Original Paper

Cell-Derived Microparticles in Patients with Type 2 Diabetes Mellitus: a Systematic Review and Meta-Analysis

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Key Words

Type 2 diabetes mellitus • Microparticles • Biomarker • Platelet-derived microparticle • Endothelium-derived microparticle

Abstract

Background/Aims: The aim of this study was to assess the association between circulating cell-derived microparticles (MPs) and type 2 diabetes mellitus (T2DM). **Methods:** A literature search was performed systematically in PubMed and Embase to identify available case-control or cross-sectional studies that compared different types of cell-derived MPs in patients with T2DM and non-diabetic controls. Pooled standardized mean differences (SMDs) of each MP type were pooled using meta-analysis. **Results:** Forty-eight studies involving 2,460 patients with T2DM and 1,880 non-diabetic controls were included for systematic review and 34 of which were included for quantitative study by meta-analysis. In the overall analysis, the levels of circulating total MPs (TMPs), platelet-derived MPs (PMPs), monocyte-derived MPs (MMPs) and endothelium-derived MPs (EMPs) were significantly higher in T2DM patients than those in controls (TMPs: SMD, 0.64; 95%CI, 0.12~1.15; P=0.02; PMPs: SMD, 1.19; 95%CI, 0.88~1.50; P <0.00001; MMPs: SMD, 0.92; 95%CI, 0.66~1.17; P <0.00001; EMPs: SMD, 0.73; 95%CI, 0.50~0.96; P <0.00001). Meanwhile, no significant difference was shown in leukocyte-derived MPs (LMPs) level between diabetic and non-diabetic groups (SMD, 0.37; 95%CI, -0.15~0.89; P=0.17). **Conclusions:** The counts of TMPs, PMPs, MMPs and EMPs elevated in patients with T2DM. And cell-derived MPs may play a role in the pathogenesis of T2DM.

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Introduction

Type 2 diabetes mellitus (T2DM) is one of the most common chronic diseases with substantial burden worldwide [1]. It induces organ damage and cell apoptosis associating with energy deficiency, oxidative stress and advanced glycation end products [2, 3]. Microparticles (MPs), small membrane vesicles measuring 0.1~1.0 μm in diameter, are produced during the apoptosis and stimulation of various cell types, such as platelets, leukocytes, monocytes, erythrocytes, and endothelial cells [4-7]. Being overlooked for years, MPs are now considered as extracellular organelles with a variety of functions involving coagulation, inflammation, vascular function and transfer of biologic information [8-11].

Even though accumulating evidence indicated the quantity changes of different MPs in type 2 diabetic patients, as well as the association between MPs and diabetic vasculopathies and neurological complications, it is still uncertain whether the MPs counts could serve as biomarkers of T2DM. In this study, we systematically collected and analyzed the available literatures to evaluate the quantity and phenotype of MPs in different population.

Materials and Methods

Literature-search strategy

The literature search was performed by two independent investigators (S.L. and J.W.) through October 2015 without restriction to regions or publication types. The sources were the electronic databases of PubMed and Embase. According to the search strategy, medical subject heading (MeSH) terms and keywords like “diabetes”, “microparticle”, “microparticles” and “cell-derived microparticle” were applied.

Inclusion and exclusion criteria

A study with the following features was considered eligible: (1) designed as a case-control or cross-sectional study, (2) including patients with type 2 diabetes mellitus and controls without T2DM, (3) compared counts of any interested MPs between case and control group. The interested MPs were as following: the total microparticles (TMPs), platelet-derived microparticles (PMPs), leukocyte-derived microparticles (LMPs), monocyte-derived microparticles (MMPs) and endothelium-derived microparticles (EMPs). The results were further limited to human studies published in English or Chinese. Conference abstracts were excluded due to insufficient information. When multiple reports based on the same population were published, only reports with larger sample size were analyzed.

Data extraction

All relevant data from the included studies were extracted independently by two of the authors (S.L. and J.W.). We extracted the following data from each study: the first author's name, publication year, country, sample size, participant characteristics (age, gender, BMI, HbA1c, fasting glucose) and interested outcomes as described above. Disagreement was settled by consensus between the two reviewers.

Quality assessment

The methodological quality of included studies was assessed by the Newcastle-Ottawa Quality assessment scale (NOS), which consists of three factors: participant selection, comparability of the study groups, and exposure. A score of 0–9 was allocated to each study.

Statistical analysis

All statistical analyses were performed using Review Manager 5.3 (Cochrane Collaboration, Oxford, UK) and STATA version 12.0 (STATA, College Station, TX, USA). The standardized mean differences (SMDs) and their 95% confidence intervals (CIs) were used to compare continuous variables. Random-effect models were used in all pooled analyses in the study due to the significant clinical heterogeneity of the included studies. Subgroup analyses were conducted according to the co-morbidities of participants. Sensitivity assays and meta-regression analyses were performed when studies showed high heterogeneity. Publication bias was evaluated using the funnel plot, Egger's test and Begg's test.

Results

Literature selection

As shown in Fig. 1, 713 records were identified, and 48 studies involving 2,460 patients with type 2 diabetes and 1,880 non-diabetic controls were included in the systematic review [12–59]. Among them, data from 34 reports were meta-analyzed since the others [12, 14, 20, 23, 24, 29, 30, 33, 34, 37, 39, 40, 46, 58] did not provide available data for pooling the interested outcomes. Among the reports for qualitative analyses only, results of TMPs [26], PMPs [12, 20, 28–30, 33, 34, 39, 40, 58] and MMPs [26, 29, 32, 40] were controversial, while the results of LMPs [39, 58] and EMPs [14, 20, 23, 24, 26, 29, 37, 39, 40, 58] were consistent with each other.

The characteristics of included studies were shown in Table 1 and Table 2. Meanwhile, we briefly summarized the methodologies for MP detection and the special detection

Table 1. Characteristics of included studies. ACS, acute coronary syndrome; AMI, acute myocardial infarction; AS, atherosclerotic disease; CAD, coronary artery disease; DVC, diabetic vascular complications; ED, erectile dysfunction; ELISA, enzyme-linked immunosorbent assay; EMPs, endothelium-derived microparticles; HC, healthy controls; HP, hypertension; HPL, hyperlipidemia; LMPs, leukocyte-derived microparticles; MMPs, monocyte-derived microparticles; PMPs, platelet-derived microparticles; TMPs, the total microparticles; T2DM, type 2 diabetes mellitus; XaCT, factor Xa based clotting assay

Study ID	Country	Patient	Control	Detection method	Outcomes of study				
					PMPs	EMPs	LMPs	MMPs	TMPs
Nomura, S. 1995 [22]	Japan	T2DM	HC	Flow cytometry	✓				
Watala, C. 1998 [25]	Poland	T2DM	HC	Flow cytometry	✓				
Omoto, S. 1999 [19]	Japan	T2DM	HC	Flow cytometry	✓				
Nomura, S. 2000 [35]	Japan	T2DM	HC	Flow cytometry	✓				
Sabatier, F. 2002 [32]	France	T2DM	HC	Flow cytometry	✓	✓	✓	✓	✓
Diamant, M. 2002 [26]	Netherlands	T2DM	HC	Flow cytometry	✓	✓		✓	✓
Nomura, S. 2002 [44]	Japan	T2DM & HP	Non-DM & HP	Flow cytometry	✓			✓	
Nomura, S. 2003 [55]	Japan	T2DM & HPL	HC	Flow cytometry	✓			✓	
Shouzu, A. 2004 [47]	Japan	T2DM	HC	Flow cytometry	✓			✓	
Morel, O. 2004 [21]	France	T2DM & AMI	Non-DM & AMI	Prothrombinase assay	✓	✓	✓		
Morel, O. 2004 [21]	France	T2DM	HC	Prothrombinase assay	✓	✓			
Nomura, S. 2004 [45]	Japan	T2DM & HP	Non-DM & HP	Flow cytometry	✓			✓	
Nomura, S. 2004a [53]	Japan	T2DM & HP & HPL	Non-DM & HP & HPL	Flow cytometry	✓	✓			
Nomura, S. 2004a [53]	Japan	T2DM & HP	HC	Flow cytometry	✓	✓			
Nomura, S. 2004b [49]	Japan	T2DM & HPL	Non-DM & HPL	Flow cytometry	✓			✓	
Nomura, S. 2004c [16]	Japan	T2DM	HC	Flow cytometry	✓	✓			
Sommeijer, D.W. 2005 [46]	Holland	T2DM	HC	Flow cytometry	✓	✓		✓	
Koga, H. 2005 [17]	Japan	T2DM & CAD/non-CAD	Non-DM & non-CAD	Flow cytometry	✓	✓			
Tan, K.T. 2005 [12]	UK	T2DM & AS/non-AS	HC	Flow cytometry	✓				
Nomura, S. 2005 [43]	Japan	T2DM	HC	Flow cytometry	✓				
Nomura, S. 2005a [50]	Japan	T2DM & HP	Non-DM & HP	Flow cytometry	✓			✓	
Nomura, S. 2005b [51]	Japan	T2DM & HP	Non-DM & HP	Flow cytometry	✓	✓		✓	
Nomura, S. 2006 [52]	Japan	T2DM & HP	Non-DM & HP	Flow cytometry	✓			✓	
Koga, H. 2006 [36]	Japan	T2DM & non-CAD	Non-DM & non-CAD	Flow cytometry	✓				
Esposito, K. 2007 [20]	Italy	T2DM & ED	Non-DM & non-ED	Flow cytometry	✓	✓			
Nomura, S. 2007 [57]	Japan	T2DM	HC	Flow cytometry	✓	✓		✓	
Nomura, S. 2007 [57]	Japan	T2DM & HP	Non-DM & HP	Flow cytometry	✓	✓		✓	
Tushuizen, M.E. 2007 [31]	Netherlands	T2DM	HC	Flow cytometry	✓	✓			
Inami, N. 2008 [59]	Japan	T2DM & HPL	Non-DM & HPL	ELISA kit	✓				
Raturi, A. 2008 [34]	USA	T2DM	HC	Flow cytometry	✓				
Esposito, K. 2008 [24]	Italy	T2DM & ED	Non-DM & ED	Flow cytometry	✓	✓			
Razmara, M. 2008 [33]	Sweden	T2DM	HC	Flow cytometry	✓				
Shimazu, T. 2009 [48]	Japan	T2DM	Non-DM & HP	ELISA kit	✓				
Van Dreden, P. 2009 [30]	Australia	T2DM	HC	XaCT assay	✓				
Nomura, S. 2009 [13]	Japan	T2DM & HP	Non-DM & HP	Flow cytometry	✓	✓		✓	
Nomura, S. 2009a [56]	Japan	T2DM & HPL	HC	ELISA kit	✓				
Nomura, S. 2009b [54]	Japan	T2DM & HPL	Non-DM & HPL	Flow cytometry	✓	✓			
Tramontano, A.F. 2010 [14]	USA	T2DM & CAD	Non-DM & CAD	Flow cytometry	✓	✓			
Curtis, A.M. 2010 [29]	Ireland	T2DM	HC	Flow cytometry	✓	✓		✓	
Feng, B. 2010 [39]	China	T2DM	HC	Flow cytometry	✓	✓	✓		
Xiang, H. 2010 [27]	China	T2DM	HC	flow cytometry	✓	✓			
Xiang, H. 2010 [27]	China	T2DM & HP	Non-DM & HP	Flow cytometry	✓	✓			
Tripodi, A. 2011 [15]	Italy	T2DM	HC	Flow cytometry	✓				✓
Tsimerman, G. 2011 [18]	Israel	T2DM & DVC	HC	Flow cytometry	✓	✓			✓
Lanuti, P. 2012 [37]	Italy	T2DM	HC	Flow cytometry	✓	✓			
Chen, Y. 2012 [58]	China	T2DM & HP/Non-HP	HC	Flow cytometry	✓	✓	✓		
Jansen, F. 2013 [42]	Germany	T2DM & CAD	Non-DM & CAD	Flow cytometry	✓	✓			
Alkhatatbeh, M.J. 2013 [40]	Australia	T2DM & Obese	Non-DM & Obese	Flow cytometry	✓	✓		✓	
Lumsden, N.G. 2013 [28]	Australia	T2DM & ACS	HC	Flow cytometry	✓	✓			
Kurtzman, N. 2013 [38]	USA	T2DM & AS	HC	Flow cytometry	✓	✓	✓		
Zhang, X. 2014 [41]	UK	T2DM	HC	Flow cytometry	✓		✓	✓	
Berezin, A.E. 2015 [23]	Ukraine	T2DM	HC	Flow cytometry		✓			

Table 2. Clinical characteristics of participants in the included studies. Data are presented as mean (type 2 diabetic patients/ non-diabetic controls). BMI, body mass index; HbA1c, glycosylated hemoglobin A1c; NA, data not available

Study ID	Number	Female proportion (%)	Age (years)	BMI (kg/m ²)	Glucose (mmol/L)	HbA1c (%)
Nomura, S. 1995 [22]	18/18	44.40%/38.90%	55/42	NA/NA	NA/NA	NA/NA
Watala, C. 1998 [25]	33/37	36.36%/24.32%	48/41	27.8/21.8	9.7/5.33	8.74/5.47
Omoto, S. 1999 [19]	48/30	NA/NA	NA/NA	NA/NA	NA/NA	NA/NA
Nomura, S. 2000 [35]	37/20	59.50%/35%	56/48	25.4/23.3	NA/NA	7.8/4.8
Sabatier, F. 2002 [32]	52/47	50%/61.70%	57/44	28.8/22.0	8.9/4.0	NA/NA
Diamant, M. 2002 [26]	16/18	25%/22.20%	54/55	25.8/24.3	7.7/5.4	5.8/4.9
Nomura, S. 2002 [44]	23/25	NA/NA	NA/NA	NA/NA	NA/NA	NA/NA
Nomura, S. 2003 [55]	23/20	45%/47.80%	61/57	27.1/22.4	NA/NA	7.8/NA
Shouzu, A. 2004 [47]	73/50	58.90%/42%	54/51	22.9/22.4	NA/NA	7.9/4.9
Morel, O. 2004 [21]	19/33	5.26%/15.15%	67/59	27.8/27.9	9.95/5.66	NA/NA
Morel, O. 2004 [21]	22/50	NA/NA	63/42	NA/NA	NA/NA	NA/NA
Nomura, S. 2004 [45]	30/18	63.30%/44.40%	67/64	24.6/23.9	NA/NA	9.4/NA
Nomura, S. 2004a [53]	16/11	56.25%/45.45%	68/65	25.3/23.8	NA/NA	8.4/4.9
Nomura, S. 2004a [53]	14/25	71.43%/36%	66/56	24.5/23.7	NA/NA	8.9/4.6
Nomura, S. 2004b [49]	27/26	40.74%/42.31%	62/59	27.9/25.8	NA/NA	NA/NA
Nomura, S. 2004c [16]	65/40	58.50%/37.50%	55/50	22.9/22.7	NA/NA	7.8/4.7
Sommeijer, D.W. 2005 [46]	48/10	NA/NA	59/NA	29/NA	NA/NA	NA/NA
Koga, H. 2005 [17]	232/102	36.60%/45.10%	66.6/66.1	24.0/24.4	7.0/5.3	6.7/5.2
Tan, K.T. 2005 [12]	18/21/21	38.9%/38.1%/61.90%	71/68/67	25.1/29.5/NA	NA/NA/NA	NA/NA/NA
Nomura, S. 2005 [43]	53/30	54.70%/26.70%	55/52	24.3/22.2	NA/NA	7.9/4.7
Nomura, S. 2005a [50]	32/11	65.60%/72.70%	66/62	23.9/23.6	NA/NA	9.6/5.2
Nomura, S. 2005b [51]	28/10	57.10%/60%	65/60	23.7/23.8	NA/NA	9.5/5.4
Nomura, S. 2006 [52]	28/25	64.30%/64%	67/61	24.4/23.9	NA/NA	9.8/5.4
Koga, H. 2006 [36]	105/92	35.20%/43.50%	62.4/64.4	23.9/23.7	7.6/5.3	7.0/5.2
Esposito, K. 2007 [20]	30/20	0%/0%	57.2/53.9	29.6/27.4	9.4/5.8	8.2/5.2
Nomura, S. 2007 [57]	15/28	33.30%/35.70%	56/56	23.5/23.2	NA/NA	7.3/4.3
Nomura, S. 2007 [57]	40/33	55%/60.60%	66/61	23.9/23.7	NA/NA	8.6/5.1
Tushuizen, M.E. 2007 [31]	15/12	0%/0%	55/NA	NA/NA	NA/NA	7.1/NA
Inami, N. 2008 [59]	52/65	53.80%/64.60%	62/65	26.5/25.5	NA/NA	NA/NA
Raturi, A. 2008 [34]	10/10	NA/NA	NA/NA	NA/NA	NA/NA	NA/NA
Esposito, K. 2008 [24]	30/24	0%/0%	56.3/ 57.2	29.1/28.6	8.3/5.4	5.9/8.0
Razmara, M. 2008 [33]	12/12	66.70%/66.70%	58/59	26.1/25.0	12.0/4.6	6.2/4.6
Shimazu, T. 2009 [48]	30/38	46.70%/44.70%	63/61	27.4/25.1	NA/NA	7.1/4.8
Van Dreden, P. 2009 [30]	12/30	NA/53.3%	42/ 42	NA/NA	NA/NA	NA/NA
Nomura, S. 2009 [13]	176/183	58.50%/55.20%	65/62	24.4/23.9	NA/NA	8.2/5.3
Nomura, S. 2009a [56]	191/30	47.12%/43.33%	65/56	27.3/25.4	NA/NA	7.0/4.9
Nomura, S. 2009b [54]	76/50	46%/48%	66/55	27.4/25.9	NA/NA	7.2/4.8
Tramontano, A.F. 2010 [14]	20/20	50%/66.70%	63.7/70.8	33.5/27.5	7.9/5.9	NA/NA
Curtis, A.M. 2010 [29]	11/22/18	36%/19%/39%	51/64/57	NA/NA/NA	NA/NA/NA	7.2/7.1/5.3
Feng, B. 2010 [39]	63/29	52.40%/52%	61.7/58.9	24.0/23.6	NA/NA	9.3/4.9
Xiang, H. 2010 [27]	48/50	58.30%/66.00%	57.1/56.5	21.9/21.8	9.0/5.8	NA/NA
Xiang, H. 2010 [27]	50/46	64%/65.20%	55.7/56.2	22.5/23.7	8.3/5.4	NA/NA
Tripodi, A. 2011 [15]	60/60	36.70%/36.70%	64/59	NA/NA	7.7/NA	6.8/NA
Tsimerman, G. 2011 [18]	123/41	35%/63%	62/55	NA/NA	NA/NA	NA/NA
Lanuti, P. 2012 [37]	20/14	25%/50%	65.2/NA	28.6/NA	7.15/NA	6.5/NA
Chen, Y. 2012 [58]	39/24/20	64.1%/33.3%/65%	64.9/56.4/ 57.9	24.3/23.5/22.7	NA/NA/NA	9.4/9.3/5.0
Jansen, F. 2013 [42]	50/126	38%/27%	68.0/66.2	29.4/27.6	9.4/6.0	NA/NA
Alkhatatbeh, M.J. 2013 [40]	33/33	45.50%/45.50%	57.1/56.2	40.0/33.6	NA/NA	7.7/NA
Lumsden, N.G. 2013 [28]	15/16	6.70%/18.75%	57.6/58.3	33.2/23.4	8.66/5.10	NA/NA
Kurtzman, N. 2013 [38]	48/48	39.58%/62.50%	66/59	31.0/24.0	NA/NA	7.0/5.6
Zhang, X. 2014 [41]	10/20	20%/35%	62/51	31.0/31.0	NA/NA	NA/NA
Berezin, A.E. 2015 [23]	54/35	37%/34.30%	48.5/46.12	28.5/21.5	5.54/4.52	7.3/4.75

markers of the included studies, for online supplementary material, see www.karger.com/doi/10.1159/000452512, Table S1 and Table S2.

Quality assessment of included studies

The median score of NOS in each included study was 4 (ranged from 2 to 7). None of these retrospective studies mentioned the non-response rate. Only three studies [24, 28, 31] provided information about the blinding method of measurement. Ten studies described the matching information [12, 15, 20, 24, 26, 28, 31-33, 40], and the matching strategies were various. The details of quality assessment of each included study were shown in the supplementary material- Table S3.

Meta-analysis

Three studies compared the count of TMPs in 139 T2DM patients and 122 non-diabetic controls. The pooled TMP count in T2DM patients was significantly higher than that in the controls (SMD, 0.64; 95%CI, 0.12~1.15; P=0.02; Fig. 2A). Twenty-four studies investigated

Fig. 1. Flow diagram of studies identified, included and excluded.

the count of PMPs in 1,255 T2DM patients and 1,051 non-diabetic controls. The pooled circulating PMP count in T2DM patients was significantly higher than that in the controls (SMD, 1.19; 95%CI, 0.88~1.50; $P < 0.00001$; Fig. 2B).

Eleven studies reported the concentration of MMPs in 496 T2DM patients and 446 non-diabetic controls. The pooled plasma MMP count in T2DM patients was significantly higher than that in the controls (SMD, 0.92; 95%CI, 0.66~1.17; $P < 0.00001$; Fig. 2C). Fifteen studies detected the count of EMPs in 995 T2DM patients and 929 non-diabetic controls. The pooled EMP concentration in T2DM patients was also significantly higher than that in the controls (SMD, 0.73; 95%CI, 0.50~0.96; $P < 0.00001$; Fig. 2E). Four studies compared LMP counts in 129 patients with T2DM and 148 non-diabetic controls. However, the pooled data displayed no significant difference between the two study groups (SMD, 0.37; 95%CI, -0.15~0.89; $P = 0.17$; Fig. 2D).

Subgroup analysis and meta-regression

Subgroup analyses based on the characteristics of participants were introduced to explore the potential source of heterogeneity. We divided studies concerning TMPs, PMPs, MMPs, LMPs and EMPs into three subgroups: unspecified T2DM patients versus healthy controls, T2DM patients with co-morbidities versus healthy controls and T2DM patients with co-morbidities versus non-diabetic patients with co-morbidities. As shown in the supplementary material Table S4 and Fig. S1, all pooled results among subgroups were consistent with the overall analysis.

In order to further understand the roles of activated/apoptotic MPs in T2DM, we conducted the analyses on the subgroup of studies which detected annexin V positive or negative EMPs and PMPs. The result of EMPs was similar to the original analysis, whereas the annexin V⁺ PMP counts showed no significant difference between T2DM and non-diabetic controls (see supplementary material Fig. S2).

Univariable meta-regression analyses on each kind of MPs were performed with the covariates including publication year, sample size, female proportion, and the mean age, mean BMI and mean HbA1c in T2DM group. The meta-regressions by the mean age, mean BMI and

continued

mean HbA1c on TMPs and mean HbA1c on LMPs were dropped due to the insufficient data. However, no significant association between interested MPs and candidate covariates was found (see supplementary material Table S5 and Fig. S3).

Fig. 2. Forest plots and meta-analyses of each microparticle type for the type 2 diabetic patients compared with non-diabetic controls. (A. Forest plot and meta-analysis of TMPs; B. Forest plot and meta-analysis of PMPs; C. Forest plot and meta-analysis of MMPs; D. Forest plot and meta-analysis of LMPs; E. Forest plot and meta-analysis of EMPs). CI, confidence interval; EMPs, endothelium-derived microparticles; IV, inverse variance method; LMPs, leukocyte-derived microparticles; MMPs, monocyte-derived microparticles; Non-DM controls, non-diabetic controls; PMPs, platelet-derived microparticles; SD, standard deviation; Std. mean difference, standardized mean difference; TMPs, the total microparticles; T2DM, type 2 diabetes mellitus.

Sensitivity analysis and publication bias assessment

Sensitivity analyses were conducted to assess the robustness of our findings. In the 24 studies concerning PMPs, excluding one study at a time, the pooled SMDs were not substantially influenced by any of the individual study (see supplementary material Fig. S4A). Sensitivity analyses for reports concerning MMPs and EMPs confirmed the stability of results as well (see supplementary material Fig. S4B, S4C). We did not conduct the sensitivity analyses on studies with regard to TMPs or LMPs since too few literatures were included.

The funnel plots, Egger's tests and Begg's tests of the studies included in this meta-analysis that compared the counts of TMPs, PMPs, MMPs, LMPs and EMPs between T2DM patients and non-diabetic controls, respectively are showed in the supplementary material Fig. S5. Studies lie with an asymmetrical distribution around the vertical, indicating the potential publication bias may exist.

Discussion

Regardless of types of controls and co-morbidities, our systematic review indicated the counts of TMPs, PMPs, MMPs and EMPs, but not LMPs, significantly elevated in patients

with T2DM. This is the first systematic review evaluating the various MPs in T2DM patients comparing with those in non-diabetic controls. Although potential heterogeneity between studies exists, our results were robust in the subgroup analyses and sensitivity analyses, indicating the elevation of these MPs counts in T2DM was significant.

In T2DM patients, exposure to persistent hyperglycemia leads to organ damage associated with oxidative-stress-induced apoptosis [2, 60], which participates in the release of various cell-derived MPs. Annexin V, a typical marker of apoptosis, was used as a marker of plasma apoptotic MPs in most of the studies on MPs. Three studies in the current analysis indicated that TMPs, labeled with annexin V, were higher in T2DM patients compared with non-diabetic controls. Although the mechanisms are not completely elucidated, the increased level of circulating MPs in T2DM could be at least partially related to hyperglycemia-associated cell apoptosis and associated dysfunction in coagulation, inflammation, autoimmunity and endothelium [9, 61, 62]. Meanwhile, the relationship between the elevated MP count and the pathogenesis of T2DM could not be denied.

PMPs constituted the majority of total plasma MPs, served as the typical marker of platelet activation [63]. Our analyses suggested that annexin V negative PMPs, but not annexin V positive PMPs, were significantly elevated in T2DM patients. Since only participants without thrombotic disease were enrolled in the included studies, it indicated that diabetes might be associated with the impaired platelet function and excessive activation of platelets, which had been confirmed by previous studies [19, 22, 64]. Furthermore, some investigators found PMPs were also elevated in patients with atherosclerosis or other diabetic macro- and micro-vascular complications [16, 18, 22, 38, 65, 66], which suggested that elevated PMPs might be associated with hyperglycemia-induced organ damage in T2DM patients.

MPs derived from activated or apoptotic endothelial cells varied in immunophenotype [67-69]. Generally, CD31 and CD105 were used as markers of apoptotic EMPs, while CD62E was used as the marker of activated EMPs [67]. Subgroup analyses for CD molecular markers were not performed because of insufficient data, and the subgroup analysis based on annexin V positive or negative EMPs showed no significant difference compared with original analysis. However, instead of activated EMPs, apoptotic EMPs counts were significantly elevated in T2DM patients according to the original reports [14, 24, 39]. Moreover, the increased ratio of CD62E⁺/CD31⁺ EMP counts in T2DM patients also reflected an increased apoptotic activity in diabetes [14, 23, 24].

Our study also has several limitations. Firstly, the methodology for detecting MPs varies among the included studies. A standardized method with stable results and convenient procedure is needed before using MP as a biomarker of diabetes. Secondly, the strength of the pooled results was restricted by the low reporting quality of included studies. Thirdly, a potential publication bias was detected by both funnel graph and Egger's test, which might result in an overestimation of the association. Nevertheless, the robustness of our results was confirmed by sensitivity analyses. Fourthly, most of the included studies were cross-sectional, and the causation between MPs changes and T2DM could hardly be drawn. Some longitudinal cohort studies are required to demonstrate how these MPs participate in the pathogenesis of T2DM and its associated organ damage.

Conclusions

In summary, counts of TMP, PMP, MMP and EMP in T2DM patients were significantly higher than those in non-diabetic controls. It indicated MPs may play a role in the pathogenesis of T2DM or its complications, which was associated with coagulation, immune and endothelial dysfunction. A standard, convenient and stable methodology for detecting each MP is essential in the future investigations before they can be used as conventional biomarkers of T2DM and associated organ damages. And subsets of each MP in longitudinal observation are still required to further explore the pathogenesis of diabetes and its complications.

Abbreviations

BMI (body mass index); CD (clusters of differentiation); CI (confidence interval); EMPs (endothelium-derived microparticles); HbA1c (glycosylated hemoglobin A1c); LMPs (leukocyte-derived microparticles); MeSH (medical subject heading term); MMPs (monocyte-derived microparticles); MPs (cell-derived microparticles); NOS (Newcastle–Ottawa Quality assessment scale); PMPs (platelet-derived microparticles); TMPs (the total microparticles); SMD (standard mean difference); T2DM (type 2 diabetes mellitus).

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Disclosure Statement

The authors report no conflict of interest.

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