Mesenchymal Stem Cells Transplantation in Diabetic Kidney Diseases: A Systematic Review and Meta-analysis

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Research

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Abstract

Background: Mesenchymal stem cells (MSCs) therapy shows great promise for diabetic kidney diseases (DKD) patients. Researches have been carried out on this topic in recent years. The main thrust of this paper is to evaluate the therapeutic effects of MSCs on DKD by a meta-analysis and systematically review the mechanism therein.

Method: An electronic search of PubMed and U.S National Library of Medicine (NLM) was performed for all articles about the MSCs therapy for DKD without species limitation up to January, 2020. Data were pooled for analysis with Stata SE 12.

Result: MSCs-treated group showed great significant hypoglycemic effect at 1 week, 2 weeks, 3 weeks, 1 month, 2 months, 3 months and 6 months. Total hypoglycemic effect was analyzed (SMD=-1.954, 95%CI: -2.389 to -1.519, I^2= 85.1%, p□0.001). Total effects on serum creatinine (SCr), blood urea nitrogen (BUN) were analyzed, suggesting MSCs decreased the SCr and BUN and had an effect on amelioration of impaired renal function (SCr: SMD= -4.838, 95%CI: -6.789 to -2.887, I^2= 90.8%, p□0.001; BUN: SMD= -4.912, 95%CI: -6.402 to -3.422, I^2= 89.3 %, p□0.001). Creatinine clearance rate (CCr) was found decreased in the MSCs-treated group at 2 months. MSCs therapy decreased the excretion of urinary albumin. The fibrosis indicators were detected, and the result showed that transforming growth factor-β, Collagen-I, fibronectin and α-smooth muscle actin were seen decreased significantly in the MSCs-treated group.

Conclusion: MSCs might improve animal body weight, glycemic control and pancreas islets function to secrete insulin, and reduced the SCr, BUN, CCr, urinary protein and renal hypertrophy. MSCs can reduce the expression of inflammatory mediators and alleviate renal fibrosis. MSCs therapy is a potential treatment for DKD.

Introduction

Diabetes mellitus (DM) is a chronic disease with high morbidity and mortality worldwide and imposes a tremendous economic burden. The kidney is one of the organs most often affected by DM [1]. Abnormal blood glucose status leads to oxidative stress and the release of inflammatory mediators, which subsequently extends to diabetic kidney lesions. Reducing cardiovascular risk, controlling blood glucose and blood pressure and inhibiting the renin-angiotensin system (RAS) are main arenas of clinically conventional approaches to treat diabetic kidney diseases (DKD) [2].

Uncovered a promising potential in various diseases, regenerative medicine has been thrown into sharp focus. Stem cells are self-renewing and self-replicating cells with pluripotency, can be divided into embryonic stem cells, adult stem cells, and induced pluripotent stem cells according to their origin. Among them, adult stem cells, the undifferentiated cells in differentiated tissues, can be isolated from bone marrow, adipose tissue, umbilical cord blood and deciduous teeth and so on. Mesenchymal stem cells (MSCs) have been used in tissue regeneration and repair [3], inflammatory disease [4], anti-transplant rejection [5] and other diseases.

For DKD, MSCs therapy offers an alternative solution as well, primarily displaying its remarkable properties in regeneration capacity and paracrine action on immunomodulation and secretion of trophic factors [6]. Accumulating researches have been carried out on this topic in recent years. We use meta-analysis and systematic review to study the effects of MSCs therapy on DKD.

Search strategy

We searched PubMed and U.S National Library of Medicine (NLM) through January, 2020 for original papers that assessed the effects of MSCs transplantation on DKD animal models or patients without language restrictions. Key words in this research included: (mesenchymal stem cells OR MSC OR multipotent stromal cells OR mesenchymal stromal cells OR mesenchymal progenitor cells OR Wharton jelly cells OR adipose-derived mesenchymal stem cells OR bone marrow stromal stem cells) AND (diabetic nephropathy OR DN OR diabetic kidney disease OR DKD).

Randomized controlled trials, comparative studies or controlled trials which assessed the efficacy or safety of MSCs therapy for treatment as interventions on DKD animal models without species limitation or patients with DKD were included. Biochemical data of renal function or adverse events were expected in included studies. Though DM was diagnosed, albuminuria and impaired renal functions occurred in the patients or animals were included. The clear distinction of DKD and diabetic nephropathy (DN) was outside the scope of this paper, and both of them were included. Reviews or case reports or meta-analysis or comments or letters were excluded. Articles studied embryonic stem cells, induced pluripotent stem cells or components from MSCs for treatment of DKD were excluded. Besides, lack of a control arm or essential data like renal functions and sample size were also not allowed for entry. Additional reports were also checked by browsing the references in the articles.

Data extraction

The main features of included studies were summarized, and the data were extracted independently by two authors using a standardized datasheet. Adverse events and the data of biochemical indicators were extracted from the articles, like blood glucose, creatinine clearance rate (CCr), serum creatinine (SCr), blood urea nitrogen (BUN), U-Albumin/U-Creatinine ratio (U-ACR), microalbumin, urinary albumin excretion, urine protein/Cr, kidney weight, body weight, kidney weight/body weight ratio, etc. On the condition of no specific information, data were obtained by measuring the chart in the papers or getting contact with primary authors. Any divergences were resolved by the third author.

Validity and quality assessment

For clinical trials, quality assessment was performed by 4 scales with the Jadad Scale [7], including randomization, concealment of allocation, blinding method and description of withdrawals and dropouts. A total score of ≥ 3 was considered as high quality.

For animal studies, the methodological quality assessment was carried out by a Risk of Bias (RoB) tool, the SYstematic Review Centre for Laboratory animal Experimentation (SYRCLE), adjusted for the animal

experiments on the basis of the Cochrane RoB tool. Ten entries were assessed, including: 1) Sequence generation: Were the subjects randomly assigned to the case or control groups with an adequate generation of allocation sequence? 2) Baseline characteristics: Were the baseline characteristics of two groups comparable? 3) Allocation concealment: Was the allocation of all the subjects adequately concealed? 4) Random housing: Were all the subjects randomly housed in same environment during the experiment? 5) Researchers blinding: Were the researchers blinded to which subjects had received MSCs treatment? 6) Random outcome assessment: Were the outcome assessments of the subjects given in a random order? 7) Outcome assessors blinding: Were the outcome assessors blinded to the group information? 8) Incomplete outcome data: Were incomplete outcome data or the dropouts adequately addressed? 9) Selective outcome reporting: Was the study free of reporting selective outcome with significant results? 10) Other sources of bias: Was the study apparently free of other problems that could result in high risk of bias, such as contamination of MSCs, inappropriate influence of funder, units of analysis errors, design-specific risks of bias and additional animals to replace drop-outs? An answer of “YES” means a low risk of bias while “NO” means a high risk of bias, and the “unclear” means the risk of bias cannot assess for lacking sufficient information. Disagreement was solved by consensus-oriented discussion.

Statistical analysis

Stata SE 12 was used for statistical analysis. For continuous variables, standard mean differences (SMD) were obtained by pooling the results of mean values, standard deviations, and sample sizes. For binary data, odds ratio (OR) was calculated. Moreover, 95% confidence intervals (95% CI) between MSCs-treated groups and control groups were counted. Corresponding to multiple MSCs-treated groups in an article, the data in the control group were reused. Heterogeneity across studies was quantified using I^2, and was considered significant at p-value 0.1. The data were pooled using a fixed-effect model was utilized without heterogeneity, or a random-effect model was used. p-value < 0.05 was regarded statistically significant for all analyses. For the robustness of the results, sensitivity analysis was tested by omitting each individual trial at a time. Potential publication bias was assessed by Begg funnel plot, Egger regression and Trim and Fill.

Results

Search result

Totally 33 trials in 29 publications were included among which there were 28 animal studies [8-35] and 1 clinical trial [36]. In addition, there are 4 on-going clinical trials registered on NLM.

Among 32 trials of animal studies, the animal models in 24 trials were rats, 7 were mice and 1 was rhesus macaques. A single method or a combination of multiple methods was used to induce DM, including streptozotocin (STZ) injection, high-fat diet (HFD) dietary induction, nephrectomy and natural development of models. However, the dosage and frequency of STZ injection, the timing of detecting

establishment of DN were different. Although MSCs were used in all the included trials, the details of source, dosage, frequency, administration and point in time varied. The sources of MSCs were bone marrow mesenchymal stem cells (BM-MSCs) in 22 trials, adipose-derived stem cells (ADSCs) in 4 trials, human umbilical cord blood-derived mesenchymal stem cells (hUCB-MSCs) in 5 trials, exfoliated deciduous teeth stem cells in 1 trial. Allogeneic transplantation was used in 23 trials while xenoplastic transplantation was used in 8 trials and autologous transplantation was used in 1 trial. The characteristic of included animal trials was summarized in Figure 1A.

The only 1 clinical trial, the multicenter, randomized, double-blind, dose-escalating, sequential, placebo-controlled study, was finished in 2016. Two doses of allogeneic mesenchymal precursor cells were separately infused into 10 patients with type 2 diabetes and advanced DN, and the efficacy and adverse events were observed. The main features of the clinical trial were showed in Figure 1B.

In animal experiments, allogeneic transplantation was seen in 23 trials while xenoplastic transplantation was 8 trials, and autologous transplantation was 1 trial. The only 1 included clinical trial was allogeneic transplantation. None of them reported the occurrence of graft-rejection after transplantation, but 2 MSCs-treated patients developed antibodies specific to the donor HLA in the clinical trial, but one transiently occurred while the other presented at baseline and persisted throughout the observation period without the appearance of adverse events. But strangely, antibodies specific to the donor HLA were also found in one placebo-treated patient. Six animal experiments specified the deaths or dropouts. Lang et al reported 6 deaths of model rats during the construction of diabetes model [22] while Wang et al reported 1 death in both MSCs-treated group and DN group besides 2 deaths because of anesthesia [16]. In the study of Li et al, there was 1 rats dead in the DN group and 2 in the MSCs-treated group [27]. During a 12-week observation, the mortality in the MSCs-treated group (75.0%, 9/12) was lower than that in the DN-group (33.3%, 4/12) [28]. Similarly, Xian et al found 2 deaths in the hUCB-MSCs group, which was obviously less than the T1DM group (6 deaths) at the end of the study [29]. An et al found no marked change in the immune system of rhesus macaques in the hUCB-MSCs treatment for DN models [34].

Quality assessment

Quality assessment of animal experiments and clinical trial were performed Table 2A and Table 2B. Table 2A showed a number of “unclear” in the quality assessment of animal experiments, and especially, the outcome assessment in a random order, concealment of allocation and outcome assessors blinding in all included experiments stayed unclear, largely due to absent awareness of randomization and blind method in animal experiments. In Table 2B, a total of 7 scores suggested high methodological quality of the included clinical trial.

Assessment of glucose

Glucose was almost detected after the MSCs treatment, except for 2 studies [27, 32]. Sixteen studies measured glucose for once at the end of the experiment [13-16, 18-24, 26, 28-31]. Seven studies had conducted blood glucose monitoring at several points in time [9-12, 17, 25, 35]. Five trials, 7 trials, 5 trials,

12 trials, 17 trials, 7 trials and 2 trials were respectively included to assess the effect of reducing blood glucose level at 1 week, 2 weeks, 3 weeks, 1 month, 2 months, 3 months and 6 months, all of which showed great significant hypoglycemic effect in the MSCs-treated group (1-week: SMD=-1.484, 95%CI: -2.586 to -0.381, I^2=80.6%, p□0.001; 2-week: SMD=-2.312, 95%CI: -3.743 to -0.882, I^2=89.6%, p=0.002; 3-week: SMD=-1.484, 95%CI: -2.586 to -0.381, I^2=80.6%, p□0.001; 1-month: SMD=-1.740, 95%CI: -2.660 to -0.821, I^2=83.8%, p□0.001; 2-month: SMD=-1.83, 95%CI: -2.633 to -1.028, I^2=86.0%, p□0.001; 3-month: SMD=-1.649, 95%CI: -2.838 to -0.461, I^2=84.6%, p=0.007; 6-month: SMD=-3.045, 95%CI: -5.895 to -0.195, I^2=76.4%, p=0.036). Total hypoglycemic effect was also analyzed (SMD=-1.954, 95%CI: -2.389 to -1.519, I^2= 85.1%, p□0.001). (Figure 1)

Assessment of serum creatinine (SCr)

There were 4 trials, 2 trials and 5 trials included in the assessment of SCr at 1 month, 2 months and 3 months. All of them showed statistically significant lower creatinine value in the MSCs-treated group (1-month: SMD=-4.126, 95%CI: -7.936 to -0.315, I^2=76.4%, p=0.034; 2-month: SMD=-3.506, 95%CI: -4.735 to -2.278, I^2=1.8%, p□0.001; 3-month: SMD=-6.736, 95%CI: -10.311 to -3.162, I^2=89.0%, p□0.001). Total effect on SCr was also analyzed, suggesting MSCs decreased the SCr and improved the renal function (SMD= -4.838, 95%CI: -6.789 to -2.887, I^2= 90.8%, p□0.001). (Figure 2)

Assessment of blood urea nitrogen (BUN)

Five different timing points of BUN were evaluated with relatively few trials included in each. At 2 weeks (2 trials included), 3 weeks (2 trials included), 1 month (2 trials included), 2 months (3 trials included), and 3 months (4 trials included), BUN decreased in the MSCs-treated group, though no statistical significance was seen at 3 weeks and 1 month (2-week: SMD=-2.463, 95%CI: -3.292 to -1.634, I^2=37.3%, p□0.001; 3-week: SMD=-4.432, 95%CI: -9.220 to -0.356, I^2=92%, p=0.070; 1-month: SMD=-10.392, 95%CI: -21.247 to -0.464, I^2=95.6%, p=0.060; 2-month: SMD=-3.389, 95%CI: -6.679 to -0.099, I^2=89.8%, p=0.044; 3-month: SMD=-5.902, 95%CI: -8.988 to -2.815, I^2=85.0%, p□0.001). Total effect on BUN was also analyzed, suggesting MSCs decreased the BUN (SMD= -4.912, 95%CI: -6.402 to -3.422, I^2= 89.3 %, p□0.001). (Figure 3)

Assessment of creatinine clearance rate (CCr)

The data of six trials were pooled to evaluate the CCr at 2 months after MSCs treatment, and CCr could be seen decreased significantly in the MSCs-treated group when comparing to the DKD group (2-month: SMD=-1.881, 95%CI: -2.842 to -0.921, I^2=79.7%, p□0.001). (Figure 4)

Assessment of blood insulin level

Two trials were included in the assessment of insulinemia. The insulin level increased at 3 months after MSCs treatment though the significance was not notable (3-month: SMD=3.051, 95%CI: -0.091 to 6.193, I^2=90.3%, p=0.057).

Assessment of urine protein

The measurement of urine protein varied in the included studies. Microalbumin, urinary albumin excretion, urinary albumin/urinary creatinine ratio and urinary protein/creatinine ration were used to assess the urine protein excretion in the DKD animals.

Urinary albumin excretion at 1 month (2 trials included) and at 2 months (7 trials included) were observed lower in the MSCs-treated group than the DKD group, though no significance of the 1-month was seen (1-month: SMD=-6.507, 95%CI: -17.935 to 4.921, I^2=98.3%, p=0.264; 2-month: SMD=-4.386, 95%CI: -5.891 to -2.881, I^2=85.5%, p□0.001). Total effect on urinary albumin excretion was also analyzed, suggesting MSCs decreased the urinary albumin excretion (SMD= -4.830, 95%CI: -6.602 to -3.058, I^2= 92.5%, p□0.001).

Microalbumin was detected at 3 weeks and 3 months, both of which had 2 trials satisfied the inclusion. Microalbumin was found decreased in the MSCs-treated group at 3 months (3-week: SMD=-9.112, 95%CI: -21.627 to 3.404, I^2=95.3%, p=0.154; 3-month: SMD=-4.431, 95%CI: -5.771 to -3.091, I^2=0.0%, p□0.001). Total effect on microalbumin was analyzed, suggesting the microalbumin was significantly lower in the MSCs-treated group than that in the DKD group (SMD= -5.791, 95%CI: -8.681 to -2.901, I^2= 86.3%, p□ 0.001).

Urinary albumin/urinary creatinine ratio at 1 month (6 trials included) and at 2 months (10 trials included) were observed significantly lower in the MSCs-treated group (1-month: SMD=-2.419, 95%CI: -3.070 to -1.769, I^2=0.0%, p□0.001; 2-month: SMD=-2.648, 95%CI: -3.454 to -1.842, I^2=58.9%, p□0.001). Total effect on urinary albumin/urinary creatinine ratio was analyzed, which suggested that the urinary albumin/urinary creatinine ratio was significantly lower in the MSCs-treated group than that in the DKD group (SMD= -2.539, 95%CI: -3.075 to -2.003, I^2=42.6%, p□0.001).

Urinary protein/creatinine ratio was found no statistical difference at 2 weeks (2 trials included) after MSCs treatment (SMD=-2.779, 95%CI: -7.617 to 2.059, I^2=92.6%, p=0.260).

Assessment of kidney weight

Kidney weight and kidney weight/body weight ratio were used to assess the kidney hypertrophia. No significance was found on the kidney weight at 1 month (2 trials included) between two groups after MSCs treatment (SMD=-0.674, 95%CI: -2.052 to 0.704, I^2=67.0%, p=0.337).

Kidney weight/body weight ratio was found significantly decreased in the MSCs-treated group at 2 months (8 trials included, SMD=-1.364, 95%CI: -2.164 to 0.565, I^2=79.7%, p=0.001), while no statistical difference was found at 3 months (2 trials included, SMD=-10.012, 95%CI: -29.753 to 9.729, I^2=97.0%, p=0.32) between two groups. Total effect on kidney weight/body weight ratio was analyzed, which suggested lower kidney weight/body weight ratio was found in the MSCs-treated group (SMD=-1.624, 95%CI: -2.594 to -0.655, I^2= 86.9%, p=0.001).

Assessment of body weight

There were 3 trials and 5 trials included in the assessment of 1-month and 2-month body weight. No significance was found on 1-month body weight between two groups (SMD=2.634, 95%CI: -0.730 to 5.999, I^2=95.5%, p=0.125). At 2 months, the body weight in the MSCs-treated groups significantly increased when compared to the DKD groups (SMD=0.869 95%CI: 0.442 to 1.296, I^2=40.2%, p□0.001). Total effect of MSCs treatment on body weight was also analyzed (SMD=1.499, 95%CI: 0.461 to 2.536, I^2= 87.3%, p=0.005).

Assessment of renal fibrosis

Four trials were included to evaluate the glomerulosclerosis% at 2 months after MSCs treatment, and no significance was found (SMD=-0.350 95%CI: -4.173 to 3.473, I^2=96.2%, p=0.858).

TGF-β was detected at different points in time in different method. At 1 month (2 trials included) and 2 months (3 trials included) by PCR, and at 2 month (2 trials included) by WB, TGF-β was seen decreased significantly in the MSCs-treated group (1-month PCR: SMD=-3.258, 95%CI: -4.133 to -2.383, I^2=4.2%, p□ 0.001; 2-month PCR: SMD=-7.594, 95%CI: -13.274 to -1.915, I^2=93.6%, p=0.009; 2-month WB: SMD=-9.287, 95%CI: -11.322 to -7.252, I^2=16.2%, p□0.001). Total expression of TGF-β was also analyzed (SMD=-6.839, 95%CI: -9.367 to -4.312, I^2= 90.5%, p□0.001).

Col-I was detected by IHC and PCR. At 2 months by PCR (3 trials included), Col-I was significantly decreased (SMD=-11.468, 95%CI: -13.685 to -9.252, I^2=41.3%, p□0.001) in the MSCs-treated group while no significance was found at 2 months by IHC (2 trials included) between two groups (SMD=-4.714, 95%CI: -10.670 to 1.242, I^2=95.3%, p=0.121). Total expression of Col-I was also analyzed (SMD= -9.081, 95%CI: -14.233 to -3.929, I^2= 95.1%, p=0.001).

Three trials were included to evaluate fibronectin (FN) by IHC at 2 months after MSCs treatment, and statistically significant decreased was found in the MSCs-treated group (SMD=-7.781, 95%CI: -10.680 to -4.881, I^2=71.3%, p□0.001).

Two trials were included to evaluate α-SMA by WB at 1 month after MSCs treatment while 3 trials included at 2 months by PCR. Both of them were seen statistically significant decreased was found in the MSCs-treated group (1-month WB: SMD=-2.514, 95%CI: -3.550 to -1.479, I^2=0.0%, p□0.001; 2-month PCR: SMD=-2.098, 95%CI: -3.721 to -0.476, I^2=83.4%, p=0.011). Total effect of MSCs treatment on the expression of α-SMA was analyzed (SMD= -2.249, 95%CI: -3.311 to -1.186, I^2= 72.1%, p□0.001).

E-cadherin was detected by WB at 1 month (2 trials included) after MSCs treatment, and it was found notable significance in decrease of E-cadherin deposition (SMD=3.600, 95%CI: -2.338 to 4.861, I^2=0.0%, p□ 0.001).

Assessment of inflammatory mediator

Monocyte chemokine protein-1 (MCP-1) was detected by IHC at 2 months (2 trials included) after MSCs treatment, no significance was found between two groups (SMD=-8.913, 95%CI: -20.994 to 3.167,

I^2=93.1%, p=0.148).

TNF-α was detected by ELISA at 2 weeks (3 trials included) and by PCR at 1 month (2 trials included) after MSCs treatment, both of which were seen statistically significant decreased was found in the MSCs-treated group (2-week ELISA: SMD=-3.853, 95%CI: -7.207 to -0.499, I^2=90.4%, p=0.024; 1-month PCR: SMD=-3.7279, 95%CI: -4.684 to -2.769, I^2=57.5%, p□0.001). Total effect of MSCs treatment on the expression of TNF-α was analyzed (SMD= -4.027, 95%CI: -5.955 to -2.098, I^2= 84.9%, p□0.001).

Risk of bias

Given the sufficient data to assess publication bias, 2-month blood glucose was used to measure. There was a bias prompted by moderate asymmetry of the funnel plot, and the Egger's test showed p=0.013. However, Trim and Fill didn't identify any missing study (Figure 5).

Discussion

MSCs treatment is highly likely to be a prospective therapeutic approach from the stand of mechanism. A concomitant apoptosis of stem cells can be seen in patients with DKD. The treatment based on MSCs from DM mice could not alleviate the kidney damage in DM mice, which might result from abnormal endogenous bone marrow MSCs caused by the high glucose (HG). Monitoring MSCs subsets in the peripheral blood was suggested to predict the diabetic progression and the effectiveness of the therapy [25, 37]. Many studies were conducted to figure out the mechanism of MSCs therapy, and one caveat is that a slight move in one part may affect the situation as a whole.

Immunomodulation

1.Anti-inflammation

The infiltration of renal macrophages and the expression of inflammatory cytokines were effectively inhibited by early intervention of MSCs in DM rats through the immune regulation and paracrine secretion of renal protective factors, restoring the homeostasis of immune microenvironment [27]. The failure of inflammatory regression may matter DM and its complications, and BM-MSCs could block the exacerbation of DKD through the LXA4-ALX/FPR2 axis to inhibit glomerulosclerosis and secretion of proinflammatory cytokines[28].

1.1 Mononuclear phagocytes

Monocyte subsets mainly include: 1. $CD14^{++}CD16^{-}$ (classical). In the early stage of inflammation, $CD14^{++}CD16^{-}$ cells act as inflammatory reactions like phagocytosis and production of reactive oxygen species (ROS). 2. $CD14^{+}CD16^{++}$ (non-classical). $CD14^{+}CD16^{++}$ cells are believed to be the source of resident macrophages. 3. $CD14^{++}CD16^{+}$. $CD14^{++}CD16^{+}$ cells are considered an intermediate phenotype between classical and non-classical subsets, indicating that 3 subsets are monocytes of different stages

during maturation. The accumulation of $CD14^{+}CD16^{++}$ may be involved in the pathogenesis of chronic inflammation [38]. In DM patients, the proportion of monocytes characterized with $CD14^{++}CD16^{+}$ and $CD14^{+}CD16^{++}$ was found higher than the normal control ones. MSCs increased the expression of anti-inflammatory gene, promoted the proliferation of monocytes and transference into M2 phenotype by activating the expression of cytokines like IL-10, IGF-1 and VEGF [39]. Not only elevating arginase 1 (Arg1), the markers of M2 macrophages, MSCs also reduced M1 level [31,33]. MSCs could restore Mφ autophagy and mitochondria bioenergetics in DN mice, alter Mφ into the M2 phenotype via TFEB-mediated autophagy and thereby inhibit inflammatory response [40]. The overexpression of Arg1 reversed the inhibition of the peroxisomal proliferator-activated receptor gamma coactivator 1α (PGC-1α) in tubular epithelial cells (TECs), thereby correcting the mitochondrial dysfunction of TECs. MSCs treatment was reported to be able to effectively inhibit the expression of MCP-1 and macrophages infiltration in the kidney [31], while elevated expressions of MCP-1 and IL-8 were also reported [24].

1.2 Inflammatory factor

ADSCs could inhibit the expression of pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α, and systematically increase the expression of anti-inflammatory cytokines IL-10 as well [18, 33]. The epithelium-mesenchymal transdifferentiation (EMT) of podocyte in DN was considered associated with stromal interaction molecule (STIM) mediated by FcγRII. In the MSCs-treated group, while the expression of FcRIIb, which could inhibit inflammation, was upregulated, and STIM and FcγRIIa, which could activate inflammation, was contrarily downregulated. Silence of STIM1 or STIM2 by siRNA alleviated the EMT induced by high glycose and inhibited activation of FcκRII in vitro [41].

1.3 Inhibition of oxidative stress

Experiments demonstrated that mitochondria from BM-MSCs given systematically was transferred into proximal tubular epithelial cells [42], indicating the mitochondria and its relevant functions might occupy a position in the therapeutic effect of MSCs. Mitochondria from MSCs could enhance the expression of superoxide dismutase 2 (SOD2) and Bcl-2 in vitro, inhibiting the production of reactive oxygen species (ROS) and cell apoptosis in PTECs under the condition of high glucose. Besides, megalin and SGLT-2 were also restored to improve blood glucose control and anti-inflammatory effect, especially the reduction of IL-16 [34, 42].

ADSCs reduced oxidative damage and inflammatory response of DN rats induced by STZ via inhibiting the p38/MAPK signaling pathway [13]. Exosomes from MSCs increased the expressions of LC3 and Beclin-1 and decreased the expressions of mTOR and fibrosis markers, but with inhibition of autophagy, the protective action was weakened [43]. Melatonin could help enhance the antioxidative and anti-fibrosis effect of MSCs, manifesting as increased SOD1 and Beclin-1, decreased TGF-β and carboxymethyllysine, a marker of advanced glycation end product [26].

2.Regeneration

MSCs could home to pancreas and kidneys in the MSCs therapy for DKD [10]. Vascularization and function of islet graft could be promoted by MSCs transplantation [44].

MiRNA-451a extracted from MSCs-microvesicles (MVs) might reactivate cell cycles which had been blocked and reverse EMT by inhibiting cell cycle inhibitors P15INK4b (P15) and P19INK4d (P19) by targeting 30-UTR locus [45]. MiRNA-124a is involved in the development of organ identity and affects the differentiation genes of BM-MSCs, having been found as a synergist of MSCs transplantation. Treatment of BM-MSCs + miRNA-124a could inhibit high expression of Notch pathway signaling molecules induced by HG, such as Notch1, NICD, Hes1 and Delta, and reduce kidney damage and podocyte apoptosis [46]. It was also reported that PI3K/Akt/mTOR signaling pathway might participate in the inhibition of abnormal apoptosis and autophagy in the BM-MSCs + miRNA-124a therapy in podocyte injury [47]. In addition, the anti-fibrosis effect of BM-MSCs was enhanced by miRNA-124a, which was potentially related to the suppression of cav-1 and β-catenin activation. ADSCs alleviated DN renal injury by activating klotho and inhibiting Wnt/β-catenin signaling pathway, and klotho gene knockout decreased the expressions of apoptosis-regulated proteins and members of the Wnt/β-catenin signaling pathway [48].

3. **Secretion of tropic factors**

Increasing evidence shows an important role of MSCs paracrine in the treatment of diseases. hUCB-MSCs conditional medium (CM) inhibited NRK-52E EMT induced by TGF-β1 in a concentration-dependent manner [14]. As mentioned before, the dysfunction of stem cells was observed in DM patients, but WJs, a mixture of growth factors, extracellular matrix and exosomes extracted from human umbilical cord, could improve BM-MSCs abnormality in proliferation, cell motility, endoplasmic reticulum, mitochondria degeneration, endoplasmic reticulum function and exosomes secretion [25]. ADSCs-CM decreased the expression of caspase-3, ameliorated podocytes apoptosis in a dose-dependent way and maintained the normal podocytes morphology. However, after blocking epithelial growth factor (EGF), one of the soluble cytoprotective factors secreted into CM, the influence of ADSCs-CM was significantly reduced in the podocytes dealt with HG [49]. There are various materials in CM. Vesicles extracted from CM are considered a dominant part in the therapeutic effect of MSCs and instrumental in intercellular communication [23, 45, 50].

Exosomes significantly increased the expression of LC3 and Beclin-1 and significantly decreased the expression of mTOR and fibrosis markers, which was eliminated by chloroquine and 3-MA, the autophagy inhibitors [43]. However, an opposite opinion was put forward, declaring that not much difference was found in the inhibition of MSCs-CM on proinflammatory factors and chemokines with or without extracellular vesicles (EV) depletion, indicating that might not be mediated by MSCs-EV [51].

MSCs secreted hepatocyte growth factor (HGF) to inhibit the expression of TGF-β1 in mesangial cells treated with HG, thus reduced the expression of GLUT1 and the absorption of glucose [19]. It was reported that BMP-7 which improved diabetic glomerular fibrosis by inhibiting TGF-β/Smad signaling pathway secreted by MSCs might reduce podocyte damage in type 1 diabetic nephropathy rats [16, 21]. PAI–1 was potentially induced by TGF-β1 and could promote the accumulation of ECM. Therefore, the balance of

fibrinolytic system might be one of the mechanisms [22]. Growth factors paracrine such as VEGF, TGF-β and TNF-α also improved renal function in DN rats [20].

Since the amount of stem cell transplantation is small, to reverse renal injury completely seems unpractical. It was reported that hyperglycemia and hypoinsulinemia had remained when giving MSCs transplantation throughout the study period [10], and no significant effect on lowering blood glucose was seen at 4 weeks after the STZ injection [14, 15]. Although decrease of the blood glucose level was observed in the MSCs-treated group, it was still higher than that of the normal control groups. The possible reason was that the DN was in the end stage of DM and was decompensated. Due to the small quantity, MSCs transplantation is difficult to completely reverse the bad outcome. It has become a research hotspot to study the timing of MSCs transplantation, improve the efficiency of MSCs transplantation and promote MSCs homing.

The dosage and administration of MSCs therapy vary greatly. Multiple intravenous infusion of ADSCs could attenuate inflammation, promote tissue repair and improve the prognosis of the long-term complications of T2DM [33]. Compared with intravenous injection, ADSCs sheet transplantation to the kidney had the advantage of higher efficiency [32]. Because of the importance of microvesicle, ultrasonic technology has been studied for microvesicles destruction to make them take effect easily. Ultrasonic targeted microvesicle destruction (UTMD), a non-invasive cell delivery method, could increase the migration of MSCs to kidney and promote kidney repair [17]. Stromal derived factor-1 (SDF-1), an important factor for the homing of MSCs, could be increased by UTMD, thereby acceleration of MSCs migration [52]. Besides, microbubble-mediated the diagnostic ultrasound irradiation help provide a suitable microenvironment for the delivery and retention of BM-MSCs by significantly increasing the levels of SDF-1, VCAM-1, E-selectin and VEGF and other trophic factors [53].

Meta-analysis of medication on clinical trials is essential for clinical decision on the basis of evidence-based medicine. Before medications entered into the clinic, great preclinical experiments to explore the efficacy and safety have to perform, which can be costly. Besides, in the absence of compelling evidence, testing directly on humans is both highly risky and unethical. A meta-analysis based on animal may have a good reference on the prediction of clinical trials. Objective to evaluate the therapeutic effects of MSCs on DKD and review the mechanisms herein, we carried out this study. Without species limitation, literature research was performed in this paper, and totally including 33 animal trials in 28 publications and 1 clinical trial, thereby a meta-analysis based on animal trials and a systematic review were conducted.

The concept of DKD was put forward to replace DN in Kidney Disease Outcomes Quality Initiative (K/DOQI) by National Kidney Foundation (NKF) in 2007, and has been used to specify renal lesion caused by DM. DN is characterized by proteinuria ≥ 300 mg/day in a diabetic patient, with or without diabetic retinopathy and hypertension. But with a new pathology classification of the diabetic kidney lesions involving tubules, interstitium and/or the vessels lesions reported by renal biopsy, the concept of DN has shifted to DKD in recent years focusing on clinical diagnose. Because of the concept update, the clear

distinction of DN and DKD was outside the scope of this article to avoid confusion, and both of them were included.

In this paper, we found that MSCs might improve the diabetic status, islet function and glucose levels, as well as having the effect of renal protection. MSCs seemed to be effective in the treatment of diabetes, manifesting on diabetic symptoms improvement like weight gain and decreased urine output and improved pancreas islets function to secrete insulin and better glycemic control. On the therapeutic effect of DKD, the reductions of SCr, BUN, CCr, urinary protein, renal hypertrophy were found in the MSCs-treated group. In addition, molecular detection showed that MSCs might reduce the expression of renal fibrosis related indicators such as TGF-β, Col-I, FN, α-SMA and E-cadherin, and the expression of inflammatory mediators such as MCP-1 and TNF-α.

For all we know, this paper is the first attempt to evaluate the MSCs transplantation in DKD systematically without species limitation. El-Badawy et al conducted a meta-analysis about the therapeutic effects of different sources of stem cells in T1DM and T2DM by the evaluation of C-peptide, HbA1c, insulin requirement and adverse effect, showing a better outcome of stem cells therapy, especially of CD34 + hematopoietic stem cells. According to the study, the incidence of adverse effects was 21.72% without death report [54]. To assess and quantify the stem cells in animal studies of chronic kidney disease (CKD), Papazova et al performed a systematic review and meta-analysis and reported notable improvement of plasma creatinine, plasma urea, urinary protein, GFR and blood pressure [55]. Wang et al screened out and pooled the data from small animal models of acute kidney injury and CKD treated by MSCs, and confirmed that impaired renal function was improved [56].

For 2-month glucose, the moderate funnel plot asymmetry suggested the presence of bias, and the Egger's test showed p=0.013, however, trim and fill did show no missing study. Significant heterogeneity was tested out, one of the inevitable drawbacks of animal meta-analysis, which might be caused by the following:

1. construction of animal models: variation of animal populations; different induction methods to DKD animal models, such as STZ injection, giving high-fat diets and SDT fatty rats with nephrectomy; different standards to diagnose DKD, the doses of STZ and duration of observation after DKD induction both of which were related to the lesion severity.
2. MSCs treatment: no uniform criteria of the MSCs treatment. Various dosages, administration methods, types of MSCs and application frequency were seen in different studies. Furthermore, the source of MSCs should also be taken into account, for the poor therapeutic effect of MSCs from DM mice [25], which indicated that the health of donor also mattered.
3. Detection methods: observed indicators and different reference values. For example, the measures of blood glucose varied, like random blood glucose, fasting blood glucose, serum glucose and plasma glucose.

The therapeutic effects of MSCs treatment seem to be promising in animal trials, but the human investigation appeared to be another story. A randomized, double-blind, placebo-controlled study of MSCs published in 2016, primarily assessed the safety with a 60-week follow-up and the efficacy in 12 weeks. With emphasis on safety and tolerance, neither adverse events associated with MSCs nor persistent donor specific anti-HLA antibodies was observed in the trial. However, except for IL-6 values and eGFR stabilization, no significant treatment outcome was found on urinary protein, CCr, lipid profile, HbA1c, blood pressure, TNF-α, adiponectin, TGF-β, uric acid and FGF23 when compared to placebo. Nevertheless, the result is not convincing with a single trial with small sample size (N=30).

Limitations

Only one clinical trial was included in this study, seriously lacking human data. As for animal experiments, notable heterogeneity and bias left the uncertain conclusion. Because of the longevity of animals, the included animal experiments generally had a short observation duration. MSCs-related adverse events were also limited. More attention should be paid to the design methodology as well as animal experiments of higher-qualitied and larger samples. Taking sufficient evidence of efficacy and safety on preclinical experiments as the premise, more human investigations are expected to conduct in the future.

Conclusion

MSCs might improve animal body weight, glycemic control and pancreas islets function to secrete insulin, and reduced the SCr, BUN, CCr, urinary protein and renal hypertrophy. MSCs can reduce the expression of inflammatory mediators and alleviate renal fibrosis. MSCs therapy may be anticipated in the treatment of DKD.

Abbreviations

MSCs: Mesenchymal stem cells; DKD: diabetic kidney diseases; NLM: National Library of Medicine; SYRCLE: SYstematic Review Centre for Laboratory animal Experimentation; SCr: serum creatinine; BUN: blood urea nitrogen; CCr: Creatinine clearance rate; UACR: urinary albumin/urinary creatinine ratio; TGF-β: transforming growth factor-β; Col-I: Collagen-I; FN: fibronectin; α-SMA: α-smooth muscle actin; TNF-α: tumor necrosis factor-α; DM: Diabetes mellitus; RAS: renin-angiotensin system; DN: diabetic nephropathy; RoB: Risk of bias; SMD: standard mean differences; OR: odds ratio; CI: confidence intervals; STZ: streptozotocin; HFD: high-fat diet; BM-MSCs: bone marrow mesenchymal stem cells; ADSCs: adipose-derived stem cells; hUCB-MSCs: human umbilical cord blood-derived mesenchymal stem cells; MCP-1: Monocyte chemokine protein-1; HG: high glucose; Arg1: arginase 1; PGC-1α: peroxisomal proliferator-activated receptor gamma coactivator 1α; TECs: tubular epithelial cells; EMT: epithelium-mesenchymal transdifferentiation; STIM: stromal interaction molecule; SOD2: superoxide dismutase 2; ROS: reactive oxygen species; MVs: microvesicles; CM: conditional medium; EGF: epithelial growth factor; EV: extracellular vesicles; HGF: hepatocyte growth factor; UTMD: Ultrasonic targeted microvesicle destruction;

SDF-1: Stromal derived factor-1; K/DOQI: Kidney Disease Outcomes Quality Initiative; NKF: National Kidney Foundation; CKD: chronic kidney disease.

Declarations

Ethical Approval

Ethical Approval is not applicable to this study.

Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects.

Statement of Informed Consent

There are no human subjects in this article and informed consent is not applicable.

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Availability of data and materials

Not applicable.

Authors' contributions

TBZ contributed to the conception and design of the study. WSL and TBZ were responsible for collection of data and performing the statistical analysis and manuscript preparation. SJL, QY, GYC and CLL were responsible for checking the data. All authors were responsible for drafting the manuscript, read and approved the final version.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Due to technical limitations, table docs is only available as a download in the Supplemental Files section.

Figures

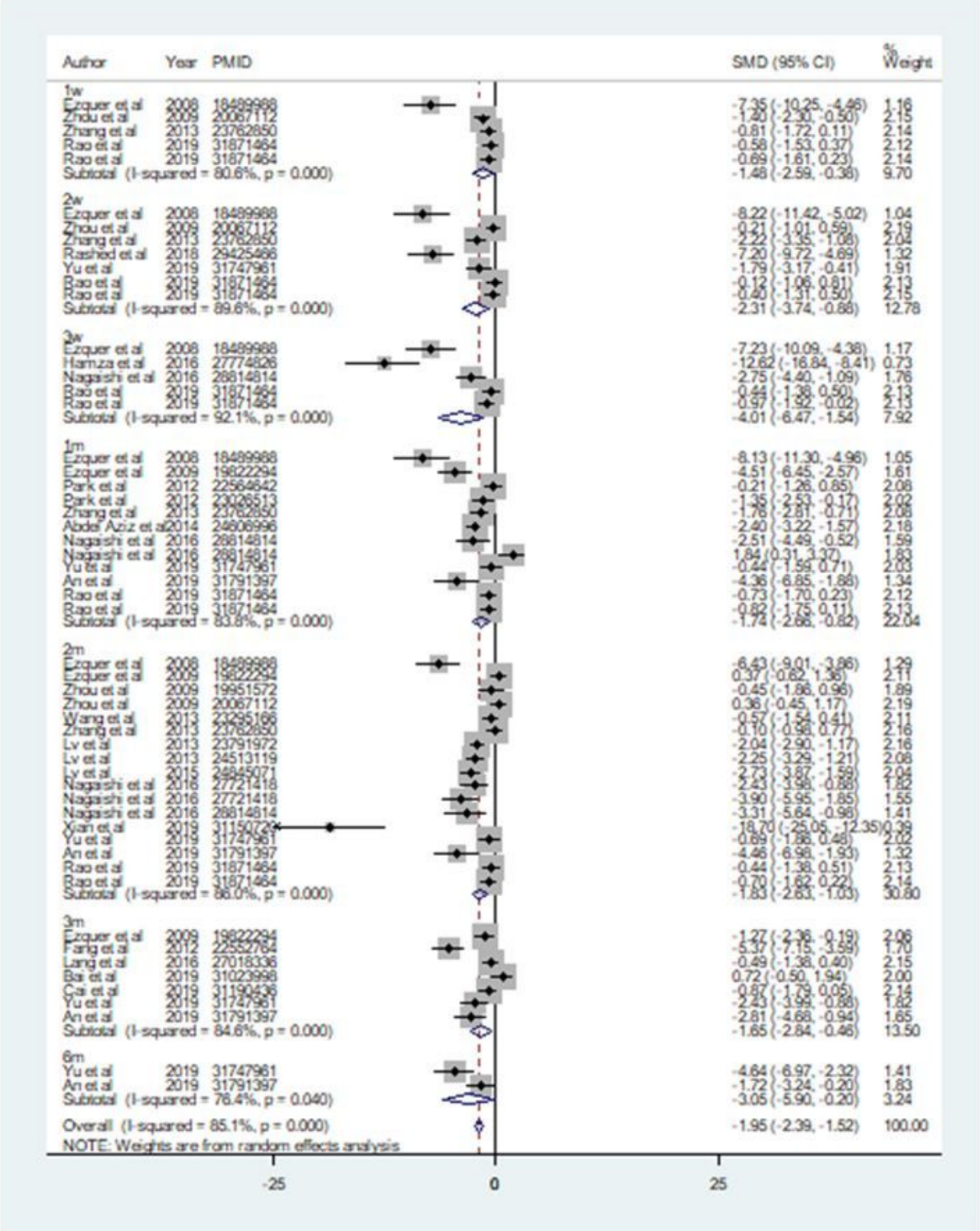

Figure 1

The effect of MSCs treatment on glycemic control. 1w: 1 week; 2w: 2 weeks; 3w:3 weeks; 1m: 1month; 2m: 2 months; 3m: 3 months; 6m: 6 months.

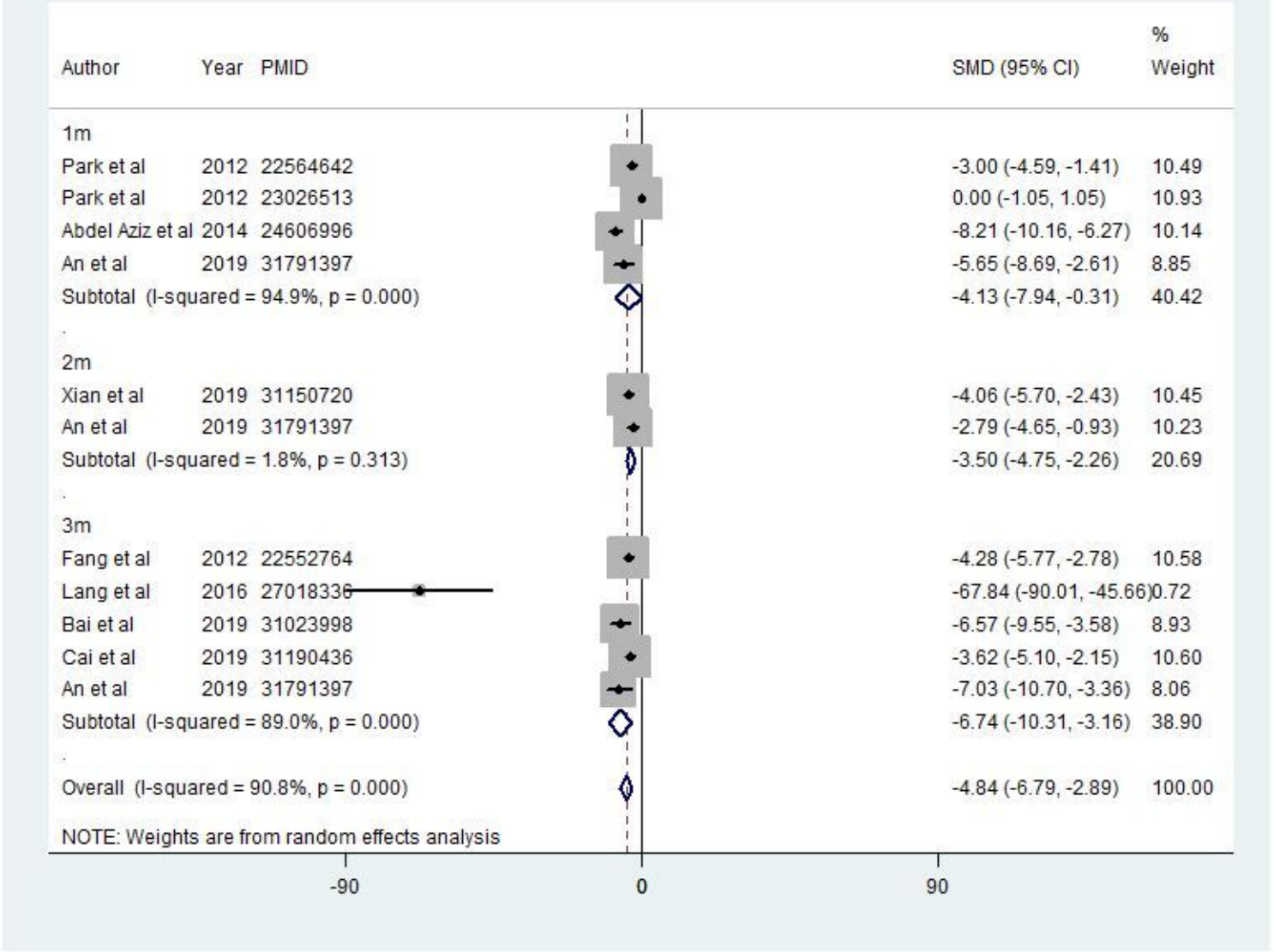

Figure 2

The effect of MSCs treatment on serum creatinine. 1m: 1month; 2m: 2 months; 3m: 3 months.

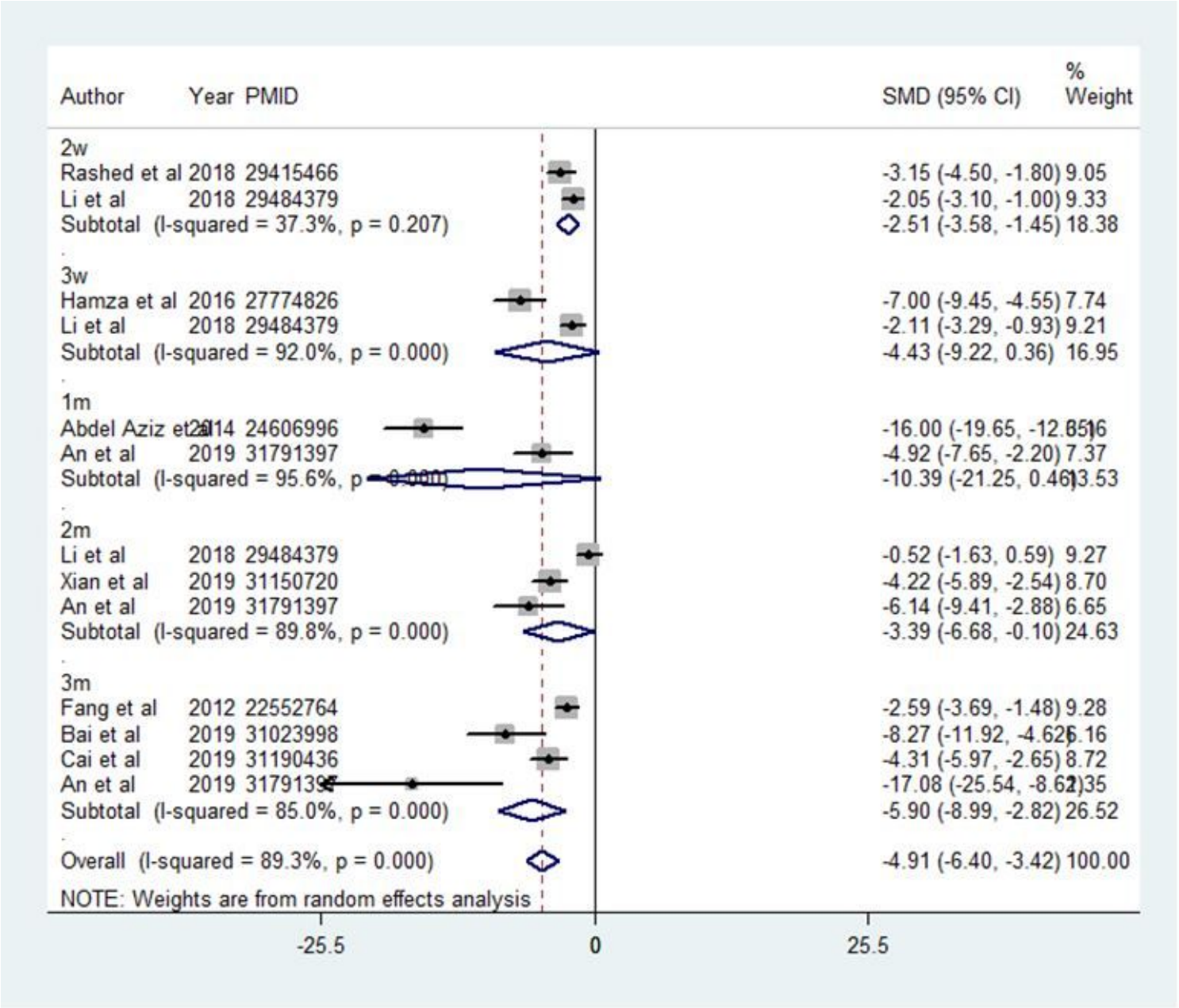

Figure 3

The effect of MSCs treatment on blood urea nitrogen (BUN). 2w: 2 weeks; 3w:3 weeks; 1m: 1month; 2m: 2 months; 3m: 3 months.

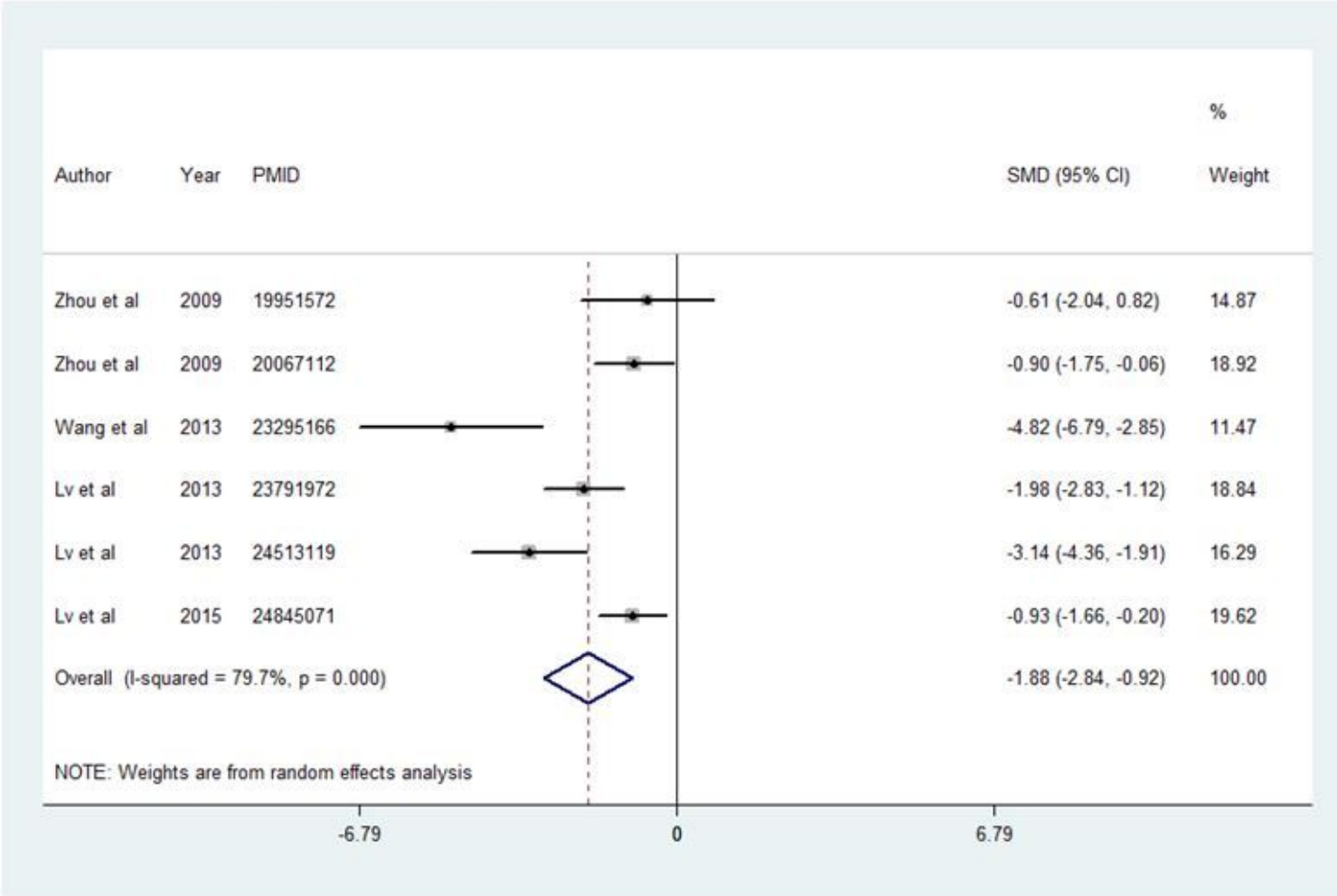

Figure 4

The effect of MSCs treatment on 2-month clearance of creatine rate (CCr).

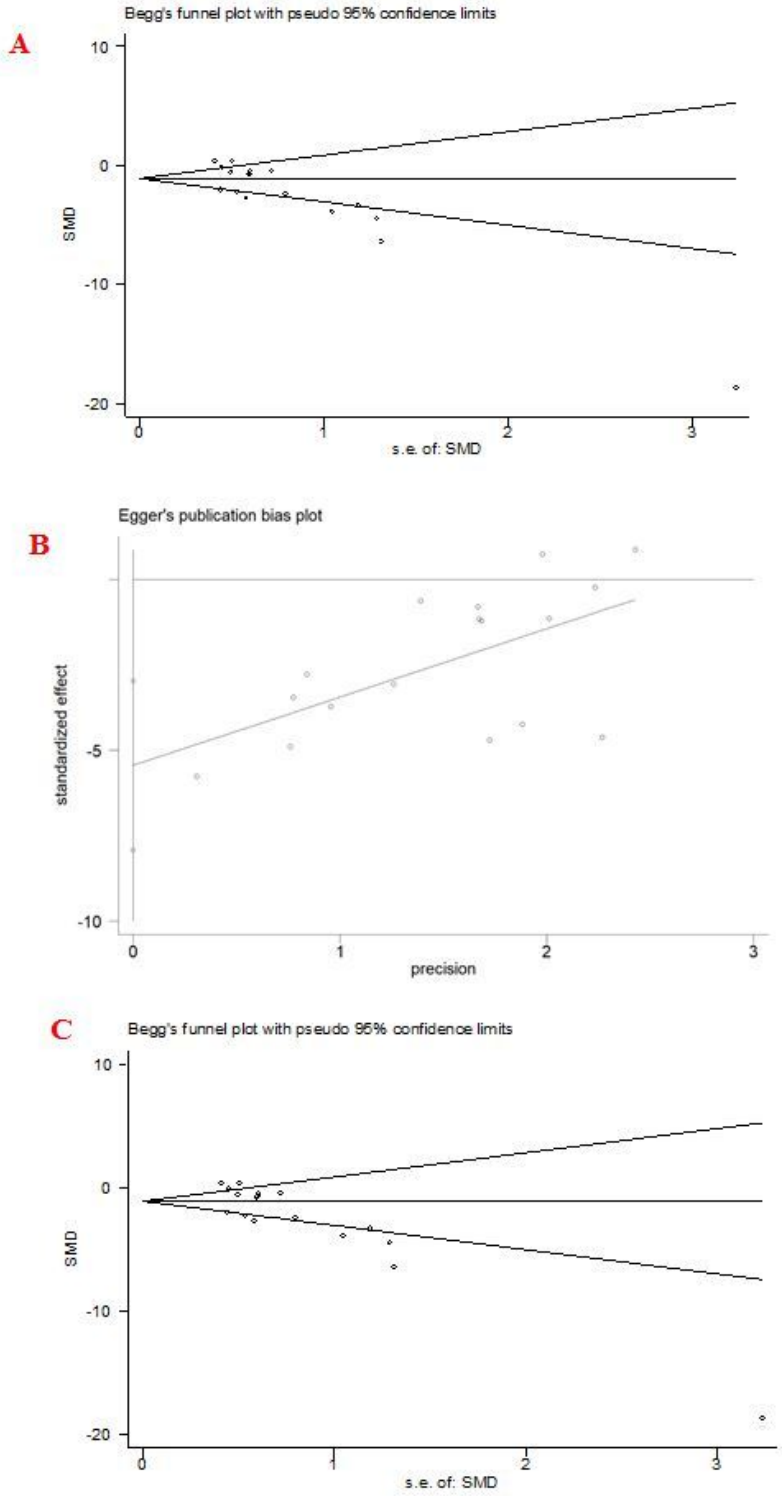

Figure 5

Publication bias: A. Funnel plot; B. Egger's test; C. Trim and Fill.

Supplementary Files

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- Table12.docx