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Serum cystatin C as an early marker of nephropathy among type 2 diabetics: A meta-analysis

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A B S T R A C T

Aim: The varying views as to the usefulness of serum cystatin C (CysC) as an early marker of diabetic nephropathy (DN) prompted us to investigate existing literature to determine whether serum CysC can be used as an early marker of DN using a meta-analysis approach.

Materials and methods: Twelve studies written in English were retrieved from PubMed using various key search terms. Data were extracted from the included studies by two of the authors and was subjected to statistical analysis using Review Manager 5.3 and Meta-Essentials. Levels of serum CysC were compared between the study groups using the standardized mean difference (SMD) and 95% confidence interval (CI).

Results: Overall outcomes indicate that serum CysC levels are higher among those with microalbuminuria (MI) and macroalbuminuria (MA) than those in the control group (CN) and those with normoalbuminuria (NO). However, these findings were heterogeneous, which warranted an investigation using the Galbraith plot. Heterogeneity was either reduced or lost in the post-outlier outcomes indicating combinability of the studies.

Conclusion: Serum CysC is shown to be a superior biomarker in the early diagnosis of DN. However, further studies are still needed to verify our claims.

1. Introduction

Diabetes mellitus (DM) continues to be a public health problem with a global prevalence rising rapidly from 4.7% in 1980 to 8.5% in 2014 [1]. The number of people with diabetes is increasing due to population growth, aging, urbanization, and the increasing prevalence of obesity and physical inactivity. According to the World Health Organization (WHO), the prevalence of diabetes for all age-groups worldwide was estimated to be 2.8% in 2000 and expected to reach 4.4% in 2030 [2]. Metabolic disease often leads to multiple organ system damages and severe health complication, including diabetic nephropathy (DN). The incidence of DN has increased in recent years, with about one-third of diabetics affected with the condition [3]. But despite a growing understanding of its pathophysiology and the availability of effective strategies for delaying progression, diagnosis of DN is often made late and is the primary cause of the end-stage renal disease (ESRD) worldwide [4].

As DN is the leading cause of chronic kidney disease and failure, early detection of nephropathy among diabetics is crucial so that prompt intervention can be put in place. The condition is characterized by persistent albuminuria and years of progressive renal structural changes associated with the decline in the glomerular filtration rate (GFR). Currently, microalbuminuria (MI) and serum creatinine are the common markers used to detect nephropathy among diabetic patients with serum creatinine level as the most widely used to measure changes in GFR [5,6]. The elevated urinary albumin excretion rate within the microalbuminuric level (30–299 mg/24 h or a spot urine albumin-to-creatinine ratio of 30–299 mg/g) allows the detection of patients with an increased risk for the development of overt DN with persistent macroalbuminuria (MA) [2]. However, there are reports of patients with normoalbuminuria (NO) yet having advanced glomerulopathy [6]. This population can miss a diagnosis if MI is used as the marker. The appearance of pathological levels of urinary albumin excretion (UAE) represents the most common clinical sign of early renal involvement in patients affected by DM [7]. MI is considered to be a risk factor for DN and progressive renal insufficiency, but recent investigations have raised questions about its predictive value owing to its variability

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for the underlying renal pathology [8].

Apart from albuminuria, clinicians have used serum creatinine for decades to diagnose acute kidney injury. However, the analyte is also an “imperfect gold standard” to detect early renal damage [9]. Serum creatinine is not very sensitive or specific of acute kidney injury because of several renal and non-renal factors affecting it [10,11].

Similar to MI and serum creatinine, serum cystatin C (CysC) level is another marker of renal function. CysC is a low molecular weight protein completely filtered by the glomerulus under normal conditions. Because it closely correlates with glomerular filtration rate, its measurement has been introduced to determine renal function [12]. Several research studies show that CysC is a superior biomarker for early renal disease. However, there are still few conflicting studies that say that CysC is not more sensitive than other markers in detecting early renal impairment among diabetics, children, in the general population, and former kidney donors [12–16]. According to some studies, serum cystatin is not superior to creatinine [17] and not useful for the early detection of nephropathy among type 2 diabetes mellitus (T2DM) patients [18]. The varying views as to the usefulness of serum CysC as a biologic marker for detection of renal disease prompted us to investigate existing literature further and determine whether serum CysC can be used as an early marker for diabetic nephropathy using a meta-analysis approach.

2. Materials and Methods

2.1. Search strategy

A literature search was conducted using the following keywords: “cystatin C”; “early marker”; and: “diabetic nephropathy” in PubMed for articles written in English. The titles and abstracts of each resulting were carefully screened. Full texts of related studies were independently evaluated by two authors for additional eligible studies.

2.2. Study selection

The following inclusion criteria were used: (1) studies that include at least two out of four groups namely: healthy controls (CN) and type 2 diabetics with normoalbuminuria (NO), microalbuminuria (MI), or macroalbuminuria (MI); (2) studies that include parametric numerical data of serum CysC (mean ± standard deviation); and (3) studies that included humans as participants. All studies identified were independently assessed for eligibility by two of the authors.

2.3. Data extraction

Two authors independently extracted data and reach an agreement on all the items. Any disagreements were resolved by a third author. For each eligible study, the following data was extracted: (1) first author’s last name; (2) date of publication; (3) country where the study was conducted; (4) sources of study participants; (4) number of patients that are normoalbuminuric, microalbuminuric, or macroalbuminuric; (5) total number of participants in the study; and (5) serum concentration of CysC.

2.4. Meta-analysis protocol

A combination of Review Manager 5.4 Copenhagen: Nordic Cochrane Center, Cochrane Collaboration, 2014) and Meta-Essentials (Erasmus Research Institute of Management, 2017) [19] was used for this study. The protocol used for this meta-analysis was based on the procedure of Pabalan et al. [20,21]. Since data used are expressed in mean ± SD, standardized mean difference (SMD) and 95% confidence interval (CI) were computed from each study. The resulting computation was then pooled and was tested using either the fixed-of random-effects model [22]. Heterogeneity was tested using the Chi-based Q test, and the degree of inconsistency was estimated using I^2 statistics [23,24]. Due to the recognized low power of the study, *p*-value (P^H) for heterogeneity testing was set at 0.10 [25]. All *p*-values (P^A) for association were two-sided at <0.05 significance threshold. Six comparison models were utilized namely: CN vs. NO; CN vs. MI; CN vs. MA; NO vs. MI; NO vs. MA; and MI vs. MA.

2.5. Sensitivity analysis and publication bias testing

Sensitivity analysis was performed to test for the robustness of the overall effects. This was done by repeating the meta-analysis and omitting one study at a time. On the other hand, publication bias was also performed on comparison models with 10 or more studies using both the Egger regression asymmetry test and the Begg-Mazumdar correlation test. Publication bias is identified if the *p*-value is < 0.05 for at least one of the tests.

3. Results

3.1. Search result and characteristics of the included studies

Fig. 1 shows the selection process utilized in the study following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [26]. The initial search yielded a total of 89 studies that were manually checked. After omitting duplicate and irrelevant studies, 12 studies were included in the meta-analysis [2,5,27–36]. Characteristics of the 12 studies included are summarized in Table 1., whereas, the summarized levels of serum CysC among the study groups per study is

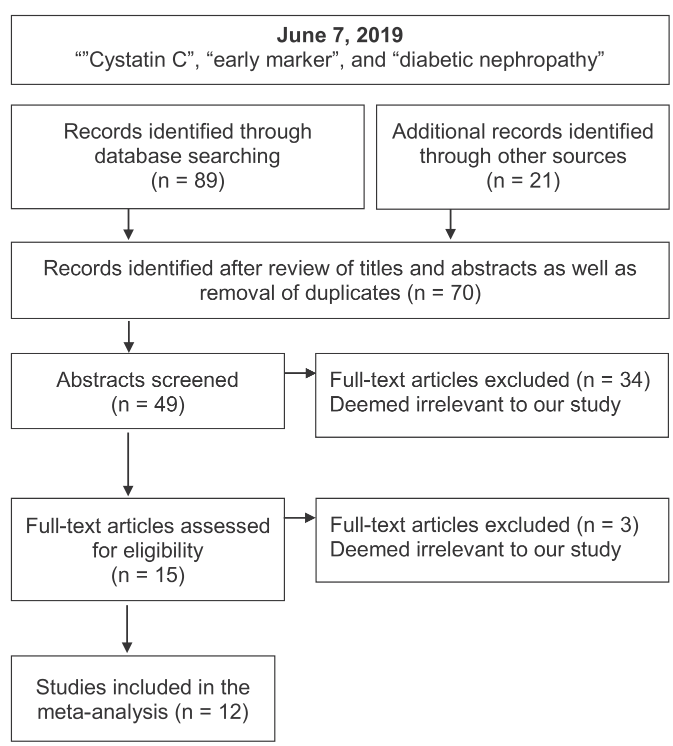

Fig. 1. Summary of the literature search.

Table 1
Characteristics of the included studies.

First author	Reference	Year	Country	Ethnicity	n
Apakkan Aksun	[27]	2004	Turkey	Western	100
Assal	[28]	2013	Egypt	Western	90
El-Shafey	[5]	2009	Egypt	Western	40
Jeon	[2]	2011	Korea	Asian	335
Li	[29]	2017	China	Asian	482
Mahfouz	[30]	2015	Saudi Arabia	Western	200
Mojiminiyi	[31]	2000	Kuwait	Western	77
Shimizu	[32]	2003	Japan	Asian	146
Siddiqi	[33]	2017	India	Asian	180
Wang	[34]	2013	China	Asian	224
Yang	[35]	2007	Taiwan	Asian	102
Ye	[36]	2013	China	Asian	96

n: total number of participants.

summarized in Table 2. Studies included were published between 2000 and 2017. The total sample size included in this study is 2072 with a narrow range of total sample sizes across all the studies (40–482). Participants in seven of the studies were from Asian countries [2,29,32–36], and five were from Western countries [5,27,28,30,31].

3.2. Overall analysis

Table 3 summarizes the results of the overall analysis of the different comparison models. Overall, using the random-effects model, our results suggest a significant difference in the levels of serum CysC among MI and MA groups than in CN or NO (SMD = 0.81–2.78, P^A = 10^{-5}-0.03). However, high degree of heterogeneity (I^2 = 74–95%, P^H = 10^{-5}-0.0001) was observed. The resulting pooled SMDs suggest that higher levels of serum CysC is observed in MI and MA groups than in CN or NO Table 4.

3.3. Post-outlier analysis

Significant heterogeneity was discovered among all the studies (I^2 = 74–95%, P^H = 10^{-5}-0.0001), which prompted an investigation using the Galbraith plot (**figure not shown**). Source of the inconsistency was identified per comparison level and is summarized in Table 3. A decrease or loss in the level of heterogeneity was observed when certain studies were omitted from the overall analysis. The results of the fixed-effects model (Table 3) analysis showed that the resulting pooled SMDs after outlier analysis (SMD = 0.89–2.45, P^A = 10^{-5}-0.008) still suggest that serum CysC levels are higher in MI and MA groups than in CN or NO.

3.4. Sensitivity analysis and publication bias

Outcomes from the different comparison were found to be robust (**data not are shown**), which indicates the stability of the overall post-outlier outcomes. On the other hand, no evidence of publication bias was observed in both the NO vs. MI and NO vs. MA comparison (see >Table 4).

4. Discussion

4.1. Summary and interpretation of findings

The present study quantitatively summarized the results of 12 studies, involving 2072 participants. Pooled SMDs and 95% CI from the individual studies showed that increasing serum CysC levels are significantly associated with DN. Higher levels of the analyte is observed as the level of albuminuria progresses. These significant findings provide adequate evidence of the biomarker potential of serum CysC as an early marker of DN. This is supported by the homogeneity of the post-outlier analysis (reduction in the heterogeneity in the post-outlier analysis, high degree of significance (multiple P^A values of 10^{-5}), consistent precision of effects (narrow CI), robustness (from sensitivity analysis), and lack of bias (non-significant result in the Egger regression asymmetry test and the Begg-Mazumdar correlation test).

4.2. Biomarker potential of CysC in DN

DN affects approximately one-third of patients with diabetes, and as the total number of diabetics is expected to increase, the prevalence of DN will also rise dramatically [3]. The goal in the management of diabetes is to find a superior early marker to correctly diagnose early stages of DN, prevent its progression to end-stage renal disease, and subsequently, reduce the burden of patients. Although serum CysC has been explored, several studies have reported that it is not significantly better than serum creatinine in diagnosing renal disease. Some of the criticisms on serum CysC say that it is not devoid of dependence on muscle mass and inflammation, and it is an expensive alternative over readily available serum creatinine [16]. Similar to creatinine that is affected by other factors, review of the literature shows that serum CysC is also correlated with other non-renal factors like age, weight, serum C-reactive protein level, and height. Knight et al. noted that when this clinical information was incorporated, serum CysC did not perform better than serum creatinine [37].

The present study explored the potential of serum CysC as a biomarker for early DN in patients with T2DM using the combined

Table 2
Summary of serum CysC levels (mg/L) per study.

First author	CN			NO			MI			MA		
	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n
Apakkan Aksun, 2004	1.04	0.31	32	1.25	0.26	29	1.70	0.42	39	–	–	–
Assal, 2013	0.65	0.07	20	1.43	0.65	20	1.93	0.63	25	3.35	1.59	25
El-Shafey, 2009	–	–	–	0.55	0.41	10	0.87	0.28	10	1.65	1.09	20
Jeon, 2011	–	–	–	0.91	0.26	210	1.05	0.38	83	2.04	1.19	42
Li, 2017	0.84	0.23	130	2.09	0.79	130	2.63	0.84	122	4.36	1.21	100
Mahfouz, 2015	0.05	0.01	50	0.05	0.01	50	0.07	0.01	50	0.07	0.01	50
Mojiminiyi, 2000	–	–	–	1.01	0.15	27	–	–	–	1.34	0.42	50
Shimizu, 2003	–	–	–	0.68	0.10	68	0.71	0.12	29	1.11	0.40	49
Siddiqi, 2017	–	–	–	0.56	0.13	90	1.74	1.40	90	–	–	–
Wang, 203	0.90	0.40	56	1.10	0.60	51	2.00	1.20	60	3.50	1.70	57
Yang, 2007	–	–	–	0.85	0.18	67	1.00	0.20	25	1.10	0.10	10
Ye, 2013	0.74	0.16	28	0.81	0.18	21	1.15	0.25	25	2.32	0.68	22

CN: control; NO: normoalbuminuria; MI: microalbuminuria; MA: macroalbuminuria; SD: standard deviation; n: total number of participants.

Table 3
Overall outcomes of the biomarker potential of serum CysC in DN.

Comparison Models		n	Test for Association			Test for Heterogeneity		AM	Omitted Studies
			SMD	95% CI	P^A	I^2	P^H		
CN vs. NO	Overall	6	0.88	0.08, 1.68	0.03*	95%	10^{-5}**	R	[29,30,34]
	w/o outlier	3	0.89	0.23, 1.55	0.008*	72%	0.03**	R	
CN vs. MI	Overall	6	2.07	1.45, 2.68	10^{-5}*	89%	10^{-5}**	R	[29,34]
	w/o outlier	**4**	**2.00**	**1.70, 2.29**	**10^{-5}***	**10%**	**0.34**	**F**	
CN vs. MA	Overall	5	2.78	1.78, 3.79	10^{-5}*	94%	10^{-5}**	R	[29,34]
	w/o outlier	3	2.45	1.70, 3.21	10^{-5}*	72%	0.03**	R	
NO vs. MI	Overall	11	0.95	0.67, 1.23	10^{-5}*	79%	10^{-5}**	R	[2,30,32,33,36]
	w/o outlier	**6**	**0.81**	**0.63, 0.98**	**10^{-5}***	**0%**	**0.53**	**F**	
NO vs. MA	Overall	10	1.77	1.46, 2.09	10^{-5}*	74%	<0.0001**	R	[29–31,34]
	w/o outlier	**6**	**1.74**	**1.53, 1.95**	**10^{-5}***	**31%**	**0.20**	**F**	
MI vs. MA	Overall	9	1.11	0.68, 1.55	10^{-5}*	86%	10^{-5}**	R	[29,30,36]
	w/o outlier	**6**	**1.09**	**0.89, 1.30**	**10^{-5}***	**0%**	**0.56**	**F**	

CN: control; NO: normoalbuminuria; MI: microalbuminuria; MA: macroalbuminuria; n: number of studies; SMD: standardized mean differences; CI: confidence interval: P^A: p-value for association; P^H: p-value for heterogeneity; AM: analysis model; R: random-effects model; F: fixed-effects model.
* *p*-value significant at < 0.05.
** *p*-value significant at < 0.10.

Table 4
Publication bias analysis for associations with 10 or more studies.

Comparison Models	n	Egger regression asymmetry test		Begg-Mazumdar correlation test	
		Intercept	*p*-value	Kendall's Tau	*p*-value
NO vs. MI	11	2.29	0.21	0.20	0.39
NO vs. MA	10	−1.61	0.53	−0.20	0.42

data from different published studies. The results show a positive correlation between serum CysC levels and albuminuria. The analysis shows that the analyte is highest in patients with MA and values subsequently lowers in patients with MI and lowest with the non-significant difference among patients in the CN and NO group. The meta-analysis showed serum CysC level is a potential predictor of DN development among patients with T2DM showing that the values increase as the disease progresses. This finding is consistent with previous studies and adds more evidence to the use of the analyte as an early biomarker in clinical practice and its ability to differentiate the degree of renal damage [2,7,38].

Several studies have noted the sensitivity of serum CysC in detecting early renal impairment. The present study coincides with previous findings suggesting the potential of CysC in discriminating the degree of renal damage and its ability in differentiating between normo- and microalbuminuric states. Similar results were noted in different other studies stating that CysC has the potential to be used in early detection of DN, even before the development of MI [39]. Physiologically, the substance is readily filtered in the glomerulus, completely reabsorbed and degraded by the proximal tubular cells, and does not return to the blood [40]. CysC is normally higher in the first year of life while the kidneys still mature, but the values tend to decline rapidly, reflecting the maturation of renal function. With a stable production rate, normal values are set at 0.51–1.31 mg/dL until about 50 years of age [41]. In case of renal disease, the inability of tubules to catabolize the serum cystatin C leads to higher levels where the increase is directly proportional to the degree of damage.

An interesting result of the present meta-analysis shows that serum CysC cannot significantly differentiate the levels between diabetic patients with NO with those of healthy control. This result is contrary to the review of Fiseha (2016), where one study noted that levels of serum CysC were found elevated in normoalbuminuric as compared to the control [10]. The difference in the result may be due to the variations in the criteria set on the control of each study.

Addressing the criticisms on the use of CysC, Stevens et al. (2009) concluded that although CysC is affected by age, sex, and race, the effect is not higher compared with the effects of these variables to creatinine [42]. Thus, in order to account for the possible non-renal elevation of CysC, the analyte should be interpreted in relation to these mentioned variables.

A second disadvantage noted on CysC is that it can be more expensive to analyze it than creatinine. However, there are assays compatible with automatic analyzers that can quickly, accurately, and precisely measure it, implying that it could become a practical laboratory test. In a review conducted by Grubb, he noted that when automated laboratory equipment is available, the cost of CysC is comparable to that of enzymatically determined creatinine [43]. Furthermore, although considered to be more expensive than creatinine, it is less expensive compared with radiolabeled traces and does not pose radiation hazards to patients and personnel [12]. It is also noteworthy to mention that in other studies, researchers have observed that serum CysC becomes elevated even before creatine and albumin levels rise in acute renal injury. Creatinine does not increase until moderate to a severe reduction in the GFR occurs [40], and NO is noted even in patients with nephropathy [6]. Overall, the clinical utility of serum CysC would still make it as a cost-effective alternative in diagnosing early stages of DN.

Although a cut-off value is essential to diagnose the early stage of DN, the present study was not able to do it because of the differences in the assays, and clinical settings used in the included studies. Thus, a largescale study involving homogenous groups is recommended to set the cut-off values for a specific clinical setting.

4.3. Strengths and limitations of the study

Interpreting the results of this study warrants the awareness of its limitations such as (1) variation in the ethnicity of the participants; (2) failure to note the method of CysC determination; (3) failure to determine other factors that could elevate CysC levels; and (4) lack of non-diabetes kidney disease controls. However, the limitations are masked by the following strengths: (1) large number of participants included with a narrow range of patient sample sizes; (2) homogenous post-outlier outcomes; (3) high degree of significance for the post-outlier outcomes; (4) robust pooled post-outlier outcomes; (5) consistent precision of effects; and (6) lack of any bias.

5. Conclusion

In conclusion, our meta-analysis confirms that serum CysC is a superior, cost-effective biomarker that can be used in the early diagnosis of DN. It can positively monitor kidney function, progression, and prediction of adverse outcomes among T2DM patients. However, further large-scale studies are needed to verify our claims.

Declaration of competing interest

The authors declare no conflict of interest.

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