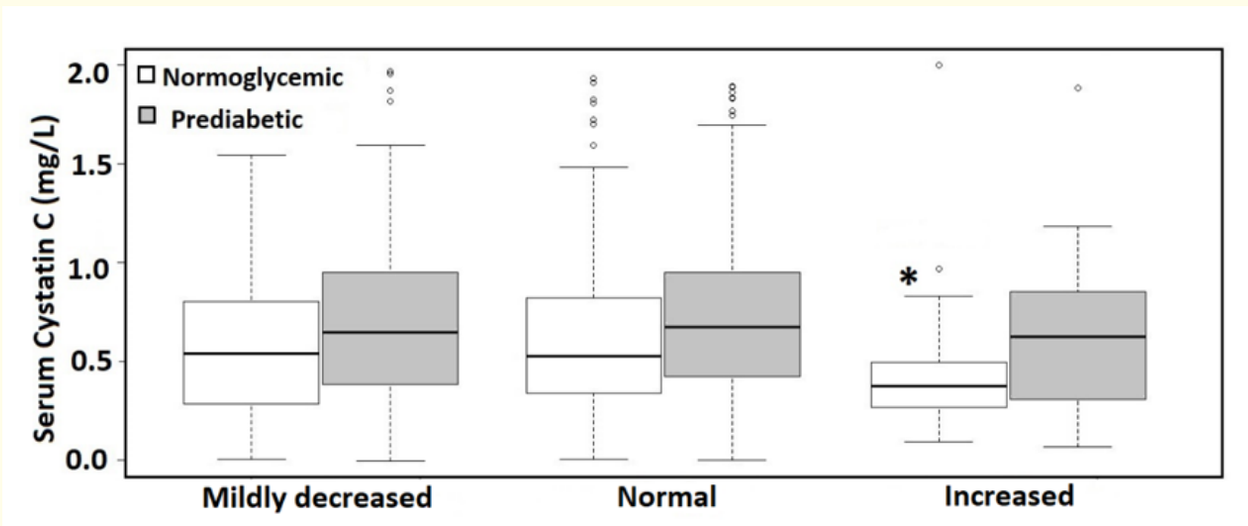

Figure 1: *Median values of serum cystatin C between normoglycemic and prediabetic participants. eGFR categories: mildly decreased (eGFR ≥ 60 and < 90 mL/min/1.73m2), normal (eGFR ≥ 90 and < 125 mL/min/1.73m2) and increased eGFR (≥ 125 mL/min/1.73m2). * p = 0.035 versus normal eGFR.*

Prediabetic participants were then divided into four groups according to the combination of renal function parameters (sCys C and ACR). Figure 2 shows that eGFR gradually dropped from G1 to G4 (G1: 96.8 ± 17.4, G2: 96.2 ± 16.9, G3: 94.0 ± 17.2 and G4: 77.2 ± 25.4 mL/min/1.73m^2, p-trend = 0.060). Such trend reached borderline significance but, as expected, mean eGFR in G4 was lower than in G1 (p = 0.017).

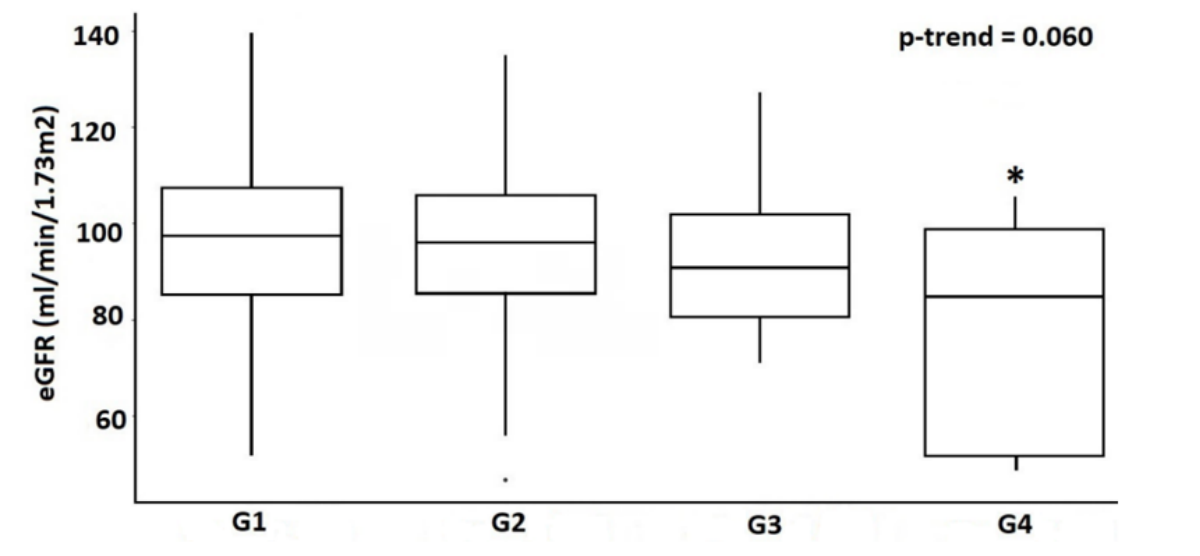

Figure 2: *Box plot of eGFR in prediabetic participants among groups. Group 1: normal sCys C and normal ACR (n = 385); Group 2: abnormal sCys C and normal ACR (n = 253); Group 3: normal sCys C and abnormal ACR (n = 13) and Group 4: abnormal sCys C and abnormal ACR (n = 7). * p = 0.017 versus Group 1.*

Discussion

Looking at sCys C levels, this study raises their potential role for early detection of renal dysfunction in prediabetic states. For the best of our knowledge, results of a higher sCys C under normoalbuminuria in prediabetic but not in normoglycemic participants, obtained in a large epidemiological study, suggest that this may be a marker of renal dysfunction in early stage of glucose metabolism disturbance, when only glomerular hyperfiltration is manifest. Since DKD has been considered a complication of overt diabetes [13], change in this marker of renal dysfunction could support a paradigm shift, indicating that slight dysglycemia is enough to cause kidney damage. This seems relevant considering that role of diabetes as a major cause of renal failure [10].

The finding of higher sCys C in the prediabetic compared to normoglycemic group, independently of eGFR categories, raises the possibility that its determination could be accurate to identify slight renal injury, before glomerular albumin loss. Considering that increased body adiposity and blood pressure could contribute to elevate albumin urinary excretion, obesity and hypertension were excluded. Median ACR values were within the normal range, and, unexpectedly, higher levels were observed among the normoglycemic participants. Although statistically different, from a clinical point of view, such difference of ACR between groups may be considered irrelevant. In addition, a higher frequency of physically active individuals in the normoglycemic group could account in part for such difference. As a matter of fact, it is recognized an intra-individual variability in albumin excretion rate under certain conditions such as physical activity practice [29,37]. The design of our study did not allow suggesting that elevations in sCys C may be useful to detect renal damage earlier

than albuminuria. This hypothesis deserves further investigation considering that some authors have already described the presence of renal injury (microalbuminuria and/or reduced GFR) in prediabetic individuals [13,38-40].

Increases in glomerular filtration are typically observed in diabetes mellitus as a consequence of sustained hyperglycemia [41], but hyperfiltration is uncommon in healthy normoglycemic subjects. Since obesity has been also associated to elevation in GFR [42], both diabetic and obese subjects were excluded from our sample. A small proportion of normoglycemic participants showed eGFR above 125 mL/min/1.73m^2, which could be attributed in part to their slightly elevated mean BMI. We speculate that lower sCys C levels in those hyperfiltrating normoglycemic participants could indicate an increased renal loss of Cys C. Once circulating Cys C is filtered by glomeruli and reabsorbed and metabolized by tubular cells [43], its reabsorption may be insufficient under hyperfiltrating conditions, decreasing serum levels. This plausible mechanism to explain lower sCys C levels in hyperfiltration could not be confirmed in our study due to the absence of urinary Cys C measurement. Interestingly, in the subset of prediabetic participants with hyperfiltration higher sCys C levels were observed which could suggest that tubular cells function was impaired at the initial natural history of diabetes mellitus.

In line with our findings, previous studies had already shown that increased urinary levels of Cys C was early correlated with DKD in adults [44], also found with acute renal disease and reduced renal volume early in life such as in neonates [45,46]. This body of evidence could reinforce a possible role of Cys C as an early marker of kidney injury.

Estimated GFR and ACR are established parameters for renal function assessment. The latest update of the Kidney Disease Improving Global Outcomes (KDIGO) recommends that both, eGFR and ACR, should be used for the diagnosis of CKD [29]. According to these criteria, approximately 5% of entire population of ELSA-Brasil had CKD [2]. In the present study, we explored on the utility of sCys C in combination with ACR to test association with eGFR. As expected, participants with both abnormal ACR and sCys C values had lower eGFR. Since there is no previous report of such association, we are suggesting that ACR combined with sCys C could also be useful markers to detect kidney dysfunction in prediabetic individuals. In fact, other investigators have proposed different approaches to assess renal function such as the eGFR based on cystatin C (eGFRcys) or in combination with serum creatinine (GFRcys-creat) [29]. Several studies demonstrated that both cystatin-based eGFR formulas are more accurate in comparison with the traditional one based on serum creatinine to assess renal function in early stages of kidney injury [47]. Additionally, positive association of sCys C with the progression of prediabetes has been reported [48,49] as well as playing a role for cardiovascular risk in prediabetic individuals [50].

Limitation of the Study

A main limitation of our study is related to the cross-sectional design of this study that impede inferring causality between the interest variables. It is not possible to state that the onset of sCys C elevation occurs earlier than the increase in ACR. We have chosen a definition for hyperfiltration (eGFR ≥ 125 ml/min/m^2), since there is not an internationally accepted consensus. Some studies suggest using eGFR above the 90th percentile adjusted by body area [51] and others suggest that should be used age and sex-specific cut-offs for better measure of hyperfiltration [52]. According to a meta-analysis [52], commonly used definition for hyperfiltration varied from 90 to 175 mL/min/m^2. Determination of urinary cystatin C would contribute to speculate on pathophysiological mechanisms.

Strength of the Study

Strengths of ELSA-Brasil [27] are its sample size and prospective design to test hypothesis raised in the present sub-study. We currently examined a relatively novel circulating biomarker - sCys C - in a large sample to assess kidney function in early stages of glucose metabolism disturbance. We excluded participants with several factors that could interfere in sCys C assay, as thyroid disorders and obesity [29], and utility of its determination at an initial phase of kidney damage to predict DKD will be further investigated. Such approach made unnecessary adjusted analyses. This can be the largest study of sCys C data in prediabetic subjects providing subsidies to raise that this may be an early marker of renal dysfunction during glomerular hyperfiltration stage, dependent of the intermittent hyperglycemia that precedes overt diabetes.

Conclusion

In conclusion, we reinforced that sCys C levels are higher in prediabetic than in normoglycemic subjects. Serum Cys C could to be a helpful marker for examining kidney function in early stages of dysglycemia when albuminuria is still within the normal range but with elevated eGFR. The follow-up of ELSA-Brasil participants should allow testing more appropriately the role of sCys C as an early marker for renal dysfunction in prediabetes, when preventive measures could be introduced.

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