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Utilization of Extracellular Vesicles for Treatment of Type 1 Diabetes Mellitus (T1DM) Along with Type 2 Diabetes Mellitus (T2DM) besides Complications Associated with Diabetes- A Systematic Review

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Abstract

We have earlier reviewed both etiopathogenesis along with therapy of both type1 diabetes mellitus (DM) (T1D) as well as (T2D) thoroughly along with advances in therapy. Despite that, there is no permanent cure and with the growing epidemic of obesity and thus the parallel enhancement of worldwide prevalence. Extracellular vesicles(ECV) by definition are physiologically bilayer vesicles that carry bioactive receptors, lipids, proteins as well as nucleic acids which cross-react with target cells, driving the modification of target cells. Maximum cells liberate ECV as well as recently have been shown to not only work as promising biomarkers for the disease but work as therapeutic agents for some diseases. ECV represent a heterogeneous population of small membrane vesicles (30-2000nm) liberated from various types of activated or apoptotic cells. In view of their ability of carrying out cell-cell communication , lot of significance has been given to them regarding their role as biomarkers or as utilization for therapy by trying to overtake cell-based therapy. DM T1D or T2D both if uncontrolled for long have the potential of causing a lot of complications like kidneys, cardiac, neuronal, eyes, feet problems ending with chronic end-stage kidney disease, blindness, stroke, myocardial infarction (MI) , erectile dysfunction, diabetic foot ulcers and gangrene , hence some permanent methods are sought to cure these. Here we conducted a systematic review utilizing the MeSH terms; Type1Diabetes mellitus; T2D; stem cells sources for DM therapy; exosomes; Extracellular vesicles; treatment potential in DM by utilizing the search engine Pubmed, Google Scholar, Web of science, Embase, Cochrane review library from 2000 to 2020. We found a total of 550 articles out of which we selected 128 articles for this review. No meta-analysis was carried out. Here we have tried to discuss the details of what are EVs, how they can be obtained, their contents, mechanism of actions in curing diabetes along with its complications like diabetic wound healing, diabetic retinopathy, diabetic nephropathy, stroke, diabetic peripheral neuropathy along with diabetic foot ulcers, erectile dysfunctions. Further the place clinically in trials we have reached in utilizing clinically as well as challenges faced in translation as well as bulk generation, methods utilized for their preservation. Hopefully, these will be overcome gradually and soon can get translated into clinical medicine.

Keywords: Type1 diabetes mellitus; T2D; Extra cellular vesicles; chronic end stage kidney disease; diabetic wound healing; diabetic retinopathy; diabetic nephropathy; stroke; diabetic peripheral neuropathy.

Introduction

Diabetes mellitus (DM) has become a major public health problem possessing complex etiology implicating 350million people all over the world. Anticipated incidence by 2045 is 700 million [1]. It is 6th major cause of death in US as well as correlated with escalated chance for cardiac disease, renal disease, eye involvement including blindness, limb gangrenes [2]. DM can be classified as type1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), as well as gestational diabetes mellitus (GDM) [3]. Commonest diagnosis is T2D, where 90% of the subjects fall in T2D category ,occurring secondary to abnormal generation of insulin, chronic low grade inflammation in person's tissues, that include adipose tissues (AT), liver and muscles [4]. T1D occurs secondary to insulin generating cells being short secondary to autoimmune impairment of pancreatic islet beta cells [5]. Earlier we have reviewed the etiopathogenesis as well as the treatment strategies of both T1DM as well as T2DM [6-11]. Right now no definite treatment for either of the DM group exists, thus alternative treatment for DM is urgently needed.

Cell based treatment is another way of DM treatment. Stem cells or immune cells have been used for treatment of DM [12-15]. Extra cellular vesicles (ECV) by definition are physiologically bilayered vesicles that carry bioactive receptors , lipids , proteins as well as nucleic acids which cross-react with target cells , driving the modification of target cells. Maximum cells liberate ECV as well as recently have been shown to not only work as promising biomarkers for disease but work as therapeutic agents for some diseases [16]. Hence EVS liberated by stem cells or immune cells have got lot of attention. It has been shown that these EVs possess a lot of treatment potential by getting their cargo into target cells as well as acting on various signalling pathways [17]. EVS act as signalling mediators among cells, that include islet cells, only recently became popular as candidate for DM therapy as well as its complications.

Extracellular Vesicles (ECVs)

Extracellular vesicles (ECVs) are fast developing areas in biomedical research as well as clinical translational medicine.

Classification as well as Generation

ECVs represent a heterogeneous population of small membrane vesicles (30-2000nm) liberated from various types of activated or apoptotic cells. Depending on their size as well as origin , EVs have been classified into 3 major groups (i) exosomes ,microvesicles (MV's) as well as apoptotic bodies [18] (Figure1).

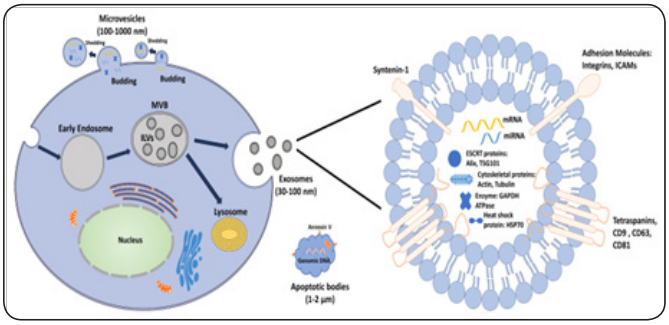

Figure 1: Scheme the biogenesis of EVs

Multivesicular bodies (MVB) are formed during endosomal maturation, and exosomes are released upon fusion of the MVBs with the plasma membrane. Differently, microvesicles are formed directly through cell membrane budding and fission. The apoptotic bodies are derived from the apoptotic cells [128].

Exosomes get obtained from the endocytic compartment as well as vary from 30-100nm in size. Particularly the cell's plasma membrane gets internalized to form an early endosome. Next, intraluminal vesicles (ILV) pinch the endosomal lining membranes inwards as well as bud into the endosome. Selected proteins as well as RNA's then get packed into the ILVs via the endosomal sorting complex needed for transport (ESCRT-dependent machinery or ESCRT independent machinery. The endosome is now generating a multivesicular body (MVB). Consequently, a partial number of MVB get digested via fusion with lysosomes, whereas others fused with plasma menmbrane via unknown mode that implicates RAB -27 as well as soluble NSF (N-ethylmaleimide- sensitive factor) attachment protein receptor (SNARE) proteins. These payloads ILVs get liberated into the extracellular membrane (ECM) as exosomes [19-20]. Though the particular mode is still not clear, it seems that the growth factor will facilitate the formation of MVBs. The cell modifies its generation of exosomes along with its requirements [21]. Exosomes get surrounded by a bilayer of phospholipids enriched with ceramides as well as cholesterol. The surface molecules anchored in the exosomes membrane include adhesion molecules integrins as well as intracellular adhesion moleculesn (ICAMs), tetraspanin proteins (CD9, CD63 as well as CD81) as well as immunity association, molecules (MHC-I as well as MHC-II). The cytoplasm of an exosomes includes ESCRT-associated proteins (apoptosis linked gene-2 interacting protein X (ALIX) as well as tumor susceptibility 101 (TSG101, RNA'S mRNA, microRNAs, long noncoding RNA (lncRNA), cytoskeletal proteins (actin as well as tubulin) as well as metabolic enzyme glyceraldehyde 3-phosphate dehydrogenase (GADPH) as well as ATPase [22-23]. Moreover exosomes possess certain particular molecules which are based on their original cells. Like researchers discovered exosomal MHC molecules, liberated by dendritic cells, cross reacting with T cells, to stimulate antitumor immunity [24].

Isolation as well as properties

Although MV's as well as exosomes are generated by a variety of modes, maximum isolation methods are unable in isolating a pure population in view of their size overlap. Thus, a variety of ECV isolation methods have got proven that are ultracentrifugation, density gradient centrifugation, ultrafiltration, polymer dependent precipitation, size exclusion chromatography (SEC) as well as microfluidic device isolation [25].

- Ultracentrifugation isolation depends on the size of the EVs classically made up of sequential escalation of centrifugal forces to pellet cells as well as debris (<-2000xg), large ECVs (-10,000-20,000xg) as well as small EVs (100,000-200,000xg)
- Density gradient centrifugation isolation is based on the size as well as mass density for isolating ECV's.
- Ultrafiltration isolation depends on the size of the EVs, where samples get passed via) a membrane that possesses particular pore size via pressure or centrifugation.
- Polymer dependent precipitation depends on the application of a polymer solution, like polyethylene glycol (PEG), to reduce solubility of EVs, as well as force their precipitation.
- Immuno precipitation isolation is when monoclonal antibodies immobilized on the surface of a plate or beads to capture these ECVs.
- Size exclusion chromatography depends on the size of the EVs that get separated with the aid of utilizing a column. Main ECVs get eluted prior to the soluble compounds.
- Microfluidic device isolation based on the designed device isolation is challenging, in view of this every one having advantage as well as disadvantages.

Following isolation, EVs populations require to get divided on Properties of ECVs. (i) Utilizing transmission electron microscopy (TEM), (ii) Scanning (SEM), (iii) nanoparticle tracking analysis (NTA), (iv) Dynamic light scattering (DLS), (v)the size of ECV's [26]. Western blotting as well as enzyme-linked immunosorbent assays represents an easy technique for deciding Properties of EVs, utilizing certain classical biomarkers like CD9, CD63, CD81, ALIX, as well as TSG101 [27]. These techniques get utilized to recognize as well as label ECV's based on their properties. Right now flow cytometry has found to be luring method for ECV's evaluation. Maximum current flow cytometry methods can pick up particles greater than 500nm. Thus, the EVs must be bound to antibodies or surface latex beads with a size which can be picked up in the range of the flow cytometer [28]. The latest flow cytometry method (alias, nanoscale flow cytometry)is markedly sensitive as well as allows the direct evaluation of single EV as well as protein profile as low as 40nm [29]. Moreover, if the markers that have been picked up as markers on a single EV, nanoscale flow cytometry will aid us in labelling the Properties of innovative particular subpopulations of EVs as well as the diagnostic markers on EVs. With these labelling of Properties might aid in gaining insight of EV biology as well as early diagnosis of disease [30]. Thus nanoscale flow cytometry will form a very robust method for further EV research as well as disease diagnosis.

Target cells crosstalk with EVs

The treatment ability of EVs is based on their capacity to crosstalk with the target cells. Different modes exist by which EVs crosstalk with the target cells (Figure 2). One such mode is the liberation of molecules from the EVs, which crosstalk with the surface molecules of the target cells to stimulate their signalling. Like, it was observed that tumor cell -liberated EVs carry programmed death ligand 1 (PDL1) on their surface that crosstalk with the programmed death 1 (PD1) receptors existing over T cells to evoke an immune checkpoint [31]. On the other hand, EVs might influence the targeted cells via the internalization as well as a transfer of their cargos. Besides that, lot of opinions over the mode via which internalization of the exosome takes place, like via membrane fusion, receptor-based endocytosis, micropinocytosis or phagocytosis [32]. These last 2 modes, namely (micropinocytosis as well as phagocytosis) might aid in the clearance of EVs. Direct proof of EVs fusing as well as getting endocytosed into recipient cells has been received by utilizing lipophilic dye labelled EVs, leading to escalation of the fluorescence of the recipient cells. This kind of real-time imaging method yields significant lessons regarding the examination of EV internalization [33].

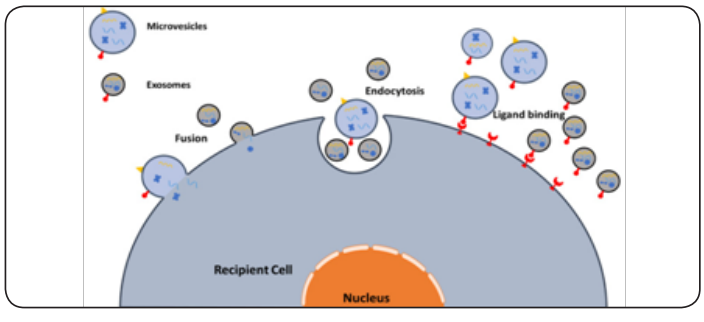

Figure 2: Uptake of EVs

EVs are taken up by the targeted recipient cells via the fusion of the vesicle membrane with the cellular membrane or by endocytosis the receptor and its ligand on EVs

Role of EVs as a treatment mode for DM as well as its complications

Lot of morbidity as well as mortality results secondary to DM as well as its complications, all over the world, giving an estimated 4.2 million deaths secondary to DM in 2019 [34]. As a cell free treatment EVs work as a robust candidate.

T1DM as well as EVs

T1DM as reviewed earlier represents a chronic disease having the properties of insulin deficit secondary to autoimmune damage of the insulin –liberating pancreatic β-cells, resulting in hyperglycemia. Usually the symptomatic onset takes place in childhood. Though the mode of T1D is still not clear , the etiopathogenesis of this disease is believed to get modulated by aberrations in lot of immune cells, that include T cells , B cells, regulatory T cells (Treg), monocytes as well as macrophages (Mo/M θ), disease as well as Dendritic cells (DC's).

Whereas lot of daily injections of exogenous insulin aid in T1D patients to control their blood sugars , this basically does not influence the basic immune aberration as well as hence does not represent cure for TID. In view of possessing same function as their parent cells, EVs as treatment mode has been an attractive mode for research. MSC'S –obtained EVs for the therapy of an autoimmune diabetic mouse model adoptive transfer T1D mouse model got utilized via Shigemoto Kuroda et al. [35] as well as saw that a delay in the onset of T1D via inhibition of T cell proliferation as well as suppression of the activation of antigen presenting cell (APC) . Additionally , Nojendahl et al. [36], showed that intraperitoneal injection of bone marrow (BM)-derived MSC'S(BMMSC)- obtained exosomes were able to abrogate inflammatory reaction in streptrozotocin (STZ)- stimulated T1D mouse model via enhancement of Treg cells population. Later Favaro et al. [37], found that MSC'S –obtained EVs stimulated the conversion of monocytes via T1D patients into immature interleukin -10 (IL-10) liberating DC's in vitro, probably aiding in the inhibition of inflammatory T cell responses to islet antigens in an STZ-induced T1D rat model . Furthermore these therapeutic EVs besides ameliorating inflammatory T cell responses in T1D, has a significant part in β-cells regeneration. Menstrual blood-obtained –MSC (MenSC)-derived exosomes escalated the β-cells mass as well as insulin generation as per Mahdipour et al. [38], via the pancreatic as well as duodenal box 1(PDX1) pathway in a STZ-induced T1D mouse model. As per Tsukita et al.[39], documented that BM-cell – obtained EVs possess miRNA's (miR-106b-5p as well as miR-222-3p) which had the ability to enhance β- cell proliferation via downregulation of the CIP/calcium as well as integrin binding protein (KIP) pathway . Additionally, the EVs showed an important part in enhancing the islet transplantation result. Human (h) BMMSC as well as peripheral blood mononuclear cells(PBMC)

cocultured exosomes , for enhancing the islet allograft survival in humanized NOD scid IL-2Rϒⁿᵘˡˡ (NSG) mice [40]. Sun et al. quite recently documented that EVs obtained from mouse pancreatic β-cells line MIN-6 could enhance insulin amount of pancreatic islets as well as preserve the architecture of the islets within STZ-induced diabetic mice [41]. Hence EVs show translational capacity for T1D treatment as well as future evaluation is needed prior to clinically applying them.

Type 2 DM as well as EVs

Type 2 diabetes is the maximum prevalent diabetic form, having the properties of 2 alterations that are dependent on each other, namely insulin resistance (IR) as well as of pancreatic islets β-cells impairment [42]. T2D occur secondary to a crosstalk among genetic, environmental, emotional, as well as behavioural risk factors. Earlier hypoglycaemic drugs delivery as well as insulin injection was the initial treatment for T2D [43]. Intriguingly current studies demonstrated that certain EVs may possess their ability of treatment of T2D. Intravenous injection of EVs that had been isolated from human umbilical cord MSCs partly converted IR through indirect enhancement of glucose metabolism as well as abrogating β-cells damage in streptozotocin (STZ)-induced diabetic rats with a high fat diet (HFD) as demonstrated by Sun et al. [44]. For finding the mechanism of action it was seen that EVs i) restored phosphorylation of insulin resistance substrate 1 (IRS1) as well as protein kinase B(PKB) in T2D rats, ii) facilitated the expression of translocation of glucose transporter 4 (GLUT4) in muscle, as well iii) sustained glucose homeostasis through escalating glycogen storage in liver. Additionally, they observed that MSC- obtained EVs aided in improving β-cells damage for restoration of insulin liberation in T2D rats. Zhao et al. [45], in another work treated obesity (HFD induced) mice with EVs that were adipose derived stem cells (ADSC) –derived as well observed that these EVs had the ability to polarize macrophages into anti-inflammatory Type 2 macrophages (M2) phenotypes by activation of signal transducer of activation and transcription 3 (STAT3) pathway that ultimately upregulated the expression of arginase 1 (ARG1) in macrophages, thus enhancing both metabolic balance as well as IR in mice.

Furthermore, an innovative stem cells source exist known as cord-blood derived multipotent stem cells (CB-SCs), as well as monocyte-obtained stem cells [46]. Both in vitro as well as animal experiments showed that CB-SCs possess a robust therapeutic ability for DM [47]. On the basis of their special characteristics of immune modulation as well as the capacity to tightly stick to the petri dishes surface, a new technology was formed by the group of Hu et al., named Stem Cell Educator (SCE) treatment, in clinical trials for the treatment of TI [48], T2D [49] as well as autoimmune –caused alopecia areata [50]. At the time of SCE therapy, the PBMC get retrieved as well as circulated via a cell separato as well as cocultured with adherent CB-SCs in vitro. Subsequently these so called ''educated ''cells then get returned back to the patient's circulation via a closed loop system. Through the clinical trials it has already been shown regards to safety as well as effectiveness of these SCE therapies for treatment of DM. Subsequent study of CB-SCs demonstrated that these liberate exosomes possessing an immune modulation function akin to that of the original cells, that stimulate monocytes to differentiation into anti-inflammatory Type 2 macrophages (M2) [51]. CB-SCs-obtained exosomes showed besides the mode of SCE therapy, the lucrative materials it is for therapy of DM.

Additionally, besides these EVs possessing treatment capacity for DM, certain candidates are present which might be applied in future. Human Tregs are necessary for sustainance of peripheral tolerance, avoid autoimmunity, as well as minimize chronic inflammation [52]. The protocol that has been well proven regards to the amplification of Tregs in vitro gave researchers the ability of isolating EVs from the Tregs-cultured conditional medium [53]. As per Aiello et al.[54] showed that EVs-obtained from the Tregs- caused immune suppression on T-cell proliferation as well as prolonged kidney allograft survival in a mouse model. Tregs- obtained EVs-stimulated DC's to attain a tolerogenic phenotype, with enhanced IL-10 as well as reduced IL-6 generation .Moreover myeloid – obtained suppressor cells (MDSC) represent a heterogenous population of cells which expand at the time of cancer, inflammatory diseases as well as autoimmune conditions was shown by Tung et al. [55]. They possess a marked capacity of suppressing immune responses [56]. MDSC- obtained EVs demonstrated immune modulation by inhibition of T-cell proliferation as well as facilitation of Tregs-expansion that avoided propagation as well as was enough for part hair regrowth in case of alopecia- areata (AA) mouse model. These observations with regards to immune modulation function of EVs-point therapeutic ability in DM.

EVs as well as DM complications

Basically DM Complications occur secondary to high glucose stimulated cellular as well as molecular dysfunction of neural as well as cardiovascular system (CVS). Currently, EVs have been considered as robust therapeutic candidates for treatment of DM. Treatment that combined gingival MSC (GMSC).

Wounds related to DM

In cases of DM, the hyperglycaemic surroundings result in wounds which heal slowly or refuse to heal, thus cause a serious problem for health care in the clinical setting . Precise etiopathogenesis of delayed Wound healing in patients with DM is not clear. Nevertheless, both human as well as animal experiments display dysfunctions at time of Wound healing process [57]. Risk of infection escalates with dysfunction at the time of Wound healing, thus increasing Wound healing remains an immediate attention in DM. A proangiogenic protein known as deleted in malignant tumor1 (DMBT1),was observed by Chen et al. [58], which was enriched in EVs from urine -obtained SC'S(USC's). In vivo studies demonstrated that DMBT1 had the ability to facilitate angiogenesis as well as wound healing in diabetic mice.

Moreover, MSC'S –obtained from various sources remain lucrative cells for isolation of EVs with regards to therapeutic applications in case of wounds secondary to DM. Li et al. [59], documented that EVs - obtained from nuclear factor erythroid 2 like 2(NRF2)- overexpressed adipose deirved stem cells (ADSCS) had the ability to facilitate cutaneous Wound healing through enhancing vascularisation in a rat model of diabetic foot ulcers. Functional Assays showed that EVs decreased inflammation cytokines (IL-6, IL-1β as well as tumor necrosis factor alpha (TNF α) as well as oxidative stress –associated proteins that EVs - from microRNA-126 overexpressing synovium MSCs (SMSCs) facilitated migration as well as tube generation of HMEC-1 cells in vitro as demonstrated by Tao et al. [60]. These EVs increased the rate of wound healing at the functional level by facilitation of re-epithelialization, stimulating angiogenesis, as well as forming mature collagen. In the same way Ding etal. [61] documented that EVs - obtained from desferoxamine -stimulated h BMMSCs delivered their exosomal miRNA-126 for downregulation of phosphatase as well as tensin homolog (PTEN) that stimulated angiogenesis in vitro as well as escalated wound healing in STZ- induced diabetic rats. Moreover Li et al [62] observed that an lncRNA's known as lncRNA 19H in exosomes obtained from MSCs avoided apoptosis as well as inflammation in fibroblasts by interfering with miRNA-152-3p-modulated PTEN inhibition, resulting in wound healing stimulation in a rat model of diabetic foot ulcers. Treatment that combined gingival MSCs (GMSCs) –obtained exosomes with chitosan/silk hydrogel resulted in better Wound healing in a diabetic rat skin defect model that received treatment with only chitosan/silk hydrogel. These GMSCs-obtained exosomes facilitated Wound healing by facilitating re-epithelialization, angiogenesis, as well as neuronal ingrowth in diabetic rats [63].

EVs- obtained from umbilical cord-blood obtained endothelial progenitor cells (UCB-EPC's)that facilitated angiogenesis of endothelial cells via activation of extracellular signal –regulated kinase (ERK)1/2 signaling as documented by Zhang et al [64]. This resulted in escalated cutaneous Wound healing as well as regeneration in a diabetic rat model. Akin to this, a study showed that EPC's- obtained exosomes increased the rate of Wound healing in diabetic rats by stimulation of endothelial cell proliferation as well as migration by escalating the amount of angiogenesis-associated molecules, like fibroblast growth factor1 (FGF1), vascular endothelial growth factor 1 (VEGF-A), vascular endothelial growth factor1 receptor 2 (VEGFR2) as well as angiopoitin (ANG1) [65]. Additionally, to these stem/progenitor cells- obtained EVs, other EVs could be utilized for therapy of diabetic Wounds. In a study it was shown that macrophages- obtained EVs increased the rate of Wound healing by causing anti-inflammatory actions as well as enhancing endothelial cell function in a diabetic rat model [66]. Guo et al. [67], demonstrated that platelet Rich plasma (PRP) - obtained EVs facilitated the healing event in a diabetic rat model. Work conducted for seeking molecular modes displayed that PRP- obtained EVs stimulated the migration as well as proliferation of fibroblast as well as endothelial cell for enhancing re-epithelialization as well as angiogenesis through activation of Rho-yes associated protein (YAP) signalling pathway in the diabetic rat model. Geiger et al. [68] observed that EVs obtained from human fibrocytes increased the rate of Wound healing in diabetic mice. They facilitated angiogenesis, caused activation of fibroblasts, as well as escalated the function of keratinocytes by carrying exosomal miRNA's (miR-126, miR-130a, miR-132) as well as anti-inflammatory miRNA's (miR-124a as well as miR-125b). Moreover artificial EVs that were loaded with particular biomolecules gave a new way of therapy of diabetic Wounds. Workers observed that various biomolecules were markedly decreased in DM that included the lncRNA 19 H as well as miR-126. In a study it was demonstrated that artificial EVs-mimetic nano vesicles (EMNVs) that were loaded with the lncRNA 19H had a robust ability to bring back the regeneration-inhibiting actions of hyperglycemia as well as could significantly increase the rate of wound healing in a diabetic rat model [69]. Summarizing, these studies utilized various EVs as their methods that had great efficacy in facilitating Wound healing as well as could be formed as other way of clinical in future.

Stroke in DM

In DM enhanced vascular permeability, that results in enhanced morbidity correlated with ischemic stroke [70]. Furthermore, changes in metabolism as well as enhanced inflammation, that causes stroke pathology as well as worsened vascular as well as white matter (WM) damage following a stroke that makes it more problematic for treatment of brains of DM pts [71]. Venkat et al. [72] documented that therapy with brain endothelial cell obtained EVs had the ability to markedly enhance the neurological as well as cognitive function in T2D –stroke mice. These enhancements might have enhancements of densities of axon, myelin as well as blood vessel's along with polarization of anti-inflammatory Type 2 macrophages (M2) differentiation. Studies for deciphering mechanism of action showed that endothelial cell obtained EVs enhance miR-126 as well as might aid in the EVs-manifested retrieval of neuronal function as well as axonal outgrowth. The commonest complications of T2D are stroke as well as cardiovascular disease (CVD) that significantly enhance patient's mortality risk [73]. Venkat et al. documented that therapy with EVs obtained from the -cord- blood – obtained $CD133^{+}SC$ had the ability to ameliorate post stroke cardiac impairment in T2D –stroke mice via reducing the myocardial cross –sectional area as well as interstitial fibrosis, downregulation of transforming growth factor beta (TGFβ) as well as amount of Type 1 macrophages (M1), as well as upregulation of miR-126 expression in heart of T2D –stroke mice [74].

Retinopathy as well as T2D

Diabetic Retinopathy (DR) represents a robust T2D complications as well as main reason of loss of vision in case of middle aged as well as elderly people. Hyperglycemia is thought to have a significant part in the formation as well as propagation of DR. DR shows

the microvascular deficits, neuroretinal impairments as well as degeneration of the retina [75]. EVs obtained from MSCs recently, demonstrated treatment capacity for therapy of DR. Safwat et al. [76] documented that intraocular or subconjunctival (although not Intravenous injection) of EVs obtained from ADSCs could shield retinal tissue structure from degeneration of the STZ)-induced model of a diabetic Retinopathy in rabbit. In the same way in a study it was demonstrated that intravitreal injection of EVs obtained from MSCs were efficacious in decreasing the amounts of inflammatory markers like IL-1β, IL-18 as well as caspase 1 in the vitreous humor of the STZ -induced diabetic rats. At the functional level, EVs obtained from MSCs possessing miR-126 to have a necessary part in reverting the effects of inflammation by the inhibition of the high mobility group box 1 (HGMB1). Moreover the author observed that EVs obtained from miR-126 overexpressed MSCs had greater efficaciousness in decreasing inflammation in case of Diabetic Retinopathy [77].

Cardiomathy as well as T2D

Diabetic Cardiomathy by definition is diabetes-correlated alterations in the structure as well as function of the myocardium that involves roughly 12% of diabetic subjects as well as cause heart failure as well as death. Wang et al. [78] displayed that HSP-20 overexpressing Cardiomyocytes obtained EVs possessing escalated amounts of HSP-20 could shield endothelial cells as well as Cardiomyocytes from hyperglycemia stimulated stress in vitro. An in vivo study observed that the of HSP-20 -rich EVs at functional level had the capacity to abrogate hyperglycemia stimulated cardiac bad remodelling via significantly enhancing the left ventricular internal diameter at the end-diastole (LVIDd), the left ventricular ejection fraction (LVEF%), as well as the density of myocardial blood vessels in STZ -induced diabetic mice. EVs obtained from MSCs had the capacity to retrieve left ventricular collagen(LVC) was documented by a study as well as decreased the expression of fatty acid (FA) transporters (FATPs) as well as FA β-oxidase in STZ -induced diabetic rats. Trying to evaluate the mechanism of action displayed that EVs obtained from MSCs inhibited the TGF-β/SMAD family member2 (SMAD2) signalling pathway ,that had a significant part in the EVs -correlated enhancement in DM –induced myocardial damage as well as fibrosis [79].

Neuropathy as well as T2D

Diabetic peripheral Neuropathy (DPN) represents one of the commonest chronic complications of DM, initiating with sensory loss in distal nerves [80]. EVs got implicated recently for improving Neuropathy impairment in DM. Schwann cells(SCs)- that are the of maximum quantity in the peripheral nervous system(PNS) , cross react with axons as well as blood vessels for controlling peripheral nerve function[81]. SCs obtained exosomes significant enhanced Neuronal regeneration in vitro as well as facilitated regeneration following sciatic nerve damage in vivo [82]. Moreover, Wang et al. [83] documented that EVs obtained from SCs (SCs-Exos)-markedly abrogated DPN by enhancing sciatic nerve conduction velocity as well as enhancing thermal as well as mechanical velocity along with enhancing thermal as well as mechanical sensitivity in a diabetic mouse model. Molecular evaluation of sciatic nerve tissues displayed that functionally SCs-Exos treatment reverses DM-decreased miR-21, miR-27a, as well as miR-146a amounts ,along with Diabetes –enhanced Semaphorin 6A(SEMA6A), PTEN as well as nuclear factor κ-B (NF-KB)amounts. Besides SCs-Exos, EVs from SC's further demonstrated therapeutic function in DPN. In case of diabetic mice therapy of DPN by EVs obtained from MSCs cured neurovascular impairment as well as facilitated the functional improvement, as per Fan et al. [84], that resulted in an enhanced amount of intraepidermal nerve fibers, myelin thickness as well as axonal diameters. Western blotting evaluation moreover showed that therapy with EVs obtained from MSCs decreased the inflammation response by reducing the amount of M1 as well as enhancing the amount of M2 macrophages, respectively.

Cognitive impairment as well as T2D

Significant proof is there that Diabetes is related to decrease in Cognitive function causing dementia in both subjects with both T1D as well as T2D. In case of T2D there exists about 1.5-2.5 times escalation in the chances of dementia as well as has been correlated with memory defects, executive function impairment, attention, and processing as well as motor speed [85]. Certain EVs were implicated which could enhance Cognitive function in case of Diabetes individuals currently. Nakano et al.[86], demonstrated that intracerbroventricular injection of EVs obtained from BMMSCs had the ability of improving Diabetes stimulated Cognitive dysfunction in a STZ -induced mouse model. On histological evaluation it was demonstrated that, whereas these EVs failed to enhance the amount of neurons, they did inhibit the oxidative stress as well as escalated the synaptic density in the CA1 area of the hippocampus. In the same way Zhao et al. [87], demonstrated that intracranial injection of EVs obtained from BMMSCs abrogated Diabetes stimulated Cognitive impairment, where the EVs-receiving group displayed a smaller escaping delay in a water maze experiment in STZ -induced diabetic mice. Further, a study demonstrated that EVs obtained from miR-146a-loaded brain endothelial cells injected into the brain ventricles of T2D db/db mice had the ability of partly resurrecting short term memory function as well as downregulation of prion protein (PrPc) that collects in brain cells of diabetic model mice [88]. These outcomes pointed that EVs might prove to be an attractive for therapy of Cognitive dysfunction stimulated by Diabetes.

Erectile dysfunction secondary to Diabetes

Erectile dysfunction (ED) is a relatively usual as well as less realized Diabetes complication. Escalated incidence has been documented regards to ED in subjects with Diabetes. Furthermore ED appears in the form of a symptom 10 years prior as well as presents greater resistance to therapy as compared to nondiabetic subjects [89]. In a recent study it was documented that EVs obtained from SCs could be utilized for abrogating ED in an animal model. Intracavernosal

injection of EVs from ADSCs had the ability to facilitate the recovery of ED as shown by Chen et al. [90], by inhibition of apoptosis of corpora cavernosal endothelial as well as smooth cells rat model of diabetic ED. In the same way a study observed that EVs obtained from ADSCs managed to restore ED in a STZ -induced diabetic rats. Bioinformatic evaluation observed that EVs possess antifibrotic miRNA's (miR-let7b as well as miR-let7c) along with preganglionic miRNA's (miR-126, miR-130a, miR-132) that had the ability of downregulation of the amount of fibrosis as well as enhanced angiogenesis in the cavernosum [91]. Intriguingly, USCs possessed a significantly abrogating impact on ED as illustrated by Ouyang et al. [92], on a STZ -induced rat model of diabetic ED. On dissecting the mechanism of action of these EVs it was documented that these were loaded with a unique class of miRNA's, that included miR-21-5p, the let7 family as well as miR-10 family, family as well as miR-3family as well as, miR-148a-3p. Also Kwon et al. [93], documented that embryonic- Stem Cell obtained Extra cellular vesicles mimetics (ESC-NV's), that got formed by cells expelled through serial filters possessing reducing size (10, 5 as well as 1μm), had the capacity to totally restore Erectile function in STZ -induced diabetic mice. On histological evaluation it was documented that these ESC-NV's stimulated neural regeneration in the corpus cavernosum in diabetic restored cavernosum endothelial, smooth muscle cells, as well as pericyte amount. Summarizing EVs (Stem Cell obtained) possess a positive as well as might be applicable in clinical diabetic patients in the future.

Nephropathy as well as T2D

Diabetic Nephropathy (DN) represents one of the worst Diabetes complications as well as remains the commonest etiology of end stage renal disease (ESRD) that is the last stage of chronic renal disease (CKD) [94]. At present haemodialysis or transplantation are the commonest modes for treatment of ESRD. There are drawbacks for both methods that include costly as well as organ availability being totally uncertain [95]. MSC obtained EVs have been considered to be an attractive therapy for DN recently. A previous study observed that MSCS enhanced DN via paracrine action of kidney trophic factors, which included EVs in both STZ as well as HFD -induced diabetic mice. These EVs caused an antiapoptotic action as well as shielded tight junction structure in tubular epithelial cells [96]. In the same way Grange et al. [97] observed that the delivery of EVs obtained from both BMMSCS, as well as human liver stem like cells (HLSCs) significantly enhanced renal function in case of diabetic mice. On histological evaluation it was documented that renal fibrosis which formed at the time of DN propagation got significantly inhibited as well as restored to normal in EVs therapy group. On deciphering mechanism of action it was displayed that these EVs possess particular miRNA's, that that downregulated profibrotic gene expression that inhibited renal fibrosis in case of DN. Moreover, Ebrahim et al. [98] documented that EVs obtained from both BMMSCs, significantly improved renal function through autophagy stimulation via mTOR signalling pathway in diabetic rats. Akin to that Jin et al. [99], documented that that EVs obtained from both ADSCs, significantly abrogated DN symptoms through exosomal miR-486 that caused inhibition of SMAD1/mTOR signalling pathway in podocytes. Additionally, EVs obtained from both USCs, had a significant part in therapy of DN. Jiang et al. [100] observed that EVs obtained from human USCs, enhanced renal function via inhibition of podocyte apoptosis as well as facilitating regeneration in case of a type1 diabetic rats. On deciphering mechanism of action it was shown that exosomal miR-16-5p had the ability of conferring protection by suppression of VEGFA as well as the podocyte apoptosis, thus improvement of renal function in DN. Subsequently the application of EVs obtained from miR-15-5p overexpressing human USCs, had capacity of greater efficiency in rectifying podocyte function in diabetic rats that gives greater understanding with regards to innovative therapies of DN [101]. These outcomes pointed that EVs may be an attractive tool with regards to therapy of DN.

EVs-dependent clinical trials both ongoing as well as finished

Till now , practical utilization of EVs have been translated into clinical trials with regards to innovative ways for diagnosis as well as therapy of various diseases, that are DM, cancers , infections, as well as inflammation or autoimmune correlated diseases [102]. At present there are 18 Diabetes- correlated clinical trials. In view of carrying MicroRNA's, lipids as well as proteins belonging to their primary cells, maximum of the clinical trials have utilized EVs in the form of biomarkers for determining the clinical diagnosis as well as to monitor the disease propagation post therapy. Nassar et al [103] utilized the intra articular injection of mesenchymal stem cell derived EVs of 20 cases of CKD at stages III as well as IV.10 of these patients were Diabetic. This therapy documented that that therapy with EVs, markedly improved the estimated glomerular filtration rate (EGFR) as well as the total renal failure in grade III as well as IV. Further they posited a clinical trial (number nNCT02138331), for the therapy of renal disease utilizing mesenchymal stem cell derived EVs .Similarly clinical trials are ongoing utilizing these EVs for treatment of inflammation or other immune –impairment – correlated diseases . MSCs- derived EVs might display equivalent treatment capacity in view of similar MSCs- secretome possessing cytokines, chemokines as well as anti- inflammatory factors. More optimization in relation to Clinical trials is required with clinical grade EVs to further propagate treatments based on utilization of EVs –dependent cell- free therapy.

Longterm considerations for further development

Despite EVs showing significant treatment capacity, the translation of EVs into clinical utilization has not been clear in lot of matters.

Mass formation of EVs

Translation of EVs into clinical utilization needs large quantity formation of Clinical grade EVs. For massive quantity production of EVs, there are 2 matters that have to be clarified i)the formation

of large amount of cells as well as ii) the retention of the cell or phenotype of the EVs [104]. For enhancing the cell culture, researchers have utilized T-flasks as cell culture surfaces of stimulated cells with different stimuli. These methods nevertheless may alter the composition as well as function of EVs [105]. Moreover 3D cultures method was utilized by Haraszti et al for maximizing the surfaces area of cell culture like microcarriers in stirred bioreactors or bioreactors with hollow fiber bioreactors system [106]. Nevertheless, these methods have their own drawbacks in view of alterations in the environmental conditions in the reactors will alter the phenotype of the cell as well as the EVs obtained from them. A lot of factors might implicate the quantity as well as a quality of the cell supernatant – obtained EVs; namely (i) cellular density, (ii) early or later passage of cells, (iii) O2 amount, (iv) cytokines or heparin as well as medium development [106]. Like it was observed by researchers that EVs obtained from early passage of BMMSCs displayed greater efficiency of Neuroprotective effects as compared to later passage obtained EVs [107]. Scientists pointed that EVs obtained from 3-5 passages of cells for Clinical utilization, since they had equivalent functions as well as abilities as MSCs [108]. However, the medium development in the form of main barrier for EVs clinical translational application. Fetal bovine serum (FBS), like RNA's possessing EVs, influences the cultured cells behaviour. Serum free cultured media can alter the composition of EVs proteins [109]. For resolution of these problems, Scientists apply platelet lysate with EV depleted medium for culturing hBM-MSCs, maintaining their phenotype as well as differentiation ability of SC as well as making sure that RNA's profile of EVs remains unaltered [110]. Such protocol gives a separate method for large scale GMP-dependent EVs generation.

Clinical grade EVs Isolation as well as preservation

At present, no state of the art –methods to generate EVs in huge clinical scales for therapeutic utilization. Despite the ultracentrifugation isolation technique represents the '' gold standard'' regarding exosomes isolation, the drawback of this is the low yield regards to clinical grade EVs isolation. Even rest of the techniques remain nonsuitable for this clinical grade EVs isolation in view of chemical reagent /antibody contamination or low purity. Currently scientists have applied the ultrafiltration for concentrating the condition medium that gets followed by size exclusion chromatography (SEC) for deriving EVs [111]. With this kind of isolation technique offers much greater yield along with more preservation of the biological characteristics of the EVs thus has like a magnet lured scientist's attention as far as clinical utilization is concerned [112].

No particular standard protocol exists as far as preservation of isolated clinical grade EVs exists regards to future utilization. Cryopreservation utilizing Cryopreservants, like glycerol as well as dimethyl sulfoxide(DMSO) ,do not represent the ideal technique regards to EVs preservation. One Study observed that 5% glycerol as well as 1% DMSO partly or totally lysed these EVs [113]. Till date a lot of groups have utilized phosphate buffered saline (PBS) regsrds to storage buffer for conservation of EVs functional as well as physical characteristics. Nevertheless, the minimal amount of Calcium included in EVs would result in generation of nanosized Calcium phosphate microprecipitates within the PBS that might interfere with quantification [114]. With regards to the temperature needed for preservation for EVs, scientists have documented that EVs remain more stable at -80 as well as -20^{0}C as compared to storing at 4^{0}C or higher temperature [115]. Otherwise certain researchers utilized lyophilisation of EVs for prolonging their shelf life as well as reducing storage demand along with cost factor. Here, the best storage temperature documented regarding lyophilised EVs s was at 4^0 C [116].

Getting EVs targeted to Cells

Specificity of EVs towards their targeted cells was illustrated by Denzer et al. [117]. MHC Class II that was expressed by the EVs stick to the follicular dendritic cells (FDC) as well as their liberated exosomes as well as could induce proliferation of particular T lymphocytes in vitro, although they do not get expressed by FDC by themselves. Whereas the dependence of targeting EVs from Platelet transfer tissue factor to monocytes as well as endothelial cells but not to neutrophils [118]. Whereas the dependence of targeting EVs remains unclear, certain molecular or cell dependent targets have come out. Changes in the presence of recipient cells, surface molecules on EVs as well as the physiological status of the recipient cells modulated the specificity of EVs internalization to recipient cells caused decrease in EVs internalization [119].

To correct a metabolic condition, or facilitate tissue regeneration in DM or its complications EVs need to be directed as well as monitored by the proper correct cells as well as then get internalized. For these EVs that are directed to correct the target cells, the technique of EVs delivery needs to be addressed at the time of treatment. Like treatment with MSCs- EVs via Intravenous injection did not restore the impairment, but subconjunctival injection totally resurrected the impairment in case of Diabetic Retinopathy. The variety of delivery routes of EVs showed separate therapeutic actions. Most of these studies concentrated on the functional alterations, without bothering to clarify the Extracellular target by these EVs. For tracing EVs at the time of ex vivo or in vivo studies, scientists, tried labelling EVs with lyophilic dyes that included PKH26, PKH67, DIO, as well as DID for tracking these EVs targeted cells [120]. Utilizing the fluorescence dye DIO-labeled stem cells CB-SC -obtained exosomes, they observed that exosomes preferred to bind to CD14+ monocytes in human PBMC, resulting in an upregulation of the mitochondrial membrane potential for treated monocytes as well as differentiation into type 2 macrophages. Other study utilized PKH67 -labelled EVs as well as observed that their incorporation into skin tissue enhanced rate of Wound healing in vivo. These lipophilic dyes give a strong tool regarding experimenting EVs targeting as well as guide regards to EV selection based on the particular cell target.

Manipulation of EV

Whereas it is obvious that EVs possess efficacy in various kinds of disease models, for ensuring administration of these EVs to the sites of their treatment action, while limiting the collection at off target areas, a lot of attention is escalating their characteristics of EVs that might aid in reducing dosage or reduce the frequency of administration. Various techniques of EVs have been used like engineering, priming, loading as well as artificial EVs [121]. Linking of EVs to a hydrogel through a photo-cleavable –linker, that upon further stimulation, stimulates the controlled liberation of exosomes for facilitation of wound healing in a murine model. Additionally, a study primed EVs by exposing MSCs to the inflammatory cytokines interferon –ϒ-, following which the liberated EVs had greater efficacy with regards to acute lung injury model [122]. Moreover MicroRNA's-181a was overexpressed in Mesenchymal Stem Cells, followed by collection of MicroRNA's-181a loaded exosomes that demonstrated higher effectiveness for the treatment of ischaemia –reperfusion injury [123].

For deriving clinical grade EVs on a huge scale, scientists posit that design as well as a construct totally synthetic EVs-mimetic particles using bio nanotechnology. Like researchers saw that the amounts of APO2 ligand (APO2L) alias (TNF-related apoptosis–inducing ligand (TRAIL) got drastically decreased in synovial fluid in patients with rheumatoid arthritis (RA). Subsequently, they conjugated APO2L with artificial lipid vesicles that mimicked Exosomes, that downregulated the T cell activation in an antigen stimulated arthritis animal model [124]. Ultimately scientists have managed to get live embryonic Stem Cells extrude through a microfilter , producing nanovesicles, that display therapeutic activity regarding Wound healing [125]. Besides having the capacity to produce multiple cell lineage(like osteoblast as well as adipocytes), MSCs have got further the ability of enhancing tissue regeneration, angiogenesis , as well as anti-inflammatory via liberation of cytokines, chemokines, growth factors, as well as EVs [126]. Of these the MSCs-secretome, MSCs-obtained EVs have got the recognition of being strong ways which might be able to take over from MSCs in the form of a cell-free therapy. For furthering this therapeutic capacity of EVs in drug administration as well as regenerative medicine, parenteral MSCs might be genetically manipulated for generation of growth factors-loaded EVs for therapy. With regards to this Li et al. [127], documented that Exosomes isolated from adipose derived stem cells (ADSCS) had the ability to facilitate proliferation as well as angiogenesis of endothelial progenitor cells (EPC). Significantly treatment with Exosomes from genetically manipulated ADSCS could significantly enhance Wound healing, the amounts of growth factors expression, as well as an anti-inflammatory actions in Diabetic rats following overexpression of the transcription factors nuclear factor erythroid 2 like 2 NRF2 in ADSCS [59], that illustrated a shielding part in a Diabetic Nephropathy model [128].

Conclusions

EVs have shown a robust translational ability for the treatment of Diabetes along with correlated complications (Figure3). Certain ongoing clinical trials are there for finding out the safety as well as clinical effectiveness. Clinical utilization continues to emphasize certain practical problems of utilizing clinical grade EVs. Future evaluations are required for making it clear the composition of these EVs biomolecules, i.e. both proteins as well as RNA are from separate cell or tissue obtained EVs for their particular therapeutic capacity resulting in the formation of bioengineered EVs. The studies regarding mechanism of action with regards to their crosstalk with target cells will promote the clinical practicalities of EVs for the treatment of Diabetes as well as other diseases.

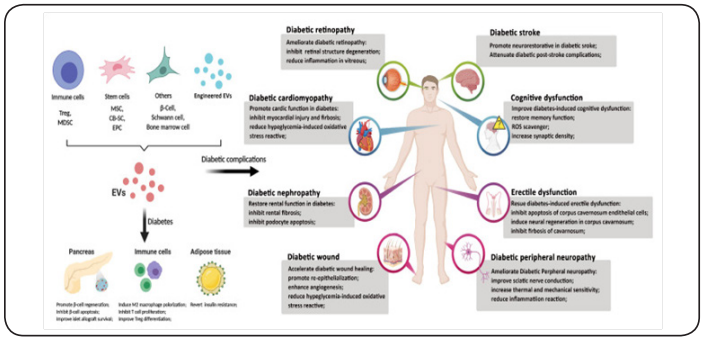

Figure 3: Therapeutic potential of EVs for the treatment of diabetes and complications [128]

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