ISSN 1948-9358 (online)

World Journal of *Diabetes*

World J Diabetes 2023 March 15; 14(3): 130-351

Published by Baishideng Publishing Group Inc

World Journal of Diabetes

Contents

Monthly Volume 14 Number 3 March 15, 2023

REVIEW

MINIREVIEWS

ORIGINAL ARTICLE

Basic Study

World Journal of Diabetes

Monthly Volume 14 Number 3 March 15, 2023

Contents

World Journal of Diabetes

Monthly Volume 14 Number 3 March 15, 2023

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Diabetes*, Guo-Xun Chen, PhD, Associate Professor, Director, Department of Nutrition, The University of Tennessee, Knoxville, TN 37909, United States. gchen6@utk.edu

AIMS AND SCOPE

The primary aim of *World Journal of Diabetes* (*WJD*, *World J Diabetes*) is to provide scholars and readers from various fields of diabetes with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

INDEXING/ABSTRACTING

The *WJD* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 Edition of Journal Citation Reports® cites the 2021 impact factor (IF) for *WJD* as 4.560; IF without journal self cites: 4.450; 5-year IF: 5.370; Journal Citation Indicator: 0.62; Ranking: 62 among 146 journals in endocrinology and metabolism; and Quartile category: Q2.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Yu-Xi Chen*; **Production Department Director:** *Xu Guo*; **Editorial Office Director:** *Jia-Ping Yan*.

NAME OF JOURNAL
World Journal of Diabetes

ISSN
ISSN 1948-9358 (online)

LAUNCH DATE
June 15, 2010

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Lu Cai, Md. Shahidul Islam, Michael Horowitz

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1948-9358/editorialboard.htm

PUBLICATION DATE
March 15, 2023

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Diabetes

Submit a Manuscript: https://www.f6publishing.com

World J Diabetes 2023 March 15; 14(3): 347-351

DOI: 10.4239/wjd.v14.i3.347

ISSN 1948-9358 (online)

LETTER TO THE EDITOR

Successful lifestyle modifications may underlie umbilical cord-mesenchymal stromal cell effects in type 2 diabetes mellitus

Alexandra Papadopoulou, Konstantinos I Papadopoulos

Specialty type: Endocrinology and metabolism

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Pappachan JM, United Kingdom; Prasetyo EP, Indonesia

Received: December 4, 2022
Peer-review started: December 4, 2022
First decision: December 26, 2022
Revised: December 30, 2022
Accepted: March 7, 2023
Article in press: March 7, 2023
Published online: March 15, 2023

Alexandra Papadopoulou, Occupational and Environmental Health Services, Feelgood Lund, Lund 22363, Skåne, Sweden

Konstantinos I Papadopoulos, Department of Research and Development, THAI StemLife Co., Ltd., Bangkok 10310, Bangkok, Thailand

Corresponding author: Konstantinos I Papadopoulos, MD, PhD, Chief Doctor, Director, Department of Research and Development, THAI StemLife Co., Ltd., 566/3 Soi Ramkhamhaeng 39 (Thepleela 1), Prachaouthit Rd., Wangthonglang, Bangkok 10310, Bangkok, Thailand. kostas@thaistemlife.co.th

Abstract

Type 2 diabetes mellitus (T2DM) is a lifelong condition and a grave threat to human health. Innovative efforts to relieve its detrimental effects are acutely needed. The *sine qua non* in T2DM management is consistent adherence to a prudent lifestyle and nutrition, combined with aerobic and resistance exercise regimens, together repeatedly shown to lead to complete reversal and even long-term remission. Non-adherence to the above lifestyle adjustments condemns any treatment effort and ultimately the patient to a grim fate. It is thus imperative that every study evaluating the effects of innovative interventions in T2DM objectively compares the novel treatment modality to lifestyle modifications, preferably through double-blind controlled randomization, before claiming efficacy.

Key Words: Type 1 diabetes mellitus; Type 2 diabetes mellitus; Human umbilical cord mesenchymal stem cells; Diabetes remission; Diabetes reversal; Lifestyle modifications.

Core Tip: The role of human umbilical cord-mesenchymal stem cells in type 2 diabetes mellitus (T2DM) could at best be seen as supportive to the irreplaceable role of consistent lifestyle modifications that, at a minimum, must include nutritional and exercise interventions. Combination of newer pharmacological treatments in T2DM, such as semaglutide or tirzepatide, with cellular components is worth exploring.

Citation: Papadopoulou A, Papadopoulos KI. Successful lifestyle modifications may underlie umbilical cord-mesenchymal stromal cell effects in type 2 diabetes mellitus. *World J Diabetes* 2023; 14(3): 347-351
URL: https://www.wjgnet.com/1948-9358/full/v14/i3/347.htm
DOI: https://dx.doi.org/10.4239/wjd.v14.i3.347

TO THE EDITOR

Type 2 diabetes mellitus (T2DM) is a grave threat to human health, and until recently, was considered a lifelong and irreversible condition[1]. Diabetes mellitus (DM) currently afflicts over 500 million individuals, and this number is projected to rise to nearly 800 million by 2045[1]. T2DM, which affects over 90% of diabetic patients, is caused by a complex interplay of genetics and lifestyle that leads to metabolic perturbations, insulin resistance (IR), loss of pancreatic β-cell identity and β-cell dedifferentiation, to ultimately failure of insulin-secreting pancreatic β-cells[2,3]. If left uncontrolled, T2DM results in a myriad of severe health complications and significantly contributes to the premature demise of the diabetic patient[3]. The syndemic of coronavirus disease 2019 and T2DM has horribly confirmed the latter's dismal effect on lethality[4]. Innovative, preventative, mitigatory, and therapeutic interventions are acutely needed, and cell-based therapies appear promising in the treatment of both types of diabetes [5]. In this context, Lian *et al*[6] present a small cohort of 16 T2DM patients that received intravenous infusions of allogeneic human umbilical cord-mesenchymal stromal cells (hUC-MSC) at a dose of 1×10^6 cells/kg per week for 3 consecutive weeks and were followed up for 12 wk. They conclude that allogeneic hUC-MSC can improve glycemia, restore islet β-cell function, and reduce the dosage of hypoglycemic agents without serious adverse events[6].

We would like to offer additional explanations to their conclusions. In preparation for the hUC-MSC intervention, Lian *et al*[6] submitted the enrolled participants to a 16-wk-long wash-in period with a daily diet not exceeding 25-30 kcal/kg body weight, and an exercise routine, composed of walking or similar exercise, for 30 min 3 times per week. These recommendations were monitored at their diabetic outpatient clinic and maintained throughout the 16-wk wash-in and the 12-wk follow-up periods. It also appears that, throughout the initial 16-wk period, fasting plasma glucose and 2-h postprandial plasma glucose were tested 7 times per week, consequently imposing an additional layer of accountability. Peculiarly, no clinical characteristics of the cohort, such as body weight (BW), body mass index (BMI), glycated hemoglobin (HbA1c), and C-peptide, at the start and at the end of the 16-wk wash-in intervention period, are given. Without these parameters, it is impossible to evaluate the effects of the ensuing three allogeneic hUC-MSC infusions in the 3 consecutive weeks, and premature to claim efficacy, particularly while the plausibly successful lifestyle modification intervention continued in parallel for another 12 wk to a total of at least 28 wk! The proper way to conduct this study would have been in a randomized controlled trial (RCT) setting, with a T2DM patient group with lifestyle modifications alone as the comparator. In our opinion, and in view of the mean duration of the cohort's diabetes (10.06 ± 5.74 years), and HbA1c (8.01 ± 0.63) values, the stringent dietary and exercise interventions during the 16-wk wash-in period, *per se*, could restore near-normal pancreatic function in several of the participants[2,7,8]. There are currently ample data through the Diabetes Remission Clinical Trials (DiRECT) supporting the notion that weight loss through very low energy diets can successfully and sustainably reverse T2DM in any ethnic population[2,8,9]. Indeed, an impressive 61% remission rate at 12 mo and an average weight loss of over 10 kg achieved at 1 year in the DiRECT study are utterly convincing[10]. The DiRECT diet entails consumption of not over 853 calories a day, mainly from soups or shakes, for up to 5 mo[9]. As patient BW in the current study[6] is not given, it is impossible to comment on the total caloric energy of the diets Lian *et al*[6] offered their patients during the 16-wk-long wash-in period[6]. Mechanistically, reducing intra-organ fat content (liver and pancreas) through weight loss-inducing low-calorie diets is able to reinstate a lost pancreatic β-cell phenotype, especially with T2DM durations of less than 11 yr[2,11,12]. It is thus highly plausible that the improvements noted in Lian *et al*[6] represent the action of a 28-wk lifestyle modification intervention.

Cell-based treatment modalities do indeed have a place in the treatment armamentarium against DM. Numerous proof of concept studies demonstrating efficacy of cell-based therapies in DM have instilled hope in addressing the intricate pathophysiology of both type 1 (T1) and T2DM[13,14]. Autologous hematopoietic stem cell (AHSC) bone marrow (BM) transplantation (AHSC-BMT) can lead to complete and durable remission in patients with new-onset T1DM[15-18]. Moreover, confirming earlier studies, early autologous MSC transplantation in newly-diagnosed T1DM children is reported as a promising, safe, and effective treatment, significantly improving HbA1c and C-peptide levels and shifting pro-inflammatory cytokines to anti-inflammatory cytokines, ultimately mitigating hypoglycemic episodes [19,20]. In T2DM, Bhansali *et al*[21,22] showed that autologous BM-MSCs (BM-AMSCs) and autologous BM-mononuclear cells (BM-AMNCs) result in sustained reduction in insulin doses, with improvement in insulin sensitivity with MSCs and increase in C-peptide response with MNCs[21-23]. Similarly, Nguyen *et al*[24] recently showed short-term therapeutic effects with autologous administration of BM-MSCs in T2DM patients with T2DM duration less than 10 years and no obesity. Evidently, the best cell-

based therapeutic outcomes are achieved by transplantation of BM-AHSCs for T1DM and BM-AMNCs along with BM-AMSCs for T2DM. Moreover, targeted rather than intravenous infusions for autologous MSC sources appear to be more effective[14]. The use of allogeneic sources, such as cadaveric pancreas and β-cell transplantation in T1DM, however, has led to variable results due to donor tissue scarcity and complications related to immunosuppression and immune rejection[5]. Allogenic MSCs have also been employed in the treatment of T2DM; Zang *et al*[25] showed modest short-term response in 20% *vs* 4.55% in the placebo arm, measured as percentage of patients reaching HbA1c levels of < 7.0% at 48 wk, clearly lower than the over 60% remission rates in the DiRECT studies[9]. Compared with allogeneic MSCs, autologous MSCs are safer, more ethical, more homogenous, have better secretome and epigenome synchronicity with the recipient, are not prone to immune rejection, and are without unknown potential candidate disease genes[26]. Allogeneic sources may elicit complications, such as pulmonary micro-embolism and other coagulation disorders, especially with increasing production passage (often seen in industrially-produced high passage allogeneic MSCs) that increase MSC size and predispose to microthrombus formation[13,27].

Human studies indicate no significant β-cell neogenesis in adults, thus any improvements in T2DM using lifestyle modifications and/or stem cell-based treatment modalities are not due to a *de novo* increase in β-cell mass[11]. In fact, Lian *et al*[6] themselves also indicate that *de novo* β-cell proliferation is not considered to be the reason for their observed improvements[6]. Instead, MSC paracrine effects on insulin sensitivity, intrahepatic/pancreatic lipid accumulation, relief of oxidative stress, and reduction of systemic inflammation might represent mechanisms by which MSCs may ameliorate T2DM[13]. Evidence shows that infusion of MSCs activates protein kinase B and adenosine monophosphate-activated protein kinase signaling pathways. MSCs also inhibit nucleotide oligomerization domain-like receptor protein 3 inflammasome formation, subsequently enhancing the function of insulin receptor substrate 1 and glucose transporter-4 (GLUT4), both crucial for modulation of glucose uptake and IR in hepatic cells[13]. Importantly, these mechanisms (and many more) described in MSC infusions are robustly stimulated through consistent aerobic and resistance exercise regimens, that, in combination with nutritional modifications, can lead to T2DM reversal and remission[4,28-30].

In general, despite the initial enthusiasm and reports of success, MSCs from diverse sources have shown underwhelming and mostly short-term therapeutic results in controlled human clinical trials, a far cry from the remission/reversal results of the DiRECT studies[2,9,10,13,31]. Most allogeneic MSC studies are performed in patients with marginally abnormal BMI and HbA1c, and include diverse cell types, sources, passage numbers, and mode of administration. These are several of the issues that make it impossible to evaluate efficacy such studies. The above issues need to be resolved *via* rigorous RCTs before making further claims of efficacy[13]. Moreover, MSC pharmacokinetics, which are intimately related to the mode of administration, need to be clarified as they are with common pharmaceutical drugs[13]. Finally, instilling unrealistic hopes that MSCs can replace a prudent lifestyle with a regular exercise regimen and mindful nutritional habits, is another perilous layman conclusion.

Weight loss and DM duration are the two most important parameters influencing T2DM reversal/remission and the probability of success of cell-based interventions[8,24,32]. There are no human studies showing efficacy of MSCs in weight loss but preconditioning with metformin or in combination with liraglutide, a glucagon-like peptide-1 (GLP-1) agonist, leads to improvements in T2DM[13,33]. The potential synergism between cell-based therapies and the newer, more effective pharmacological weight loss treatments in T2DM is worth exploring. Examples of such drugs include GLP-1 agonists (*e.g.*, semaglutide), or tirzepatide, a dual agonist of glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors[34,35]. In view of the exceptional improvements in the key components related to diabetes pathophysiology (*e.g.*, β-cell function, insulin sensitivity, glucagon secretion with GIP/GLP-1 agonists), it is highly improbable that MSC-based therapies alone will have a meaningful prospect of success in T2DM cure[35]. The use of teplizumab in delaying T1DM onset while preparing for an AHSC-BMT could plausibly lead to T1DM remission[15-18,36].

ACKNOWLEDGEMENTS

We are thankful to James TA, Marshall for his invaluable editorial assistance.

FOOTNOTES

Author contributions: Papadopoulou A and Papadopoulos KI contributed equally to the present manuscript; Papadopoulou A conceived and conceptualized the argumentation, designed the layout, drafted the initial manuscript, and reviewed and revised the manuscript; Papadopoulos KI performed the literature search, extracted vital information, contributed to the synthesis of the argumentation, made substantial and direct intellectual contributions, and reviewed and revised the manuscript. Papadopoulou A and Papadopoulos KI approved the submitted final manuscript and agree to be accountable for all aspects of the work.

Conflict-of-interest statement: No conflicts of interest are reported by Alexandra Papadopoulou. Konstantinos I

Papadopoulos is an employee and shareholder of THAI StemLife, Co., Ltd.

Country/Territory of origin: Thailand

ORCID number: Alexandra Papadopoulou 0000-0002-7488-8271; Konstantinos I Papadopoulos 0000-0003-0041-7853.

S-Editor: Liu GL
L-Editor: Filipodia
P-Editor: Liu GL

REFERENCES

1 **IDF Diabetes Atlas**. 10th edn. ed. Brussels, Belgium: International Diabetes Federation, 2021: Online version International Diabetes Federation
2 **Taylor R**, Al-Mrabeh A, Sattar N. Understanding the mechanisms of reversal of type 2 diabetes. *Lancet Diabetes Endocrinol* 2019; **7**: 726-736 [PMID: 31097391 DOI: 10.1016/S2213-8587(19)30076-2]
3 **Cai L**, Wheeler E, Kerrison ND, Luan J, Deloukas P, Franks PW, Amiano P, Ardanaz E, Bonet C, Fagherazzi G, Groop LC, Kaaks R, Huerta JM, Masala G, Nilsson PM, Overvad K, Pala V, Panico S, Rodriguez-Barranco M, Rolandsson O, Sacerdote C, Schulze MB, Spijkerman AMW, Tjonneland A, Tumino R, van der Schouw YT, Sharp SJ, Forouhi NG, Riboli E, McCarthy MI, Barroso I, Langenberg C, Wareham NJ. Genome-wide association analysis of type 2 diabetes in the EPIC-InterAct study. *Sci Data* 2020; **7**: 393 [PMID: 33188205 DOI: 10.1038/s41597-020-00716-7]
4 **Papadopoulos KI**, Sutheesophon W, Aw TC. Too hard to die: Exercise training mediates specific and immediate SARS-CoV-2 protection. *World J Virol* 2022; **11**: 98-103 [PMID: 35433336 DOI: 10.5501/wjv.v11.i2.98]
5 **Yang L**, Hu ZM, Jiang FX, Wang W. Stem cell therapy for insulin-dependent diabetes: Are we still on the road? *World J Stem Cells* 2022; **14**: 503-512 [PMID: 36157527 DOI: 10.4252/wjsc.v14.i7.503]
6 **Lian XF**, Lu DH, Liu HL, Liu YJ, Han XQ, Yang Y, Lin Y, Zeng QX, Huang ZJ, Xie F, Huang CH, Wu HM, Long AM, Deng LP, Zhang F. Effectiveness and safety of human umbilical cord-mesenchymal stem cells for treating type 2 diabetes mellitus. *World J Diabetes* 2022; **13**: 877-887 [PMID: 36312002 DOI: 10.4239/wjd.v13.i10.877]
7 **Shibib L**, Al-Qaisi M, Ahmed A, Miras AD, Nott D, Pelling M, Greenwald SE, Guess N. Reversal and Remission of T2DM - An Update for Practitioners. *Vasc Health Risk Manag* 2022; **18**: 417-443 [PMID: 35726218 DOI: 10.2147/VHRM.S345810]
8 **Taylor R**, Ramachandran A, Yancy WS Jr, Forouhi NG. Nutritional basis of type 2 diabetes remission. *BMJ* 2021; **374**: n1449 [PMID: 34233884 DOI: 10.1136/bmj.n1449]
9 **Lean ME**, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, Peters C, Zhyzhneuskaya S, Al-Mrabeh A, Hollingsworth KG, Rodrigues AM, Rehackova L, Adamson AJ, Sniehotta FF, Mathers JC, Ross HM, McIlvenna Y, Stefanetti R, Trenell M, Welsh P, Kean S, Ford I, McConnachie A, Sattar N, Taylor R. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. *Lancet* 2018; **391**: 541-551 [PMID: 29221645 DOI: 10.1016/S0140-6736(17)33102-1]
10 **Feinmann J**. Type 2 diabetes: 5000 patients to test feasibility of "remission service". *BMJ* 2018; **363**: k5114 [PMID: 30504130 DOI: 10.1136/bmj.k5114]
11 **White MG**, Shaw JA, Taylor R. Type 2 Diabetes: The Pathologic Basis of Reversible β-Cell Dysfunction. *Diabetes Care* 2016; **39**: 2080-2088 [PMID: 27926891 DOI: 10.2337/dc16-0619]
12 **Al-Mrabeh A**, Hollingsworth KG, Shaw JAM, McConnachie A, Sattar N, Lean MEJ, Taylor R. 2-year remission of type 2 diabetes and pancreas morphology: a post-hoc analysis of the DiRECT open-label, cluster-randomised trial. *Lancet Diabetes Endocrinol* 2020; **8**: 939-948 [PMID: 33031736 DOI: 10.1016/S2213-8587(20)30303-x]
13 **Gao S**, Zhang Y, Liang K, Bi R, Du Y. Mesenchymal Stem Cells (MSCs): A Novel Therapy for Type 2 Diabetes. *Stem Cells Int* 2022; **2022**: 8637493 [PMID: 36045953 DOI: 10.1155/2022/8637493]
14 **Bani Hamad FR**, Rahat N, Shankar K, Tsouklidis N. Efficacy of Stem Cell Application in Diabetes Mellitus: Promising Future Therapy for Diabetes and Its Complications. *Cureus* 2021; **13**: e13563 [PMID: 33815977 DOI: 10.7759/cureus.13563]
15 **Voltarelli JC**, Couri CE, Stracieri AB, Oliveira MC, Moraes DA, Pieroni F, Coutinho M, Malmegrim KC, Foss-Freitas MC, Simões BP, Foss MC, Squiers E, Burt RK. Autologous nonmyeloablative hematopoietic stem cell transplantation in newly diagnosed type 1 diabetes mellitus. *JAMA* 2007; **297**: 1568-1576 [PMID: 17426276 DOI: 10.1001/jama.297.14.1568]
16 **Couri CE**, Oliveira MC, Stracieri AB, Moraes DA, Pieroni F, Barros GM, Madeira MI, Malmegrim KC, Foss-Freitas MC, Simões BP, Martinez EZ, Foss MC, Burt RK, Voltarelli JC. C-peptide levels and insulin independence following autologous nonmyeloablative hematopoietic stem cell transplantation in newly diagnosed type 1 diabetes mellitus. *JAMA* 2009; **301**: 1573-1579 [PMID: 19366777 DOI: 10.1001/jama.2009.470]
17 **Malmegrim KC**, de Azevedo JT, Arruda LC, Abreu JR, Couri CE, de Oliveira GL, Palma PV, Scortegagna GT, Stracieri AB, Moraes DA, Dias JB, Pieroni F, Cunha R, Guilherme L, Santos NM, Foss MC, Covas DT, Burt RK, Simões BP,

Voltarelli JC, Roep BO, Oliveira MC. Immunological Balance Is Associated with Clinical Outcome after Autologous Hematopoietic Stem Cell Transplantation in Type 1 Diabetes. *Front Immunol* 2017; **8**: 167 [PMID: 28275376 DOI: 10.3389/fimmu.2017.00167]

18 **Ye L**, Li L, Wan B, Yang M, Hong J, Gu W, Wang W, Ning G. Immune response after autologous hematopoietic stem cell transplantation in type 1 diabetes mellitus. *Stem Cell Res Ther* 2017; **8**: 90 [PMID: 28420440 DOI: 10.1186/s13287-017-0542-1]

19 **Izadi M**, Sadr Hashemi Nejad A, Moazenchi M, Masoumi S, Rabbani A, Kompani F, Hedayati Asl AA, Abbasi Kakroodi F, Jaroughi N, Mohseni Meybodi MA, Setoodeh A, Abbasi F, Hosseini SE, Moeini Nia F, Salman Yazdi R, Navabi R, Hajizadeh-Saffar E, Baharvand H. Mesenchymal stem cell transplantation in newly diagnosed type-1 diabetes patients: a phase I/II randomized placebo-controlled clinical trial. *Stem Cell Res Ther* 2022; **13**: 264 [PMID: 35725652 DOI: 10.1186/s13287-022-02941-w]

20 **Carlsson PO**, Schwarcz E, Korsgren O, Le Blanc K. Preserved β-cell function in type 1 diabetes by mesenchymal stromal cells. *Diabetes* 2015; **64**: 587-592 [PMID: 25204974 DOI: 10.2337/db14-0656]

21 **Bhansali S**, Dutta P, Kumar V, Yadav MK, Jain A, Mudaliar S, Bhansali S, Sharma RR, Jha V, Marwaha N, Khandelwal N, Srinivasan A, Sachdeva N, Hawkins M, Bhansali A. Efficacy of Autologous Bone Marrow-Derived Mesenchymal Stem Cell and Mononuclear Cell Transplantation in Type 2 Diabetes Mellitus: A Randomized, Placebo-Controlled Comparative Study. *Stem Cells Dev* 2017; **26**: 471-481 [PMID: 28006991 DOI: 10.1089/scd.2016.0275]

22 **Bhansali S**, Dutta P, Yadav MK, Jain A, Mudaliar S, Hawkins M, Kurpad AV, Pahwa D, Yadav AK, Sharma RR, Jha V, Marwaha N, Bhansali S, Bhansali A. Autologous bone marrow-derived mononuclear cells transplantation in type 2 diabetes mellitus: effect on β-cell function and insulin sensitivity. *Diabetol Metab Syndr* 2017; **9**: 50 [PMID: 28690682 DOI: 10.1186/s13098-017-0248-7]

23 **Sood V**, Bhansali A, Mittal BR, Singh B, Marwaha N, Jain A, Khandelwal N. Autologous bone marrow derived stem cell therapy in patients with type 2 diabetes mellitus - defining adequate administration methods. *World J Diabetes* 2017; **8**: 381-389 [PMID: 28751962 DOI: 10.4239/wjd.v8.i7.381]

24 **Nguyen LT**, Hoang DM, Nguyen KT, Bui DM, Nguyen HT, Le HTA, Hoang VT, Bui HTH, Dam PTM, Hoang XTA, Ngo ATL, Le HM, Phung NY, Vu DM, Duong TT, Nguyen TD, Ha LT, Bui HTP, Nguyen HK, Heke M, Bui AV. Type 2 diabetes mellitus duration and obesity alter the efficacy of autologously transplanted bone marrow-derived mesenchymal stem/stromal cells. *Stem Cells Transl Med* 2021; **10**: 1266-1278 [PMID: 34080789 DOI: 10.1002/sctm.20-0506]

25 **Zang L**, Li Y, Hao H, Liu J, Cheng Y, Li B, Yin Y, Zhang Q, Gao F, Wang H, Gu S, Li J, Lin F, Zhu Y, Tian G, Chen Y, Gu W, Du J, Chen K, Guo Q, Yang G, Pei Y, Yan W, Wang X, Meng J, Zhang S, Ba J, Lyu Z, Dou J, Han W, Mu Y. Efficacy and safety of umbilical cord-derived mesenchymal stem cells in Chinese adults with type 2 diabetes: a single-center, double-blinded, randomized, placebo-controlled phase II trial. *Stem Cell Res Ther* 2022; **13**: 180 [PMID: 35505375 DOI: 10.1186/s13287-022-02848-6]

26 **Li C**, Zhao H, Cheng L, Wang B. Allogeneic vs. autologous mesenchymal stem/stromal cells in their medication practice. *Cell Biosci* 2021; **11**: 187 [PMID: 34727974 DOI: 10.1186/s13578-021-00698-y]

27 **Leibacher J**, Dauber K, Ehser S, Brixner V, Kollar K, Vogel A, Spohn G, Schäfer R, Seifried E, Henschler R. Human mesenchymal stromal cells undergo apoptosis and fragmentation after intravenous application in immune-competent mice. *Cytotherapy* 2017; **19**: 61-74 [PMID: 27836573 DOI: 10.1016/j.jcyt.2016.09.010]

28 **Ojuka EO**, Jones TE, Nolte LA, Chen M, Wamhoff BR, Sturek M, Holloszy JO. Regulation of GLUT4 biogenesis in muscle: evidence for involvement of AMPK and Ca(2+). *Am J Physiol Endocrinol Metab* 2002; **282**: E1008-E1013 [PMID: 11934664 DOI: 10.1152/ajpendo.00512.2001]

29 **Richter EA**, Hargreaves M. Exercise, GLUT4, and skeletal muscle glucose uptake. *Physiol Rev* 2013; **93**: 993-1017 [PMID: 23899560 DOI: 10.1152/physrev.00038.2012]

30 **Friedrichsen M**, Mortensen B, Pehmøller C, Birk JB, Wojtaszewski JF. Exercise-induced AMPK activity in skeletal muscle: role in glucose uptake and insulin sensitivity. *Mol Cell Endocrinol* 2013; **366**: 204-214 [PMID: 22796442 DOI: 10.1016/j.mce.2012.06.013]

31 **Feinmann J**. Low calorie and low carb diets for weight loss in primary care. *BMJ* 2018; **360**: k1122 [PMID: 29535083 DOI: 10.1136/bmj.k1122]

32 **Lee J**, Yoon KH. Diabetes duration and obesity matter in autologous mesenchymal stem/stromal cell transplantation in type 2 diabetes patients. *J Diabetes Investig* 2022; **13**: 230-232 [PMID: 34837356 DOI: 10.1111/jdi.13721]

33 **Mikłosz A**, Nikitiuk BE, Chabowski A. Using adipose-derived mesenchymal stem cells to fight the metabolic complications of obesity: Where do we stand? *Obes Rev* 2022; **23**: e13413 [PMID: 34985174 DOI: 10.1111/obr.13413]

34 **Frías JP**, Davies MJ, Rosenstock J, Pérez Manghi FC, Fernández Landó L, Bergman BK, Liu B, Cui X, Brown K; SURPASS-2 Investigators. Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes. *N Engl J Med* 2021; **385**: 503-515 [PMID: 34170647 DOI: 10.1056/NEJMoa2107519]

35 **Heise T**, Mari A, DeVries JH, Urva S, Li J, Pratt EJ, Coskun T, Thomas MK, Mather KJ, Haupt A, Milicevic Z. Effects of subcutaneous tirzepatide versus placebo or semaglutide on pancreatic islet function and insulin sensitivity in adults with type 2 diabetes: a multicentre, randomised, double-blind, parallel-arm, phase 1 clinical trial. *Lancet Diabetes Endocrinol* 2022; **10**: 418-429 [PMID: 35468322 DOI: 10.1016/S2213-8587(22)00085-7]

36 **Sims EK**, Bundy BN, Stier K, Serti E, Lim N, Long SA, Geyer SM, Moran A, Greenbaum CJ, Evans-Molina C, Herold KC; Type 1 Diabetes TrialNet Study Group. Teplizumab improves and stabilizes beta cell function in antibody-positive high-risk individuals. *Sci Transl Med* 2021; **13** [PMID: 33658358 DOI: 10.1126/scitranslmed.abc8980]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com