Dear Editor,

Thank you for allowing us to revise our manuscript. We want to thank the Reviewers for their valuable comments and suggestions that have helped us to improve our manuscript's quality. Following the Reviewers' suggestions, we have rewritten parts of the manuscript as requested and provided all the requested additional information. The newly introduced changes in the manuscript are marked in red. We also prepared additional Figures as requested by the Reviewers.

We have addressed all of the Reviewers' concerns, and we hope our manuscript is now suitable for publication in the *World Journal of Diabetes*.

Response to 'Reviewers' comments

Reviewer #1:
SCIENTIFIC QUALITY: Grade B (Very good)
LANGUAGE QUALITY: Grade B (Minor language polishing)
CONCLUSION: Minor revision
SPECIFIC COMMENTS TO AUTHORS: It is a well-written manuscript, in which the authors reviewed novel insights regarding the role of non-coding RNAs in diabetes. Some minor suggestions.

1. What about the roles of circRNA and lncRNA in diabetes? If the authors only reviewed microRNAs, the title of the manuscript needs to be changed.

Response: We thank the Reviewer for this comment. As requested by the Reviewer, we have included additional sections on the roles of circRNAs and lncRNAs in diabetes in the revised version of the manuscript, which reads as follows:

LONG NON-CODING RNAs ROLES IN DM

Long noncoding RNAs (lncRNAs) are a common type of long (>200 nucleotides) linear transcript that regulates gene expression at the transcriptional and posttranscriptional levels, influencing mRNA stability, pre-mRNA splicing, and translation (1-4). Mechanistically, lncRNAs can act as miRNA sponges, scaffolds for protein complexes, and decoys for regulatory factors (3). The interaction of lncRNAs with transcription factors results in transcription regulation (2, 5). It has also been observed that some lncRNAs may interact with pre-mRNAs to influence splicing (6). LncRNAs can potentially block protein interactions with target mRNAs or change protein catalytic activity, acting as decoys (1, 3). It was also discovered that lncRNAs binding to translating mRNAs change the target mRNA's stability and translation (1).

LncRNAs regulate critical physiological processes such as cell proliferation, growth, differentiation, senescence, aging, and secretion (7, 8). They are also implied in the pathogenesis of several diseases, including cardiovascular disease and DM, and they were also implicated in the pathophysiology of various disorders like cardiovascular disease and DM. In humans, lncRNAs are primarily produced by RNA Polymerase II or III (9) and are characterized as sense- or antisense-overlap, bidirectional, intronic, or intergenic lncRNAs based on their proximity to the next protein-coding gene (10). The functions of lncRNAs are governed by their cellular location, with nuclear lncRNAs modulating transcription and splicing and cytoplasmic lncRNAs regulating posttranscriptional events such as mRNA stability, protein synthesis, and posttranscriptional alterations (3).

Various lncRNAs are expressed in a cell-type specific manner in pancreatic β-cells such as *GAS5* (growth arrest-specific transcript 5), *PLUTO* (PDX1 locus upstream transcript), *TUG1* (taurine upregulated gene 1), *MEG3* (maternally expressed gene 3), and *βLINC* (β-cell long intergenic non-coding RNAs).

GAS5 is a lncRNA that regulates cell development and proliferation. *GAS5* levels in diabetic patients' serum are considerably lower than in healthy controls (11), and db/db mice (12), and *GAS5* silencing *in vitro* is related to cell cycle arrest and decreased insulin production and secretion. *PLUTO* is an antisense transcript lncRNA upstream of the gene that codes for PDX1, a transcription factor involved in β-cell differentiation and pancreatic development. Both *PLUTO* and *PDX1* are significantly downregulated in T2DM patients (13). Reduced *PLUTO* expression is related to chromatin changes that limit the interaction of the PDX1 promoter with its enhancer, resulting in lower PDX1 expression (13), implying that *PLUTO* plays a role in the control of β-cell function. *TUG1* and *MEG3* are extensively expressed in the pancreas and are controlled by glucose levels (14, 15). *TUG1* and *MEG3* knockdown reduces insulin synthesis and secretion and promotes β-cell death (15), supporting their roles in β-cell development and insulin production control. *βLINC1* is a highly conserved lncRNA linked to increased glucose intolerance and aberrant insulin secretion (16). *βLINC2* and *βLINC3* are more abundant in pancreatic islets than other organs. *βLINC2* expression levels correlate favourably with body weight, glycemia, and insulinemia, but *βLINC3* expression correlates negatively with BMI and is considerably lower in T2DM patients compared to healthy controls (17).

FUNCTIONS OF CIRCULAR RNAs IN DM

CircRNAs are abundant, conserved tissue-specific covalently closed loop circular RNAs (18-22) produced by the direct ligation of 5′ and 3′ ends of linear RNAs as intermediates in RNA processing or generated by backsplicing where a downstream 5' splice donor attacks an upstream 3' splice acceptor site of pre-mRNA forming a covalently closed circRNA lacking the 5' and 3' ends (23, 24). CircRNAs regulate gene expression by acting as miRNA sponges, modulating protein-protein interactions, binding to ribosomes and interfering with translation or modifying transcription (25). CircRNAs are thought to play a role in the aetiology of many diseases, including DM (26). CircRNA *Cdr1as*, for example, regulates insulin production and secretion by acting as a sponge for miR-7, reducing insulin secretion. *Cdr1as* contains about sixty miR-7 binding sites (20), and *Cdr1as* upregulation increases insulin secretion by inhibiting miR-7 activity (27). miR-7 directly targets and inhibits the expression of paired box 6 (Pax 6) and the myosin VIIA and Rab interacting protein (Myrip). Pax 6 is a transcription factor that interacts with the promoters of the *ins*1 and *ins*2 genes to stimulate insulin production and secretion, whereas Myrip is involved in secretory granule transport and release. *Cdr1as* expression is downregulated in db/db mouse islets (28), but *Cdr1as* overexpression increases Pax 6 and Myrip expression, resulting in enhanced insulin transcription and secretion in pancreatic islets (29).

CircHIPK3 is abundantly expressed in pancreatic β-cells, and decreased *circHIPK3* levels are associated with reduced proliferation of β-cells (28). *CircHIPK3* silencing decreases insulin mRNA levels and perturbs glucose-stimulated insulin secretion (28).

CircAFF1 (101), another highly expressed circRNA in pancreatic islets, causes β-cell death *in vitro*, implying its role in β-cell growth and function (28).

2. More figures are recommended.

Response: As the Reviewer suggested, we have included two additional figures in the revised manuscript. The newly added figures in the revised manuscript are titled as follows:

Figure 1. Mechanism of action of miRNAs.

Figure 3. miRNAs mediating glucose metabolism and insulin secretion in pancreatic β-cells.

Reviewer #2:
SCIENTIFIC QUALITY: Grade C (Good)
LANGUAGE QUALITY: Grade B (Minor language polishing)
CONCLUSION: Major revision
SPECIFIC COMMENTS TO AUTHORS:

1. The use of exosomes should be included in the manuscript.

Response: We thank the Reviewer for the valuable suggestion. We have included the subsection discussing the use of exosomes in the manuscript's revised version. The newly added text reads as follows:

Extracellular vesicles (EVs), specifically exosomes, play a vital role in inter-organ communication by carrying lncRNAs and miRNAs that modulate metabolic pathways. EVs are tiny vesicles enclosed by a membrane, originate from the endosome, and are released by cells into the extracellular fluids depending on their cargo (30). According to the Minimal Information for Studies of Extracellular Vesicles 2018 (MISEV 2018) recommendations, EVs are a component of the total secretome released by the cell, and no specific marker can distinguish EV subtypes and their subcellular origin (31). Exosomes and microvesicles, two forms of EVs released by cells, are distinguished by their manner of synthesis rather than their size. Cells undergo EV biogenesis, a process that includes inward invagination of the plasma membrane within the cytosol, forming early and late endosomes (LEs). These LEs join together to create multivesicular bodies (MVBs), which invaginate to form intraluminal vesicles (ILVs) (32). Exocytosis occurs when these ILVs fuse with the cell's plasma membrane and release exosomes into the extracellular environment (155). Exosomes are found in various bodily fluids and are released by various cell types, including lymphocytes and pancreatic islets (33). The transfer of nucleic acids by exosomes is enhanced in inflammatory conditions, and miRNAs represent one of the main cargos transported by exosomes (34).

In DM, these molecules target specific tissues regulating their activity. Therefore, to understand the pathogenesis of T1DM and T2DM, it is crucial to investigate the communication between affected organs in response to elevated blood glucose levels. Exosomes act as messengers, linking the immune response to pancreatic damage and adipocyte stimulation, leading to IR in the liver and muscles. Exosomes containing LncRNAs and miRNAs also contribute to cellular communication by altering metabolic and insulin signals, impacting inflammatory processes in

pancreatic cells. Exosome-carried miRNAs, particularly, hold great promise as biomarkers or in developing innovative therapeutics for diabetes and its consequences (35).

Islet insulitis is connected with the transfer of a specific group of miRNAs from lymphocytes to cells via exosomes, including miR-142-3p, miR-142-5p, and miR-155, leading in the selective death of insulin-secreting cells. Inactivation of these miRNAs protected cells against apoptosis caused by T lymphocyte exosomes *in vitro* and reduced T1D development in NOD mice *in vivo*. As a result, it has been postulated that miRNA transfer mediated by exosomes released by lymphocytes causes β-cell death and may be one of the mechanisms contributing to the development of T1DM (36).

Katayama et al. used microarrays to evaluate the expression profile of exosomal miRNAs in healthy people and those with T2DM (37). They discovered that miR-20b-5p in exosomes is abundant in people withT2DM. Further *in vitro* studies revealed that this miRNA targets the AKT interacting protein (AKTIP), which modifies AKT protein activity and decreases glycogen buildup in muscles and IR (37).

Downregulation of exosomal lncRNA-p3134 in diabetic mice reduced glucose-stimulated insulin production by lowering key regulators (Pdx-1, MafA, GLUT2, and Tcf7l2) in β-cells. This shows that lncRNA-p3134 regulates insulin secretion and that its downregulation leads to diabetes pathogenesis (38).

On the other hand, exosomal miRNAs (miR-20b-5p, miR-155, miR-450b-3p, miR-151-3p, and miR-29b-3p) were found to be elevated in diabetic mice and targeted skeletal muscles *via* insulin signaling regulatory proteins (PPAR, AKT, GLUT4, and FOXO). This contributes to diabetes pathogenesis by influencing insulin signaling and glucose absorption in skeletal muscles (39). Other exosomal miRNAs (miR-122, 192, 27a/b, 155, and 29b-3p) were upregulated in diabetic models and targeted adipocytes *via* PPAR proteins. This impairs lipid metabolism and contributes to diabetes development (40).

Exosomal miRNAs (miR-142-3p and miR-142-5p) were also found to be enhanced in diabetic mice and target pancreatic cells *via* cytokines that are elevated. This contributes to diabetes pathogenesis by encouraging immune cell recruitment and β-cell death during autoimmune attacks

(36). Other exosomal miRNAs that target organs such as astrocytes, retinal tissue, and renal cells (miR-106, miR-146a, miR-222, and miR-486) have potential therapeutic roles in protecting pancreatic cells or treating diabetic complications (41).

Exosomal miRNAs and lncRNAs influence diabetes development in various ways, including regulating pancreatic inflammation and regulating metabolic and insulin signaling in target organs. Despite mounting evidence, research on the involvement of exosomes harbouring ncRNAs in diabetes is still in its early stages, but they have promise and significant roles in pathogenesis, diabetic diagnosis, and treatments (42, 43).

2. Applications of nanomaterials should be included in the manuscript.

Response: We appreciate the suggestion. We have included a section on nanomaterials in the revised manuscript, which reads as follows:

microRNAs AND NANOTECHNOLOGY

In recent years, bio-nanomedicine has turned its attention to EVs as a novel disease treatment approach. One of the most promising applications is the delivery of tolerogenic nanoparticles (TNps) to combat autoimmune diseases like T1DM. EVs and nanoparticles, as opposed to traditional medicines, provide advantages such as tailored delivery, lower toxicity, and enhanced stability. TNps can induce immunological tolerance in T1DM patients by regulating the immune response *via* various mechanisms (44). On the other hand, EVs can deliver cargo such as cytokines, growth factors, and miRNAs to recipient cells, influencing immune responses *via* a paracrine impact and during the development of the immunological synapse (45).

A recent study has focused on developing EVs to contain TNps to treat T1DM. For example, immunomodulatory nanoparticles containing antisense oligonucleotides to CD40, CD80, and CD86 have been utilized to prevent T1DM in mice by increasing Foxp3+ Treg cells (46). Another study found that the co-culture of islets and bone marrow stem cells enhanced islet-cell survival and functionality in mice, mediated by exosomes *via* a paracrine action (47). Furthermore, clinical studies (48) have shown that exosomes derived from mesenchymal stem cells can suppress immune targeting in allogeneic grafts. These findings imply that EVs have regenerative, anti-

apoptotic, immunomodulatory, and angiogenic capabilities, making them a prospective tool for restoring islet-cell function and treating autoimmune disorders (49).

Nanotechnology has gained prominence in diabetes research by leveraging nanomaterials, nanostructures, and nanoparticle design to obtain more exact information on diabetes mellitus diagnosis. Nanoparticles can be used to deliver RNA and proteins to identify and monitor illness progression (50). A recent study aimed to identify critical miRNAs that are dysregulated in pancreatic islets during T1DM progression and to create a theranostic strategy to modulate their expression using an MRI-based nano-drug. Iron oxide nanoparticles combined with miRNA-targeting oligonucleotides were used to treat a mouse model of T1DM (35, 51).

Reviewer #3:
SCIENTIFIC QUALITY: Grade C (Good)
LANGUAGE QUALITY: Grade B (Minor language polishing)
CONCLUSION: Minor revision
SPECIFIC COMMENTS TO AUTHORS:

1. Author is talking about non-coding RNA, long non-coding RNA should be discussed at least.

Response: We thank the Reviewer for the suggestion. A section on long non-coding RNAs is included in the revised manuscript, which reads as follows:

LONG NON-CODING RNAs ROLES IN DM

Long noncoding RNAs (lncRNAs) are a common type of long (>200 nucleotides) linear transcript that regulates gene expression at the transcriptional and posttranscriptional levels, influencing mRNA stability, pre-mRNA splicing, and translation (1-4). Mechanistically, lncRNAs can act as miRNA sponges, scaffolds for protein complexes, and decoys for regulatory factors (3). The interaction of lncRNAs with transcription factors results in transcription regulation (2, 5). It has also been observed that some lncRNAs may interact with pre-mRNAs to influence splicing (6). LncRNAs can potentially block protein interactions with target mRNAs or change protein catalytic activity, acting as decoys (1, 3). It was also discovered that lncRNAs binding to translating mRNAs change the target mRNA's stability and translation (1).

LncRNAs regulate critical physiological processes such as cell proliferation, growth, differentiation, senescence, aging, and secretion (7, 8). They are also implied in the pathogenesis of several diseases, including cardiovascular disease and DM, and they were also implicated in the pathophysiology of various disorders like cardiovascular disease and DM. In humans, lncRNAs are primarily produced by RNA Polymerase II or III (9) and are characterized as sense- or antisense-overlap, bidirectional, intronic, or intergenic lncRNAs based on their proximity to the next protein-coding gene (10). The functions of lncRNAs are governed by their cellular location, with nuclear lncRNAs modulating transcription and splicing and cytoplasmic lncRNAs regulating posttranscriptional events such as mRNA stability, protein synthesis, and posttranscriptional alterations (3).

Various lncRNAs are expressed in a cell-type specific manner in pancreatic β-cells such as *GAS5* (growth arrest-specific transcript 5), *PLUTO* (PDX1 locus upstream transcript), *TUG1* (taurine upregulated gene 1), *MEG3* (maternally expressed gene 3), and *βLINC* (β-cell long intergenic non-coding RNAs).

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2. Author should show some picture how miRNA influences the pathways. Like targeting mRNA to regulate glucose metabolism.

Response: We would like to thank the Reviewer for the valuable suggestion. We have included a **Figure 3** depicting the role of miRNAs in regulating glucose metabolism and insulin secretion.

4. LANGUAGE POLISHING REQUIREMENTS FOR REVISED MANUSCRIPTS SUBMITTED BY AUTHORS WHO ARE NON-NATIVE SPEAKERS OF ENGLISH

Response: Corrected as suggested.

5 ABBREVIATIONS

In general, do not use non-standard abbreviations, unless they appear at least two times in the text preceding the first usage/definition.

Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, and mAb, do not need to be defined and can be used directly.

Response: Corrected as suggested.

(2) COMPANY EDITOR-IN-CHIEF: I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Diabetes, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

Response: Completed following the instructions

Newly added references:

1. Yoon JH, Abdelmohsen K, Gorospe M. Posttranscriptional gene regulation by long noncoding RNA. Journal of molecular biology. 2013;425(19):3723-30.
2. Mercer TR, Mattick JS. Structure and function of long noncoding RNAs in epigenetic regulation. Nature structural & molecular biology. 2013;20(3):300-7.
3. Wang KC, Chang HY. Molecular mechanisms of long noncoding RNAs. Molecular cell. 2011;43(6):904-14.
4. Ponting CP, Oliver PL, Reik W. Evolution and functions of long noncoding RNAs. Cell. 2009;136(4):629-41.

5. Wang X, Arai S, Song X, Reichart D, Du K, Pascual G, et al. Induced ncRNAs allosterically modify RNA-binding proteins in cis to inhibit transcription. Nature. 2008;454(7200):126-30.
6. Romero-Barrios N, Legascue MF, Benhamed M, Ariel F, Crespi M. Splicing regulation by long noncoding RNAs. Nucleic acids research. 2018;46(5):2169-84.
7. Grammatikakis I, Panda AC, Abdelmohsen K, Gorospe M. Long noncoding RNAs(lncRNAs) and the molecular hallmarks of aging. Aging. 2014;6(12):992-1009.
8. Abdelmohsen K, Panda A, Kang MJ, Xu J, Selimyan R, Yoon JH, et al. Senescence-associated lncRNAs: senescence-associated long noncoding RNAs. Aging cell. 2013;12(5):890-900.
9. Barski A, Chepelev I, Liko D, Cuddapah S, Fleming AB, Birch J, et al. Pol II and its associated epigenetic marks are present at Pol III-transcribed noncoding RNA genes. Nature structural & molecular biology. 2010;17(5):629-34.
10. Ma L, Bajic VB, Zhang Z. On the classification of long non-coding RNAs. RNA biology. 2013;10(6):925-33.
11. Carter G, Miladinovic B, Patel AA, Deland L, Mastorides S, Patel NA. Circulating long noncoding RNA GAS5 levels are correlated to prevalence of type 2 diabetes mellitus. BBA clinical. 2015;4:102-7.
12. Jin F, Wang N, Zhu Y, You L, Wang L, De W, et al. Downregulation of Long Noncoding RNA Gas5 Affects Cell Cycle and Insulin Secretion in Mouse Pancreatic β Cells. Cellular physiology and biochemistry : international journal of experimental cellular physiology, biochemistry, and pharmacology. 2017;43(5):2062-73.
13. Akerman I, Tu Z, Beucher A, Rolando DMY, Sauty-Colace C, Benazra M, et al. Human Pancreatic β Cell lncRNAs Control Cell-Specific Regulatory Networks. Cell Metab. 2017;25(2):400-11.
14. Yin DD, Zhang EB, You LH, Wang N, Wang LT, Jin FY, et al. Downregulation of lncRNA TUG1 affects apoptosis and insulin secretion in mouse pancreatic β cells. Cellular physiology and biochemistry : international journal of experimental cellular physiology, biochemistry, and pharmacology. 2015;35(5):1892-904.
15. You L, Wang N, Yin D, Wang L, Jin F, Zhu Y, et al. Downregulation of Long Noncoding RNA Meg3 Affects Insulin Synthesis and Secretion in Mouse Pancreatic Beta Cells. Journal of cellular physiology. 2016;231(4):852-62.
16. Arnes L, Akerman I, Balderes DA, Ferrer J. βlinc1 encodes a long noncoding RNA that regulates islet β-cell formation and function. 2016;30(5):502-7.
17. Motterle A, Gattesco S, Peyot ML, Esguerra JLS, Gomez-Ruiz A, Laybutt DR, et al. Identification of islet-enriched long non-coding RNAs contributing to β-cell failure in type 2 diabetes. Molecular metabolism. 2017;6(11):1407-18.
18. Salzman J, Gawad C, Wang PL, Lacayo N, Brown PO. Circular RNAs are the predominant transcript isoform from hundreds of human genes in diverse cell types. PLoS One. 2012;7(2):e30733.
19. Hansen TB, Jensen TI, Clausen BH, Bramsen JB, Finsen B, Damgaard CK, et al. Natural RNA circles function as efficient microRNA sponges. Nature. 2013;495(7441):384-8.
20. Memczak S, Jens M, Elefsinioti A, Torti F, Krueger J, Rybak A, et al. Circular RNAs are a large class of animal RNAs with regulatory potency. Nature. 2013;495(7441):333-8.

21. Jeck WR, Sorrentino JA, Wang K, Slevin MK, Burd CE, Liu J, et al. Circular RNAs are abundant, conserved, and associated with ALU repeats. RNA (New York, NY). 2013;19(2):141-57.
22. Xia S, Feng J, Lei L, Hu J, Xia L, Wang J, et al. Comprehensive characterization of tissue-specific circular RNAs in the human and mouse genomes. Briefings in bioinformatics. 2017;18(6):984-92.
23. Chen LL, Yang L. Regulation of circRNA biogenesis. RNA biology. 2015;12(4):381-8.
24. Zhang Y, Xue W, Li X, Zhang J, Chen S, Zhang JL, et al. The Biogenesis of Nascent Circular RNAs. Cell reports. 2016;15(3):611-24.
25. Chen LL. The biogenesis and emerging roles of circular RNAs. Nature reviews Molecular cell biology. 2016;17(4):205-11.
26. Haque S, Harries LW. Circular RNAs (circRNAs) in Health and Disease. Genes (Basel). 2017;8(12).
27. Latreille M, Hausser J, Stützer I, Zhang Q, Hastoy B, Gargani S, et al. MicroRNA-7a regulates pancreatic β cell function. The Journal of clinical investigation. 2014;124(6):2722-35.
28. Stoll L, Sobel J, Rodriguez-Trejo A, Guay C, Lee K, Venø MT, et al. Circular RNAs as novel regulators of β-cell functions in normal and disease conditions. Molecular metabolism. 2018;9:69-83.
29. Xu H, Guo S, Li W, Yu P. The circular RNA Cdr1as, via miR-7 and its targets, regulates insulin transcription and secretion in islet cells. Sci Rep. 2015;5:12453.
30. Raghav A, Tripathi P, Mishra BK, Jeong GB, Banday S, Gautam KA, et al. Mesenchymal Stromal Cell-Derived Tailored Exosomes Treat Bacteria-Associated Diabetes Foot Ulcers: A Customized Approach From Bench to Bed. Frontiers in microbiology. 2021;12:712588.
31. Bongiovanni L, Andriessen A, Wauben MHM, Nolte-'t Hoen ENM, de Bruin A. Extracellular Vesicles: Novel Opportunities to Understand and Detect Neoplastic Diseases. Veterinary pathology. 2021;58(3):453-71.
32. Raghav A, Khan ZA. Mesenchymal Stem Cell-Derived Exosomes Exhibit Promising Potential for Treating SARS-CoV-2-Infected Patients. 2021;10(3).
33. Pang H, Luo S, Xiao Y, Xia Y, Li X, Huang G, et al. Emerging Roles of Exosomes in T1DM. Front Immunol. 2020;11:593348.
34. Chen H, Wang L, Zeng X, Schwarz H, Nanda HS, Peng X, et al. Exosomes, a New Star for Targeted Delivery. Front Cell Dev Biol. 2021;9:751079.
35. Raghav A, Ashraf H, Jeong GB. Engineered Extracellular Vesicles in Treatment of Type 1 Diabetes Mellitus: A Prospective Review. 2022;10(12).
36. Guay C, Kruit JK, Rome S, Menoud V, Mulder NL, Jurdzinski A, et al. Lymphocyte-Derived Exosomal MicroRNAs Promote Pancreatic β Cell Death and May Contribute to Type 1 Diabetes Development. Cell Metab. 2019;29(2):348-61.e6.
37. Katayama M, Wiklander OPB, Fritz T, Caidahl K, El-Andaloussi S, Zierath JR. Circulating Exosomal miR-20b-5p Is Elevated in Type 2 Diabetes and Could Impair Insulin Action in Human Skeletal Muscle. 2019;68(3):515-26.
38. Sufianov A, Kostin A, Begliarzade S, Kudriashov V, Ilyasova T, Liang Y, et al. Exosomal non coding RNAs as a novel target for diabetes mellitus and its complications. Non-coding RNA research. 2023;8(2):192-204.
39. Chang W, Wang J. Exosomes and Their Noncoding RNA Cargo Are Emerging as New Modulators for Diabetes Mellitus. Cells. 2019;8(8).

40. Castaño C, Kalko S, Novials A, Párrizas M. Obesity-associated exosomal miRNAs modulate glucose and lipid metabolism in mice. 2018;115(48):12158-63.
41. Improta-Caria AC, De Sousa RAL, Roever L, Fernandes T, Oliveira EM, Aras Júnior R, et al. MicroRNAs in type 2 diabetes mellitus: potential role of physical exercise. Reviews in cardiovascular medicine. 2022;23(1):29.
42. Yamashita T, Takahashi Y, Nishikawa M, Takakura Y. Effect of exosome isolation methods on physicochemical properties of exosomes and clearance of exosomes from the blood circulation. European journal of pharmaceutics and biopharmaceutics : official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik eV. 2016;98:1-8.
43. Li P, Kaslan M, Lee SH, Yao J, Gao Z. Progress in Exosome Isolation Techniques. Theranostics. 2017;7(3):789-804.
44. Neef T, Miller SD. Tolerogenic Nanoparticles to Treat Islet Autoimmunity. Current diabetes reports. 2017;17(10):84.
45. Gutiérrez-Vázquez C, Villarroya-Beltri C, Mittelbrunn M, Sánchez-Madrid F. Transfer of extracellular vesicles during immune cell-cell interactions. Immunological reviews. 2013;251(1):125-42.
46. Petzold C, Riewaldt J, Watts D, Sparwasser T, Schallenberg S, Kretschmer K. Foxp3(+) regulatory T cells in mouse models of type 1 diabetes. Journal of diabetes research. 2013;2013:940710.
47. Milanesi A, Lee JW, Li Z, Da Sacco S, Villani V, Cervantes V, et al. β-Cell regeneration mediated by human bone marrow mesenchymal stem cells. PLoS One. 2012;7(8):e42177.
48. Yu B, Zhang X, Li X. Exosomes derived from mesenchymal stem cells. International journal of molecular sciences. 2014;15(3):4142-57.
49. Gomzikova MO, James V, Rizvanov AA. Therapeutic Application of Mesenchymal Stem Cells Derived Extracellular Vesicles for Immunomodulation. Front Immunol. 2019;10:2663.
50. Pudlarz A, Szemraj J. Nanoparticles as Carriers of Proteins, Peptides and Other Therapeutic Molecules. Open life sciences. 2018;13:285-98.
51. Wang P, Liu Q, Zhao H, Bishop JO, Zhou G, Olson LK, et al. miR-216a-targeting theranostic nanoparticles promote proliferation of insulin-secreting cells in type 1 diabetes animal model. Sci Rep. 2020;10(1):5302.