Systematic review/Meta-analysis

Diabetology

Association of circulating cystatin C levels with type 2 diabetes mellitus: a systematic review and meta-analysis

Cheng-Cheng Ma, Chun-Cui Duan, Rong-Cai Huang, Hai-Qin Tang

Department of General Medicine, The First Affiliated Hospital of Anhui Medical University, Hefei, China

Submitted: 2 December 2018
Accepted: 8 February 2019

Arch Med Sci 2020; 16 (3): 648–656
DOI: https://doi.org/10.5114/aoms.2019.83511
Copyright © 2019 Termedia & Banach

Corresponding author:
Hai-Qin Tang
Department
of General Medicine
The First Affiliated
Hospital of Anhui
Medical University
230022 Hefei, China
E-mail: tanghqinayfy@126.com

Abstract

Introduction: This study aimed to systemically summarize the present literature about circulating cystatin C (Cys C) levels in type 2 diabetes mellitus (T2DM) and provide a more precise evaluation of Cys C levels in T2DM.
Material and methods: Relevant studies about Cys C concentrations in T2DM were searched in PubMed, EMBASE and the Cochrane Library database (up to Oct 31 2018). We computed the pooled standard mean difference (SMD) with its 95% confidence interval (CI) of Cys C levels through a random-effect model. The *Q* test and the I^2 statistic were used to assess and quantify between-study heterogeneity; publication bias was evaluated through a funnel plot and Egger's linear regression test.
Results: After the literature search and screening process, 14 studies with 723 T2DM patients and 473 healthy controls were finally included in the meta-analysis. The results showed that T2DM patients had significantly higher Cys C levels compared to healthy controls (SMD = 1.39, 95% CI: 0.92–1.86, $p < 0.001$). Publication bias was not detected based on the symmetrical shape of the funnel plot and the results of Egger's test ($p = 0.452$). Subgroup analyses suggested that variables of human race, age, gender, study sample size and disease duration have a relationship with Cys C level in T2DM patients.
Conclusions: Overall, our study suggests that patients with T2DM have an elevated circulating Cys C level compared to healthy controls, and it is associated with race, age, gender, study sample size and disease duration. Further investigations are still needed to explore the causal relationship of aberrant Cys C concentrations in T2DM.

Key words: type 2 diabetes mellitus, cystatin C, meta-analysis.

Introduction

Type 2 diabetes mellitus (T2DM) is one of the most common chronic metabolic diseases, featuring hyperglycemia resulting from resistance to insulin action and an inadequate compensatory insulin secretory response. The lasting chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction and complications, such as diabetic nephropathy, cardiovascular disease (CVD) and retinopathy. These complications threaten the life span and the quality of life in T2DM [1–5].

Cystatin C (Cys C), with molecular weight of 13,343 Da, is a potent competitive extracellular inhibitor of cysteine proteinases that can be steadily produced and constitutively secreted by all nucleated cells and mainly controls extracellular protease activity [6–8]. It has been shown that Cys C is able to modulate lysosomal protein turnover after cellular internalization

Creative Commons licenses: This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International (CC BY -NC -SA 4.0). License (http://creativecommons.org/licenses/by-nc-sa/4.0/).

via endocytosis, thereby indicating the role of Cys C in modulating target tissue homeostasis after cellular reuptake *in vivo*. Moreover, Cys C also contributes to endothelial cell (EC) tubule formation and shows angiogenic characteristics *in vitro* [9, 10].

Cystatin C is mainly removed from the blood stream by renal glomerular filtration, and is almost completely reabsorbed in the distal tubule without tubular secretion [11]. Unlike serum creatinine, Cys C is not susceptible to external factors such as age, diet, or body mass. Cys C has been shown to be superior to serum creatinine as a marker in assessment of renal function and improves estimates of glomerular filtration rate (GFR) compared to creatinine-based methods alone [12–15]. In addition, studies have suggested that Cys C could be an independent factor in the prediction of all-cause mortality, CVD and incident congestive heart failure in subjects with coronary heart disease (CHD) [16–20].

A number of studies have investigated the expression of Cys C in T2DM patients. Some reported an increased Cys C level in T2DM when compared to healthy controls; however, others reported a heterogeneous result. It seems that those results did not reach a consensus yet. Hence, we conducted a comprehensive review and meta-analysis. The aim of this meta-analysis was to give a precise estimation of circulating Cys C level in T2DM patients compared to healthy controls, and to investigate the possible factors.

Material and methods

Search strategy

This study was conducted and reported according to a study protocol based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [21].

A systematic literature search was performed on the major online databases including PubMed, EMBASE and the Cochrane Library to identify related studies published between database inception and October 31, 2018. The literature search items were applied using the following search terms with multiple combinations: ("type 2 diabetes mellitus" OR "T2DM" OR "diabetes type 2" OR "type 2 dm" OR "non-insulin-dependent diabetes mellitus" OR "diabetes mellitus" OR "DM" AND "cystatin C" OR "Cys C" OR "cystatin"). The blood source for detection of Cys C was defined according to use of serum or plasma. To avoid the underlying loss of related literature, we manually reviewed all the references from the retrieved literature, to acquire other potential relevant articles. No method restrictions were applied; articles from all countries were accessible.

Inclusion criteria and exclusion criteria

Studies were retained in this meta-analysis if they met the following inclusion criteria: (1) they were case-control, cohort or cross-sectional studies with data on both patients diagnosed with T2DM and healthy controls; (2) they reported the detailed data (including mean and standardized difference (SD)) about Cys C levels in both T2DM and control groups; (3) English publications. If a study was found in more than one publication, all publications were considered for data abstraction, but only one was included in the final analysis.

Studies regarding T1DM and an unclear diagnostic standard of T2DM were excluded. Furthermore, studies were excluded if they were (1) re-

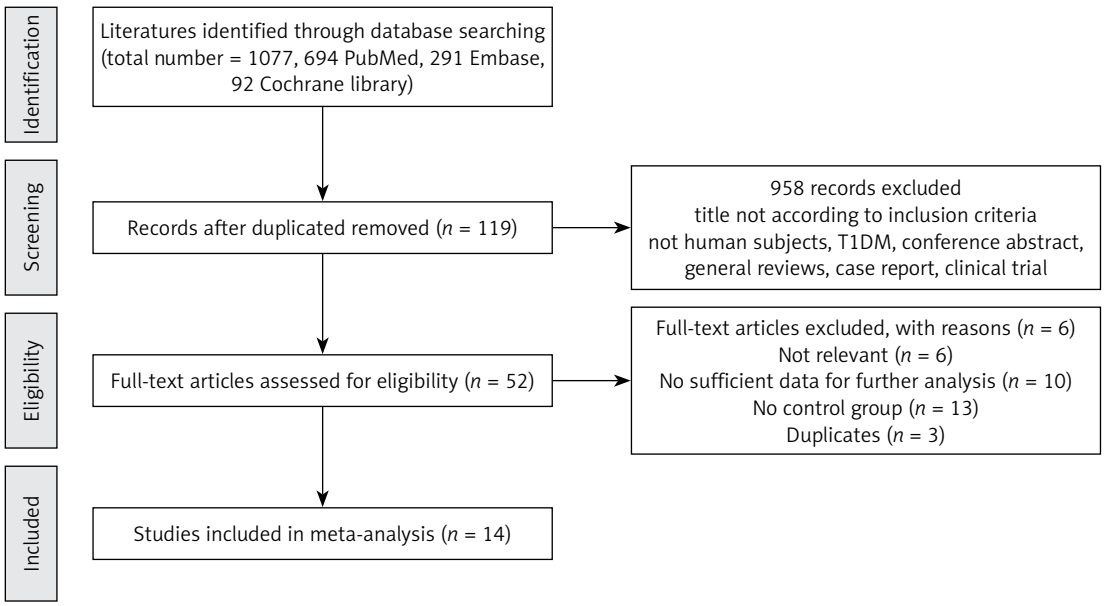

Figure 1. Flowchart of selected articles

view articles, case reports and discussion papers; (2) contained overlapping or insufficient data. The study selection process is presented in Figure 1.

Data extraction

We used pre-designed standardized forms to extract data from each selected study, including the following variables: primary author, year of publication, country, sample size, mean and SD of Cys C levels, mean age, major clinical and demographic variables. If original data of articles were not available, we contacted the corresponding authors for additional information.

Quality evaluation of the literature

Cheng-Cheng Ma and Chun-Cui Duan independently assessed the methodological quality of each study with the validated Newcastle-Ottawa Quality Assessment Scale (NOS) [22]. In case of disagreement during the process of quality evaluation, the third investigator (Hai-Qin Tang) independently reconciled the discrepancies.

Statistical analysis

Statistical differences of Cys C between T2DM patients and control subjects was calculated by using the standardized mean difference (SMD), and its 95% confidence intervals (95% CI) were illustrated by a forest plot [23]. If there was no significant heterogeneity ($p > 0.05$) among these studies, the fixed-effect model was used. Otherwise, a random-effect model was used for further analyses [24, 25].

Cochran's *Q* statistic was conducted to evaluate the between-study heterogeneity, then quantified with I^2, which was used to estimate the effect of heterogeneity among studies [26]. We estimated the effect of heterogeneity of each study by the method, $I^2 = [(Q - df)/ Q] \times 100\%$ [27]. Egger's linear regression test was implemented to statistically test publication bias, and a forest plot was used to graphically depict the results of publication bias [28]. To explore the source of between-study heterogeneity, subgroup analysis was performed according to the stratification of human race, age, gender, study sample size and disease duration. The detailed stratification criteria for each of the included studies in subgroup analysis were shown as follows: (1) Human race was stratified according to whether study subjects were Caucasian or non-Caucasian; (2) based on the age distribution of T2DM patients of all the included studies (range from 46.0 to 61.0), the stratification for age was partitioned by age of 55 years, namely age ≤ 55 and age > 55 groups; (3) according to the female proportion distribution (range from 46.0% to 95.2%) among the included studies, we chose the female proportion 50% as a cut-off point; thus the gender stratification into female% ≥ 50 and female% < 50 groups; (4) to exclude an error due to samples size on the size of SMD of Cys C, we calculated that the minimum sample size is 45 (type one error (α) as 5%, power of the test as 90% with anticipated mean difference of Cys C between groups was 0.5 and anticipated standard difference (SD) 0.7). In accordance with the distribution of study sample size of each study, we chose the sample size of 50 as a cut-off point, and the stratification for study sample size was divided into sample size < 50 and sample size ≥ 50 groups; (5) the distribution of disease duration among included studies ranged from 4.2 to 9.7 years; we set the cut-off point of 7 years as the stratification value, and the subgroup of disease duration was defined as duration ≤ 7 years and duration > 7 years groups.

Furthermore, sensitivity analyses were conducted to determine the stability and reliability of the results using the leave-one-out method. All statistical analysis was performed using Stata 12.0 software (Stata Corporation, College Station, Texas, USA).

Results

Study characteristics

Our search yielded 1077 relevant articles by using electronic and manual search methods; 14 articles were finally included in this meta-analysis according to the rigid inclusion and exclusion criteria. The final 14 studies included a total of 1195 subjects (723 patients with T2DM and 473 healthy controls) after examining title, type, abstracts and full text up to October 31 2018. The study population came from 5 continents and covered 10 different countries. Demographic and clinical data of the 14 incorporated studies are summarized in Table I [29–42]. All the included studies have a case-control design and have a clear method of diagnosis for T2DM. The measurement types for Cys C concentration were as follows: eleven studies measured by immunoturbidimetric method, one study measured by spectrometric immunoassay and two studies did not mention measurement methods. The age and sex were matched between T2DM patients and healthy controls in each included study. NOS scores were determined to assess the quality of included studies (Table I). The studies included in this meta-analysis were generally of moderate to high quality.

Meta-analysis of Cys C levels in T2DM patients and healthy controls

Heterogeneity test results and overall effects

In this meta-analysis, the results showed that there was marked heterogeneity among the stud-

Table I. Demographic and clinical data of T2DM patients and controls of included studies

Author, year	Region	Patients with T2DM						Control					Measurement type	NOS
		N	Age (mean ± SD) [years]	% female	BMI	Duration [years]	% HbA_{1c}	*N*	Age (mean ± SD) years	% female	BMI	% HbA_{1c}		
Qamar *et al.*, 2018	Pakistan	119	NA	NA	NA	NA	NA	50	NA	NA	NA	NA	Immunoturbidimetric	6
Sangeeta *et al.*, 2018	India	50	NA	NA	NA	NA	NA	50	NA	NA	NA	NA	NA	5
Li *et al.*, 2017	China	200	60.0 ±10.3	46	28.0	9.0 ±2.3	8.5 ±1.8	50	58.0 ±11.0	48	25.0	5.4 ±0.5	NA	8
Yassine *et al.*, 2016	USA	34	52.0 ±11.8	50	36.3	NA	NA	33	43.8 ±14.9	70	24.4	NA	Spectrometric immunoassay	7
Szopa *et al.*, 2015	Poland	39	58.9 ±10.3	56	30.5	6.8 ±6.4	NA	23	38.0 ±11.7	35	23.9	NA	Immunoturbidimetric	7
Petrica *et al.*, 2015	Romania	48	57.5 ±2.6	NA	31.5	9.0 ±1.3	6.9 ±0.3	11	58.0 ±1.75	NA	24.2	6.0 ±0.1	Immunoturbidimetric	7
Wang *et al.*, 2013	China	51	48.2 ±12.6	53	NA	NA	NA	56	49.2 ±13.7	54	NA	NA	Immunoturbidimetric	7
Triki *et al.*, 2013	Tunisia	15	50.7 ±10.6	95.2	31.3	5.0 ±7.2	NA	30	53.6 ±3.9	33	26.6	NA	Immunoturbidimetric	6
Zhao *et al.*, 2012	China	107	59.0 ±6.0	46	NA	9.0 ±3.0	NA	47	53.0 ±5.0	49	NA	NA	Immunoturbidimetric	8
Wolff *et al.*, 2009	Chile	22	61.0 ±5.4	NA	NA	NA	8.9 ±1.5	8	56.9 ±10.1	NA	NA	NA	Immunoturbidimetric	5
Surendar *et al.*, 2009	India	40	46.0 ±8.0	NA	25.0	4.2 ±3.0	7.6 ±1.7	43	42.0 ±11.0	NA	23.0	5.5 ±0.6	Immunoturbidimetric	6
Kalansooriya *et al.*, 2007	UK	40	NA	50	NA	8.5 ±0.8	6.9 ±0.8	20	NA	50	NA	5.2 ±0.4	Immunoturbidimetric	7
Ozmen *et al.*, 2002	Turkey	35	55.0 ±1.9	NA	NA	9.7 ±1.4	6.3 ±0.5	40	54.6 ±1.7	55	NA	5.5 ±0.1	Immunoturbidimetric	7
Piwowar *et al.*, 1997	Poland	41	NA	80	NA	NA	NA	12	NA	58	NA	NA	Immunoturbidimetric	6

NA – not available, NOS – Newcastle-Ottawa Scale, BMI – body mass index, HbA_{1c} – hemoglobin A_{1c}.

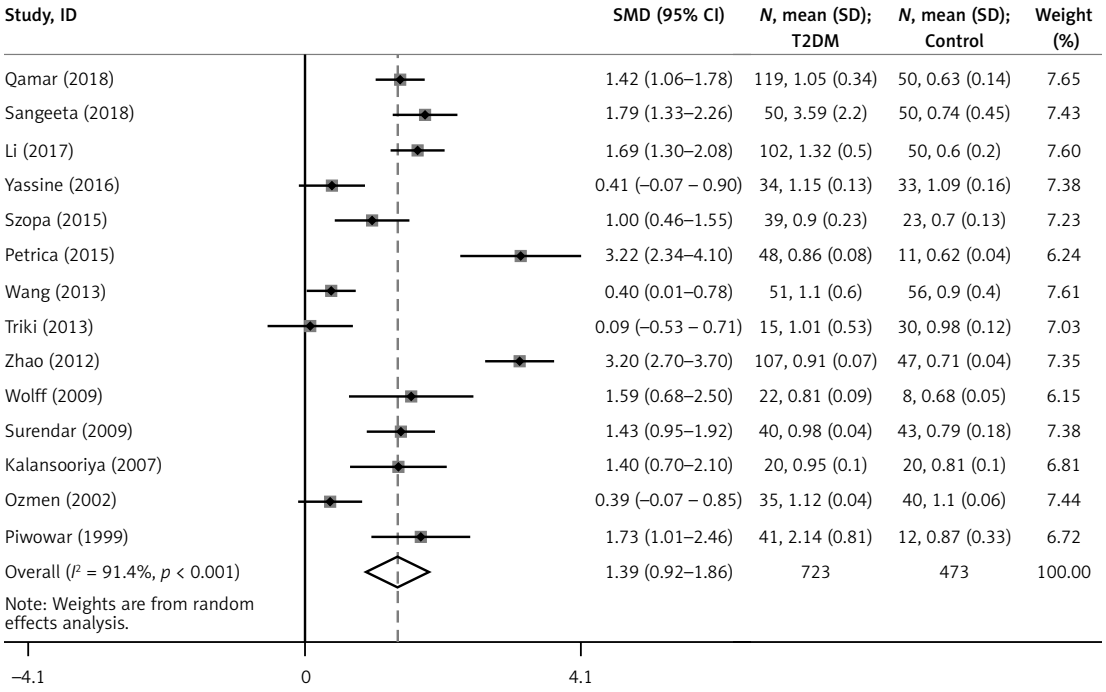

Figure 2. Meta-analysis of 14 studies reporting on Cys C levels in T2DM compared with healthy controls

ies (I^2 = 91.50%, p < 0.001) (Figure 2, Table I). The incorporated analysis showed that T2DM patients had significantly higher levels of Cys C compared to healthy controls (SMD = 1.39, 95% CI: 0.92–1.86, p < 0.001) (Figure 2, Table I).

Sensitivity analysis

Considering the existence of strong heterogeneity in this meta-analysis, we performed a sensitivity analysis by using random effect methods, which compared the meta-analysis results of the studies as a whole to the same meta-analysis with one study excluded in each round to determine how robust the findings were. In our study, sensitivity analysis indicated that the results of this meta-analysis were reliable and stable when any one study was excluded (Figure 3).

Publication bias

Publication bias was evaluated by Egger's test and represented graphically by funnel plots of the standard difference in means vs. the standard error. Egger's linear regression test did not reveal significant evidence of publication bias as a whole (t = 0.780, p = 0.452) (Figure 4).

Subgroup analysis

Subgroup analysis was performed to explore the potential source of between-study heteroge-

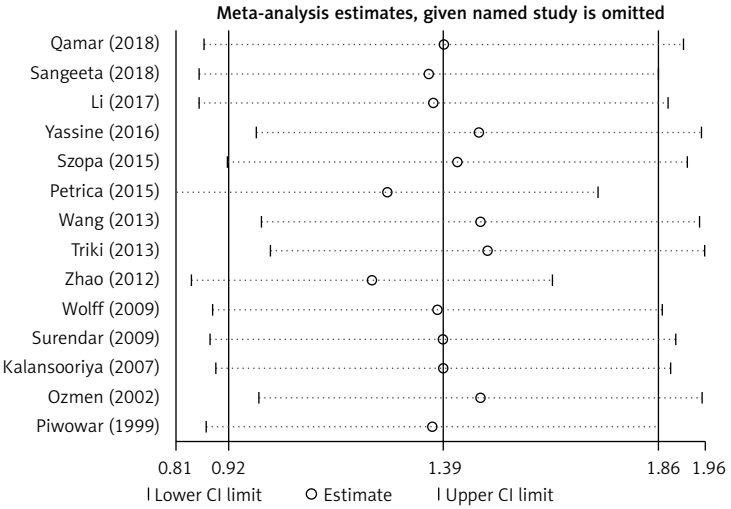

Figure 3. Sensitivity analyses by excluding one study at a time

neity. The stratification of subgroups was based on the variables of human race, age, gender, study sample size and disease duration. The results revealed an increased Cys C level for non-Caucasian (SMD = 1.64, 95% CI: 1.01–2.27), age > 55 (SMD = 1.88, 95% CI: 0.82–2.93), female% ≥ 50 (SMD = 2.22, 95% CI: 1.18–3.25), sample size (n < 50) (SMD = 1.69, 95% CI: 0.87–2.51) and disease duration > 7 years (SMD = 1.96, 95% CI: 0.90–3.02) groups. It suggested that the concentration of Cys C was associated with human race, age, gender, study sample size and disease duration (Table II).

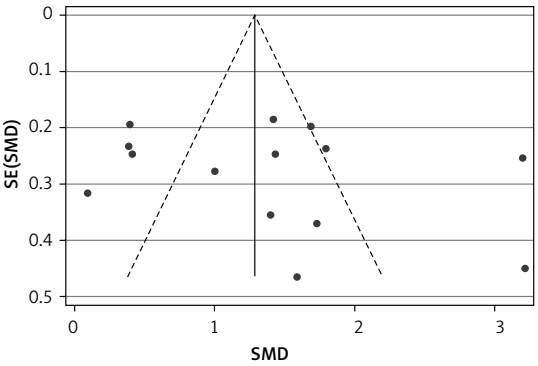

Figure 4. Funnel plot (with pseudo 95% confidence intervals) with the standard error of the Cys C difference plotted against the mean difference of Cys C of each study

Discussion

Diabetes mellitus has posed a huge challenge to health care systems across the globe; the diabetic complications are a leading cause of mortality and morbidity and a serious threat to the life of diabetes patients. Cys C is an effective cysteine protease inhibitor that is produced by all nucleated cells at a fairly constant rate and freely filtered by glomeruli due to its low molecular weight. The cellular reuptake of secreted Cys C may take place particularly in the vascular endothelium and may lead to vascular endothelial specific accumulation of Cys C. Even small increases in Cys C plasma levels could have significant effects on the homeostasis of the vascular endothelium. Several previous studies have disclosed the association of Cys C with the risk of diabetic complications in T2DM, including di-

Table II. Subgroup analysis of Cys C level in T2DM

Subgroup	*N*	SMD (95% CI)	Heterogeneity test			Publication bias	
			Q	*P*-value	I^2 (%)	*t*	*P*-value
Total	14	1.39 (0.92–1.86)	150.35	< 0.001	91.40	0.78	0.452
Race:							
Caucasian	7	1.12 (0.48–1.77)	48.82	< 0.001	87.70	2.25	0.024
Non-Caucasian	7	1.64 (1.01–2.27)	79.52	< 0.001	92.50	1.35	0.176
Overall	14	1.39 (0.92–1.86)	150.35	< 0.001	91.40	0.78	0.452
Age [years]:							
≤ 55	5	0.74 (0.21–1.28)	19.84	< 0.001	79.80	0.75	0.453
> 55	5	1.88 (0.82–2.93)	84.20	0.007	95.20	1.57	0.117
Overall	10	1.32 (0.67–1.97)	141.95	< 0.001	93.70	0.77	0.463
Sex:							
Female% < 50	5	0.63 (0.23–1.03)	11.36	0.023	64.80	0.52	0.602
Female% ≥ 50	3	2.22 (1.18–3.25)	23.79	< 0.001	91.60	0.98	0.327
Overall	8	1.24 (0.52–1.96)	110.56	< 0.001	93.70	0.18	0.863
Sample size:							
N < 50	5	1.69 (0.87–2.51)	79.32	< 0.001	95.00	1.96	0.050
N ≥ 50	9	1.20 (0.67–1.73)	54.90	< 0.001	85.40	1.67	0.095
Overall	14	1.39 (0.92–1.86)	150.35	< 0.001	91.40	0.78	0.452
Disease duration:							
Duration ≤ 7 years	3	0.86 (0.12–1.61)	11.19	0.004	82.10	0.49	0.624
Duration >7 years	5	1.96 (0.90–3.02)	78.49	< 0.001	94.90	–1.57	0.117
Overall	8	1.54 (0.80–2.28)	106.20	< 0.001	93.40	0.27	0.795

abetic nephropathy, CVD, and diabetic peripheral neuropathy [43–46].

Some of the most important findings about Cys C are in the area of renal disease. Vijay *et al*. demonstrated that there was an increased urine Cys C level in T2DM with early diabetic nephropathy as compared to patients without nephropathy, and the increase of Cys C level was positively correlated with microalbuminuria [47]. Zhang *et al*. reported that serum Cys C was more sensitive than serum creatinine for estimation of GFR in T2DM [48]. Cys C is a good marker of incipient renal disease and represents an ideal endogenous index reflecting the GFR [49]. Serum Cys C could be a more precise indicator than serum creatinine because it is less affected by other factors, thereby reflecting renal function much more precisely in early renal function lesions of T2DM.

Since Cys C is more reliable for assessment of renal function, it is also a potential indicator and has an associative relationship with the CV risk prediction of diabetes patients. A recent study that included 523 T2DM patients revealed that, compared to the T2DM with non-subclinical atherosclerosis group, there was an increased serum Cys C level in the subclinical atherosclerosis group, and the concentration of Cys C was correlated with brachial-ankle pulse wave velocity, suggesting a potential role of Cys C in predicting arterial stiffness [45]. Other studies have also found an association of serum Cys C with vascular complications, carotid arterial wall elasticity and subclinical atherosclerosis in T2DM [45, 50, 51]. A study by Vaduganathan *et al*. revealed that the renal biomarker of Cys C was independently associated with subsequent cardiovascular (CV) risk [52]. Moreover, there was a positive association of serum Cys C with CV autonomic neuropathy in patients with T2DM [44]. Those studies suggested the important role of Cys C involved in T2DM with CV complications.

The Japanese Fukuoka Diabetes Registry study suggested that Cys C based eGFR has a stronger association with all-cause mortality and is superior to creatinine based eGFR for predicting all-cause mortality in patients with T2DM [46]. They also found that a lower creatinine to Cys C ratio is a risk factor for bone fracture in T2DM [53].

In the present study, we reviewed data from 14 studies with Cys C levels reported, including subjects with T2DM patients (n = 723) and healthy controls (n = 473). Our findings revealed that the circulating Cys C levels are higher in T2DM patients than in the healthy controls, suggesting that increased Cys C levels may be a factor related to the presence of T2DM. Heterogeneity test results showed marked between-study heterogeneity. As is well known, positive studies showing favorable results are more likely than negative studies showing harmful or null results to be reported and published. Hence, strong heterogeneity may impair the validity of the overall results. Publication bias was not detected, and sensitivity analyses showed that the overall effect sizes were all stabilized in the circulating Cys C levels between cases and controls. To minimize the possible factors influencing the results, and to explore underlying sources of heterogeneity, we applied subgroup analyses. The results suggested that related factors (human race, age, gender, study sample size and disease duration) are relevant to the circulating Cys C levels and may be sources of heterogeneity.

Although our meta-analysis included relatively high-quality studies, there were still several limitations should be acknowledged. First, in the included studies, some of them did not have complete clinical characteristic variables reported, such as hemoglobin A_{1c}% (HbA_{1c} %), body mass index (BMI) and eGFR. Therefore, the association between serum/plasma Cys C levels and clinical characteristic variables cannot be fully understood and may lead to underpowered results. Second, the number of included studies and their study sample sizes are relatively small; a sample size that is too small increases the likelihood of a type II error skewing the results, which decreases the power of the study. Third, this review only included studies published in English, which might inevitably cause language bias. Furthermore, meta-analysis, as a kind of retrospective study (evidence-based medicine), could not prove causation, which is susceptible to the methodological deficiencies of the pooled studies.

Regardless of these limitations, it is worth emphasizing some strengths of this study. Compared to individual studies, our study could provide an overall result of Cys C level and give an accurate estimation on the relationship between Cys C level and T2DM. We carried out subgroup analysis to find possible sources of heterogeneity in our study. In addition, publication bias was not detected, suggesting that the included results may be unbiased.

In conclusion, this study demonstrates that serum/plasma Cys C levels were significantly higher in T2DM patients compared with the healthy controls. In addition, subgroup analysis suggested that Cys C levels are influenced by human race, age, gender, study sample size and disease duration. Further investigations are still needed to explore the causal relationship of aberrant expression of Cys C in T2DM.

Conflict of interest

The authors declare no conflict of interest.

References

1. Svensson AM, Miftaraj M, Franzen S, Eliasson B. Clinical effects, cardiovascular and renal outcomes associated with rapid-acting insulin analogs among individuals with type 2 diabetes: a nation-wide observational cohort study. Clin Diabetes Endocrinol 2017; 3: 5.
2. Sun X, He J, Ji XL, et al. Association of chronic kidney disease with coronary heart disease and stroke risks in patients with type 2 diabetes mellitus: an observational cross-sectional study in Hangzhou, China. Chin Med J (Engl) 2017; 130: 57-63.
3. Richard C, Cristall L, Fleming E, et al. Impact of egg consumption on cardiovascular risk factors in individuals with type 2 diabetes and at risk for developing diabetes: a systematic review of randomized nutritional intervention studies. Can J Diabetes 2017; 41: 453-63.
4. Wielgosz A, Dai S, Walsh P, McCrea-Logie J, Celebican E. Comorbid conditions in Canadians hospitalized because of diabetes. Can J Diabetes 2018; 42: 106-11.
5. Teng Y, Wang S, Wang N, Li M. STOP-Bang questionnaire screening for obstructive sleep apnea among Chinese patients with type 2 diabetes mellitus. Arch Med Sci 2018; 14: 971-8.
6. Abrahamson M, Olafsson I, Palsdottir A, et al. Structure and expression of the human cystatin C gene. Biochem J 1990; 268: 287-94.
7. Mussap M, Plebani M. Biochemistry and clinical role of human cystatin C. Crit Rev Clin Lab Sci 2004; 41: 467-550.
8. Turk V, Stoka V, Turk D. Cystatins: biochemical and structural properties, and medical relevance. Front Biosci 2008; 13: 5406-20.
9. Shi GP, Sukhova GK, Kuzuya M, et al. Deficiency of the cysteine protease cathepsin S impairs microvessel growth. Circ Res 2003; 92: 493-500.
10. Zhang J, Wang P, Huang YB, et al. Plasma cathepsin L and its related pro/antiangiogenic factors play useful roles in predicting rich coronary collaterals in patients with coronary heart disease. J Int Med Res 2010; 38: 1389-403.
11. Stevens LA, Schmid CH, Greene T, et al. Factors other than glomerular filtration rate affect serum cystatin C levels. Kidney Int 2009; 75: 652-60.
12. Nakai K, Kikuchi M, Omori S, Saito K, Suwabe A. Evaluation of urinary cystatin C as a marker of renal dysfunction. Nihon Jinzo Gakkai Shi 2006; 48: 407-15.
13. Grubb AO. Cystatin C: properties and use as diagnostic marker. Adv Clin Chem 2000; 35: 63-99.
14. Laterza OF, Price CP, Scott MG. Cystatin C: an improved estimator of glomerular filtration rate? Clin Chem 2002; 48: 699-707.
15. Colantonio LD, Tanner RM, Warnock DG, et al. The role of cystatin-C in the confirmation of reduced glomerular filtration rate among the oldest old. Arch Med Sci 2016; 12: 55-67.
16. Rasul S, Reiter MH, Ilhan A, Lampichler K, Wagner L, Kautzky-Willer A. Circulating angiopoietin-2 and soluble Tie-2 in type 2 diabetes mellitus: a cross-sectional study. Cardiovasc Diabetol 2011; 10: 55.
17. Risch L, Blumberg A, Huber A. Rapid and accurate assessment of glomerular filtration rate in patients with renal transplants using serum cystatin C. Nephrol Dial Transplant 1999; 14: 1991-6.
18. van der Laan SW, Fall T, Soumare A, et al. Cystatin C and cardiovascular disease: a mendelian randomization study. J Am Coll Cardiol 2016; 68: 934-45.
19. Song T, Luo Y, Wang X, et al. Clinical characteristics of Chinese patients with duration of type 2 diabetes > 40 years. J Diabetes 2017; 9: 45-52.
20. Faridi KF, Lupton JR, Martin SS, et al. Vitamin D deficiency and non-lipid biomarkers of cardiovascular risk. Arch Med Sci 2017; 13: 732-7.
21. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009; 62: 1006-12.
22. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010; 25: 603-5.
23. Nakken B, Szodoray P. Accelerated atherosclerosis in rheumatoid arthritis: rationale for mannose-binding lectins? J Rheumatol 2010; 37: 482-4.
24. Zhai C, Li S, Feng W, et al. Association of interleukin-17a rs2275913 gene polymorphism and asthma risk: a meta-analysis. Arch Med Sci 2018; 14: 1204-11.
25. Mazidi M, Rezaie P, Banach M. Effect of magnesium supplements on serum C-reactive protein: a systematic review and meta-analysis. Arch Med Sci 2018; 14: 707-16.
26. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21: 1539-58.
27. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557-60.
28. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-34.
29. Qamar A, Hayat A, Ahmad TM, Khan A, Hasnat MNU, Tahir S. Serum cystatin C as an early diagnostic biomarker of diabetic kidney disease in type 2 diabetic patients. J Coll Physicians Surg Pak 2018; 28: 288-91.
30. Sangeeta S, Ambekar J, Sudhakar Tu, Waz MS, Dongre N. Assessment of eGFR, using cystatin-C and creatinine based equations for the early detection of renal injury in diabetic and non diabetic patients. J Clin Diagn Res 2018; 12: BC30-3.
31. Li L, Jiang XG, Hu JY, et al. The association between interleukin-19 concentration and diabetic nephropathy. BMC Nephrol 2017; 18: 65.
32. Yassine HN, Trenchevska O, Dong Z, et al. The association of plasma cystatin C proteoforms with diabetic chronic kidney disease. Proteome Sci 2016; 14: 7.
33. Szopa M, Kapusta M, Matejko B, et al. Comparison of glomerular filtration rate estimation from serum creatinine and cystatin C in HNF1A-MODY and other types of diabetes. J Diabetes Res 2015; 2015: 183094.
34. Petrica L, Vlad A, Gluhovschi G, et al. Glycated peptides are associated with the variability of endothelial dysfunction in the cerebral vessels and the kidney in type 2 diabetes mellitus patients: a cross-sectional study. J Diabetes Complications 2015; 29: 230-7.
35. Wang T, Wang Q, Wang Z, Xiao Z, Liu L. Diagnostic value of the combined measurement of serum hcy, serum cys C, and urinary microalbumin in type 2 diabetes mellitus with early complicating diabetic nephropathy. ISRN Endocrinol 2013; 2013: 407452.
36. Triki S, Fekih O, Hellara I, et al. Association between serum cystatin C levels and cardiovascular disease in type 2 diabetic patients. Ann Biol Clin (Paris) 2013; 71: 438-42.
37. Zhao LS, Bai WW, Xiang GD, Yue L, Sun HL. Clinical evaluation of valsartan and metoprolol tartrate in treatment of diabetic nephropathy with positive beta1-adrenergic and anti-angiotensin II type 1 receptor antibody. Chin Med J (Engl) 2012; 125: 3543-7.
38. Wolff C, Durruty P, Espinoza J, Ripamonti S, Diaz J. Cystatin C and adiponectin in diabetics with and without coronary artery disease. Rev Med Chil 2009; 137: 729-36.

39. Surendar J, Anuradha S, Ashley B, et al. Cystatin C and cystatin glomerular filtration rate as markers of early renal disease in Asian Indian subjects with glucose intolerance (CURES-32). Metab Syndr Relat Disord 2009; 7: 419-25.
40. Kalansooriya A, Holbrook I, Jennings P, Whiting PH. Serum cystatin C, enzymuria, tubular proteinuria and early renal insult in type 2 diabetes. Br J Biomed Sci 2007; 64: 121-3.
41. Ozmen B, Ozmen D, Turgan N, Habif S, Mutaf I, Bayindir O. Association between homocysteinemia and renal function in patients with type 2 diabetes mellitus. Ann Clin Lab Sci 2002; 32: 279-86.
42. Piwowar A, Knapik-Kordecka M, Buczynska H, Warwas M. Plasma cystatin C concentration in non-insulin-dependent diabetes mellitus: relation with nephropathy. Arch Immunol Ther Exp (Warsz) 1999; 47: 327-31.
43. Zhao J, Deng W, Zhang Y, et al. Association between serum cystatin C and diabetic foot ulceration in patients with type 2 diabetes: a cross-sectional study. J Diabetes Res 2016; 2016: 8029340.
44. Chung JO, Cho DH, Chung DJ, Chung MY. Serum cystatin C levels are positively associated with cardiovascular autonomic neuropathy in patients with type 2 diabetes. Exp Clin Endocrinol Diabetes 2015; 123: 627-31.
45. Chung YK, Lee YJ, Kim KW, et al. Serum cystatin C is associated with subclinical atherosclerosis in patients with type 2 diabetes: a retrospective study. Diab Vasc Dis Res 2018; 15: 24-30.
46. Ide H, Iwase M, Fujii H, et al. Comparison of cystatin C- and creatinine-based estimated glomerular filtration rates for predicting all-cause mortality in Japanese patients with type 2 diabetes: the Fukuoka Diabetes Registry. Clin Exp Nephrol 2017; 21: 383-90.
47. Vijay S, Hamide A, Senthilkumar GP, Mehalingam V. Utility of urinary biomarkers as a diagnostic tool for early diabetic nephropathy in patients with type 2 diabetes mellitus. Diabetes Metab Syndr 2018; 12: 649-52.
48. Zhang PP, Zhan JF, Xie HL, Li LS, Liu ZH. Evaluation of glomerular filtration rate using cystatin C in diabetic patients analysed by multiple factors including tubular function. J Int Med Res 2010; 38: 473-83.
49. Dhia RB, Hellara I, Harzallah O, et al. Evaluation of the renal function in type 2 diabetes: clearance calculation or cystatin C? Ann Biol Clin (Paris) 2012; 70: 287-94.
50. Kim HJ, Byun DW, Suh K, Yoo MH, Park HK. Association between serum cystatin C and vascular complications in type 2 diabetes mellitus without nephropathy. Diabetes Metab J 2018; 42: 513-8.
51. Kaneko R, Sawada S, Tokita A, et al. Serum cystatin C level is associated with carotid arterial wall elasticity in subjects with type 2 diabetes mellitus: a potential marker of early-stage atherosclerosis. Diabetes Res Clin Pract 2018; 139: 43-51.
52. Vaduganathan M, White WB, Charytan DM, et al. Relation of serum and urine renal biomarkers to cardiovascular risk in patients with type 2 diabetes mellitus and recent acute coronary syndromes (from the EXAMINE Trial). Am J Cardiol 2019; 123: 382-91.
53. Komorita Y, Iwase M, Fujii H, et al. The serum creatinine to cystatin C ratio predicts bone fracture in patients with type 2 diabetes: the Fukuoka Diabetes Registry. Diabetes Res Clin Pract 2018; 146: 202-10.