REVIEW ON PANCREATIC β CELL REGENERATION: POTENTIAL DRUG THERAPY FOR DIABETES MELLITUS

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Abstract

Type 1 diabetes mellitus, also known as T1DM, is the most frequent form of chronic autoimmune sickness found in young people. It is characterised by a lack of pancreatic cells, which ultimately results in hyperglycemia and an insulin shortage. It is not possible for exogenous insulin, whether it is taken orally or injected, to take the place of the insulin that is created naturally by a pancreas that is working properly. Pancreas and islet transplantation have only relatively lately been recognised as viable therapeutic options for type 1 diabetics seeking to reestablish normal levels of glucose control in their bodies. There is a major shortage of pancreases and islets derived from human organ donors, challenges related with transplantations, a high cost, and limited procedural availability. These are just some of the constraints that prevent the widespread application of these treatments. There has been some work done in order to better serve the ever-increasing population of people who are living with type 1 diabetes. Stem cell therapy has the potential to one day be utilised to treat patients suffering from Type 1 diabetes and entirely cure the condition. The advent of research into stem cell therapy for a variety of diseases has coincided with the documentation of progress made in the treatment of type 1 diabetes using stem cells. But there are still a lot of unanswered problems that need to be resolved before stem cell therapy can be considered a therapeutically feasible option for diabetes patients. In this article, we will discuss various methods for isolating insulin-producing cells (IPCs) from a wide variety of progenitor

cells, as well as summarise recent breakthroughs in stem cell-based therapies for the treatment of diabetes.

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Introduction

All types of diabetes mellitus (DM) result from the pancreas's inability to produce enough insulin to maintain normal blood sugar levels in the body. Exogenous insulin injection, insulin-stimulating drugs, insulin-resistance-lowering pharmaceuticals, and β -cell mass replacement are all viable options for bringing blood sugar levels back under physiological control (the producers of insulin)[1]. Regaining the pancreas's lost functional cell mass through regeneration is a promising treatment option. Islet transplantation from cadavers, activation of endogenous regeneration, and delivery of stem cell-derived cells are some of the current methods used to replace damaged cells in the pancreas[2]. Successful transplantation of pancreatic islets has been shown to restore functional capacity to islets that have been damaged. In order to maintain metabolic regulation for a year after transplantation, however, at least 2 million cells per kg body weight must be transplanted[3]. This creates a shortage of healthy islets for use in this context. Stem cell therapy has the ability to deliver 100-200 million cells per graft, ushering in a new era of cell replacement therapy as the success rate of producing glucose sensitive β -like cells from human stem cells increases[4-6]. The current epidemiologic burden of diabetes, worldwide and especially in Latin America, urges the scientific community to focus on the key influencers of endogenous cell regeneration that can be applied to increase the successful rate of differentiated functional cells in the hopes that in the near future, the load of diabetic patients will be alleviated through stem cell therapy. Stem cell research in Latin America has progressed slowly but surely. This review will focus on ideal ways for collecting stem cell-derived cells, since their development is being driven by the regional epidemiology and expenses of DM[7].

All forms of diabetes mellitus (DM) are brought on by an inability of the pancreas to produce an adequate amount of insulin[8]. The infusion of exogenous insulin, drugs that promote insulin production, pharmaceuticals that lower insulin resistance, and the replacement of the β cell mass are some of the methods that are available for bringing blood sugar levels back under physiological control. Other methods include the use of insulin that is produced in the body naturally (the producers of insulin). It's possible that one potential treatment would involve regenerating the lost functional cell mass in the pancreas[9]. At the moment, damaged β cells in the pancreas can be replaced by means such as cadaveric islet transplantation, activation of endogenous regeneration, and injection of stem cell-derived cells. If the transplantation of pancreatic islets is successful, normal function can be restored, and the number of islets that were lost as a result of the injury can also be restored[10]. However, this strategy is currently limited because of the significant amount of healthy islets that are required for one year of metabolic regulation following transplantation (at least 2 million cells per kg of body weight). As the success rate of creating glucose sensitive β -like cells from human stem cells grows, a new era of β cell replacement therapy has been ushered in. This new era has been ignited by the likelihood that stem cell therapy might provide between 100 and 200 million β cells each graft[11]. The current epidemiologic burden of diabetes, which is felt all over the world and particularly in Latin America, compels the scientific community to focus on the key influencers of endogenous cell regeneration.

This is done in the hope that, in the not-too-distant future, stem cell therapy will be able to reduce the burden that is placed on diabetic patients. Specifically in Latin America[12-14]. In spite of its glacial pace, stem cell research has made substantial progress in Latin America despite the region's slow progress. This review will concentrate on the most effective methods for obtaining stem cell β -derived cells, as this is where local stem cell researchers in the area are investing the majority of their time and effort due to the high prevalence of DM and the accompanying costs in this particular location.

Costs and prevalence of type 2 diabetes in Latin America

It wasn't until the 1950s and 1960s that researchers in Latin America and the Caribbean began compiling accurate data on the frequency of diabetes mellitus in adult populations[15]. According to data that was published by Barceló in 2001, the incidence of type 1 diabetes ranged from 0.1 cases of the condition occurring per 100,000 people in Venezuela to 17.4 cases of the condition occurring per 100,000 persons in Puerto Rico. Despite this, the authors called attention to the minimal literature that exists on the prevalence of type 2 diabetes in the LatAm region and emphasised how close to nonexistent diabetes surveillance is in that region.

Estimates for the prevalence of diabetes mellitus in Latin America from 2005 to 2021 have varied widely, depending on the source of the data, from 3% all the way up to 36.3% of the population (Fig. 1). Some of the national surveys that we looked at measured the prevalence of diabetes by using samples that were representative of the population and sampling methods that were similar to those used for the population as a whole (for example, multi-stage, clustered, and probabilistic sampling), while others concentrated on particular geographic regions or communities, recruited participants from clinical settings, or focused on particular age groups[16]. Because of the large age gap that existed across the various study populations, there was also considerable fluctuation in the data that had been adjusted for age.

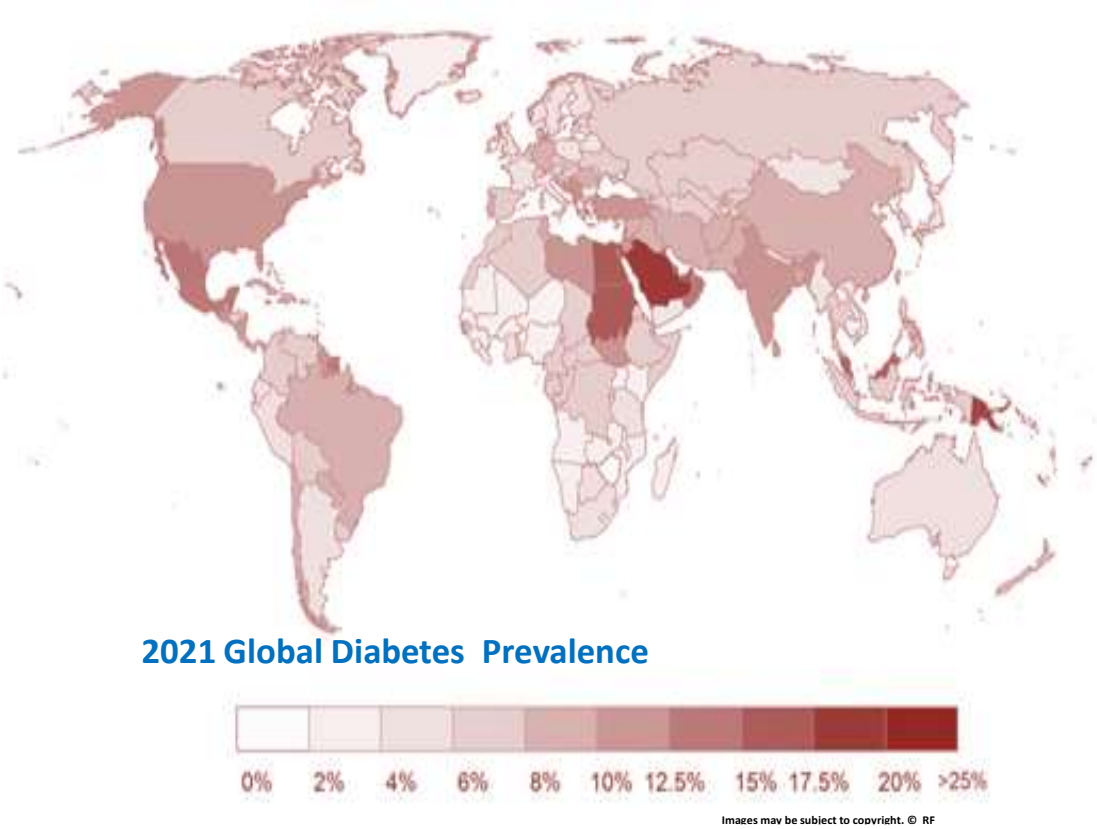

Fig: 1 Global distribution diabetes prevalence in 2021

Clinical Aspects and Treatment of Diabetes

Diabetes is a disease with a difficult physiology and therapy, which requires a wide variety of approaches to care due to the complexity of both aspects of the condition. Patients diagnosed with diabetes are expected to take an active role in their own care and treatment. Patients see improved results when they restrict carbohydrates and overall calorie intake, engage in consistent physical activity (for more than 150 minutes per week), and conduct independent glucose monitoring. It is sometimes necessary to continue treatment for the rest of one's life in order to prevent more complications[17]. The ideal range for glucose is between 90 and 130 mg/dL, and the HbA1c should be below 7%. Although it is critical to keep a healthy blood glucose level, it is possible to develop hypoglycemia if therapy is administered too quickly[18].

The administration of insulin is the primary focus of treatment for diabetes mellitus type 1, which might take the form of daily injections or an insulin pump. Alterations to one's lifestyle, such as eating more healthily and engaging in greater physical activity, may be all that is required to control type 2 diabetes, at least initially. Therapies that enhance insulin sensitivity or boost the synthesis of insulin by the pancreas are potentially a possibility[19]. Different drug subclasses include things like biguanides (like metformin), sulfonylureas, meglitinides, alpha-glucosidase inhibitors, thiazolidinediones, glucagonlike-peptide-1 agonists, selective dipeptidyl peptidase IV inhibitors (DPP-4), amylin mimetics, and sodium-glucose transporter-2 (SGLT-2) inhibitor Metformin is a first-line medication for diabetes that lowers plasma glucose levels both when the patient is fasting and after they have eaten[20]. Patients diagnosed with type 2 diabetes who are unable to adequately maintain their glucose levels, particularly those who are in the later stages of the disease, may

require extra insulin therapy. People who are morbidly obese have a chance of regaining normal glucose levels after undergoing bariatric surgery. Individuals who have not responded well to previous therapies and who furthermore struggle with significant co-morbidities are ideal candidates for therapy[21]. GLP-1 agonists like liraglutide and semaglutide, which both have the same effect, are linked to improved cardiovascular outcomes. It has been demonstrated that the SGLT-2 inhibitors empagliflozin and canagliflozin improve cardiovascular outcomes, and it is possible that these drugs might have renoprotective and heart failure preventing properties.

Checkups should be maintained on a consistent basis for those who have diabetes because microvascular complications are a key cause for concern regarding their health. Medical tests of the retina that are performed on a regular basis by skilled specialists are able to detect diabetic retinopathy. A neurologic evaluation that utilises monofilament testing can be used to identify patients with neuropathy who are at a high risk for amputation[22]. Patients who have neuropathy might not feel any discomfort in their feet; as a result, their doctors might recommend that they check their feet every day for any lesions. It is probable that diabetics will need to take low dosages of tricyclic antidepressants, duloxetine, anticonvulsants, topical capsaicin, and pain medications in order to achieve adequate management of their neuropathic pain[23]. In addition to measuring GFR, analysing the urine for microalbumin can reveal early renal problems owing to diabetes if albuminuria is more than 30 mg/g creatinine. Because of their antiproteinuric effect, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are the drugs of choice for preventing the progression of microalbuminuria to macroalbuminuria in patients with type 1 and type 2 diabetes mellitus[24].

The Food and Drug Administration (FDA) has given the go-ahead for the use of pregabalin and duloxetine in the treatment of diabetic peripheral neuropathy[25]. Tricyclic antidepressants and anticonvulsants are two types of medications that have been tested in the treatment of diabetic neuropathy's painful symptoms, with varied degrees of efficacy.

In addition, the American Diabetes Association recommends having your blood pressure checked regularly, with a goal of maintaining a systolic reading of 130 mm Hg and a diastolic reading of 85 mm Hg[26]. In the pharmacological treatment of hypertension in diabetics, common medications include calcium channel blockers, beta-blockers, diuretics, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers. Angiotensin-converting enzyme inhibitors are also sometimes utilised[27]. According to the guidelines provided by the American Diabetes Association, a person's level of low-density lipoprotein cholesterol (LDL-C) should be less than 100 mg/dL if there is no evidence of cardiovascular disease (CVD), and less than 70 mg/dL if atherosclerotic cardiovascular disease (ASCVD) is present (ADA). Utilization of statins is the usual first step in the treatment of dyslipidemia in diabetic patients. Although it is still unclear whether or not aspirin is effective in preventing cardiovascular events in diabetics, the American Diabetes Association (ADA) suggests that diabetic patients who are at a high risk for cardiovascular events may benefit from taking low doses of aspirin[28]. This is despite the fact that the effectiveness of aspirin in preventing cardiovascular events in diabetics is still up for debate.

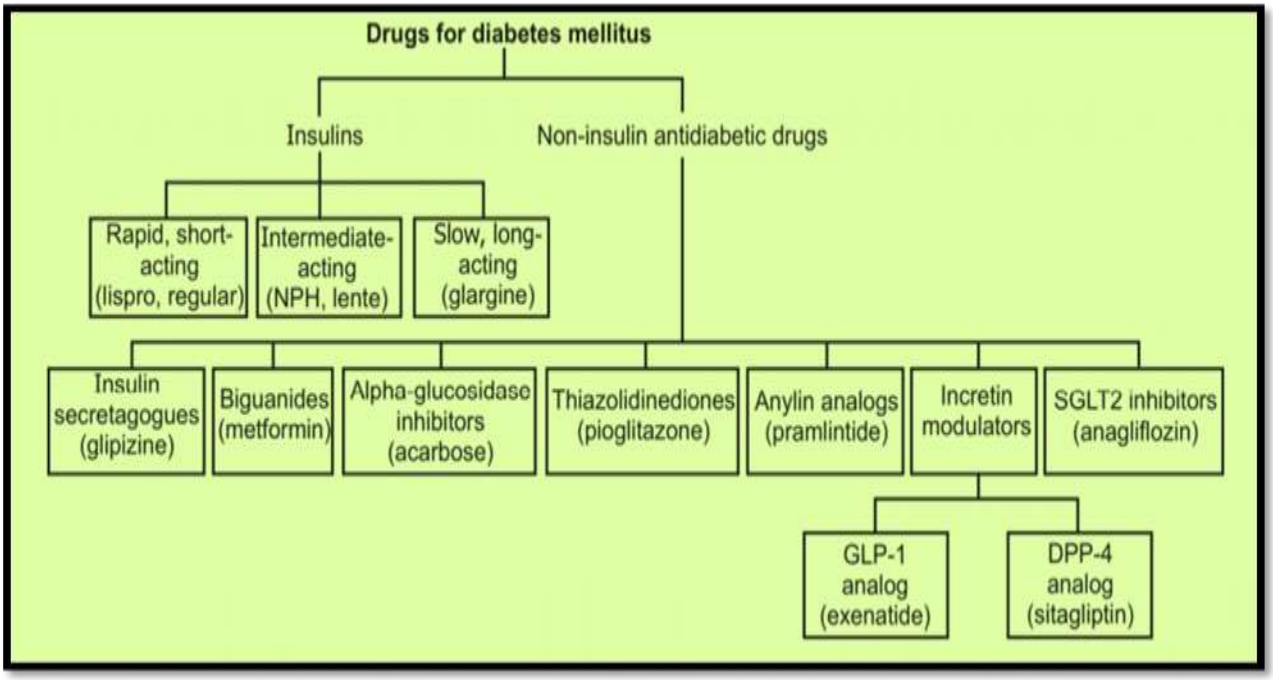

Fig: 2 Clinical Aspects medication & its Treatment in Diabetes

Stem cell-derived therapies for the treatment of diabetes

As a result of recent progress made in the differentiation of human stem cells into pancreatic islet cells, there are now obvious and workable alternatives to the more conventional therapy methods for type 1 diabetes and type 2 diabetes that were previously discussed. These alternatives have been made possible as a result of recent developments in the field of stem cell research[29]. In the past ten years, there has been considerable progress made in the capacity to create functional beta cells from human stem cell populations. This ability was first demonstrated in 2006. The fundamental concept is to duplicate, to the greatest extent possible, the developmental path taken by pluripotent stem cells in an embryo that is still in the process of developing (from definitive endoderm to pancreatic endoderm to endocrine progenitors to pancreatic islet cells; see Fig. 3). Isolating hormone-positive beta cells that are capable of producing insulin in response to glucose has been the primary focus of study in relatively recent times (GSIS)[30]. There are a number of research facilities working on the development of artificial beta and islet cells that can one day replace human islets because they are capable of performing the same functions as human islets. There are clinical trials that use pancreas progenitors that have been produced from stem cells and have the potential to mature into functional beta and islet cells. These clinical trials are currently being conducted. This article provides a comprehensive review of the current state of research concerning the differentiation of human embryonic stem cells into pancreatic islet cell types (hESC)[31].

Despite significant progress made in the generation of insulin-producing cells from human embryonic stem cell populations, a cell that is fully functional and replicates all of the properties of endogenous beta cells has not yet been discovered. It is prudent to develop a "full complement" of islet cells since beta cells in vivo do not exist independently of the intricate three-dimensional architecture of the islets of Langerhans (Figure 3). In point of fact, it has been found that the intricate cytoarchitecture of the islet plays a significant role in the maintenance of the activity of beta cells. The

behaviour of beta cells in isolation is distinct from the behaviour of beta cells within intact islets[32]. It has been demonstrated that the GSIS is compromised in single beta cells that are isolated from the rest of the islet, with higher basal insulin production and decreased peak insulin secretion in response to glucose. This is in comparison to complete islets. It is essential to have gap junctions, in particular Connexin-36, as well as other mechanisms for coordinating cell-cell communication in order to maintain the coupling of beta cells and the synchronisation of the islets with insulin oscillations[33]. Methods for replicating endogenous islet structure, cell-cell interactions, and communication with the islet environment will need to be studied alongside those for generating the human embryonic stem cell-derived unit that functions the most ideally in order to rescue diabetics.

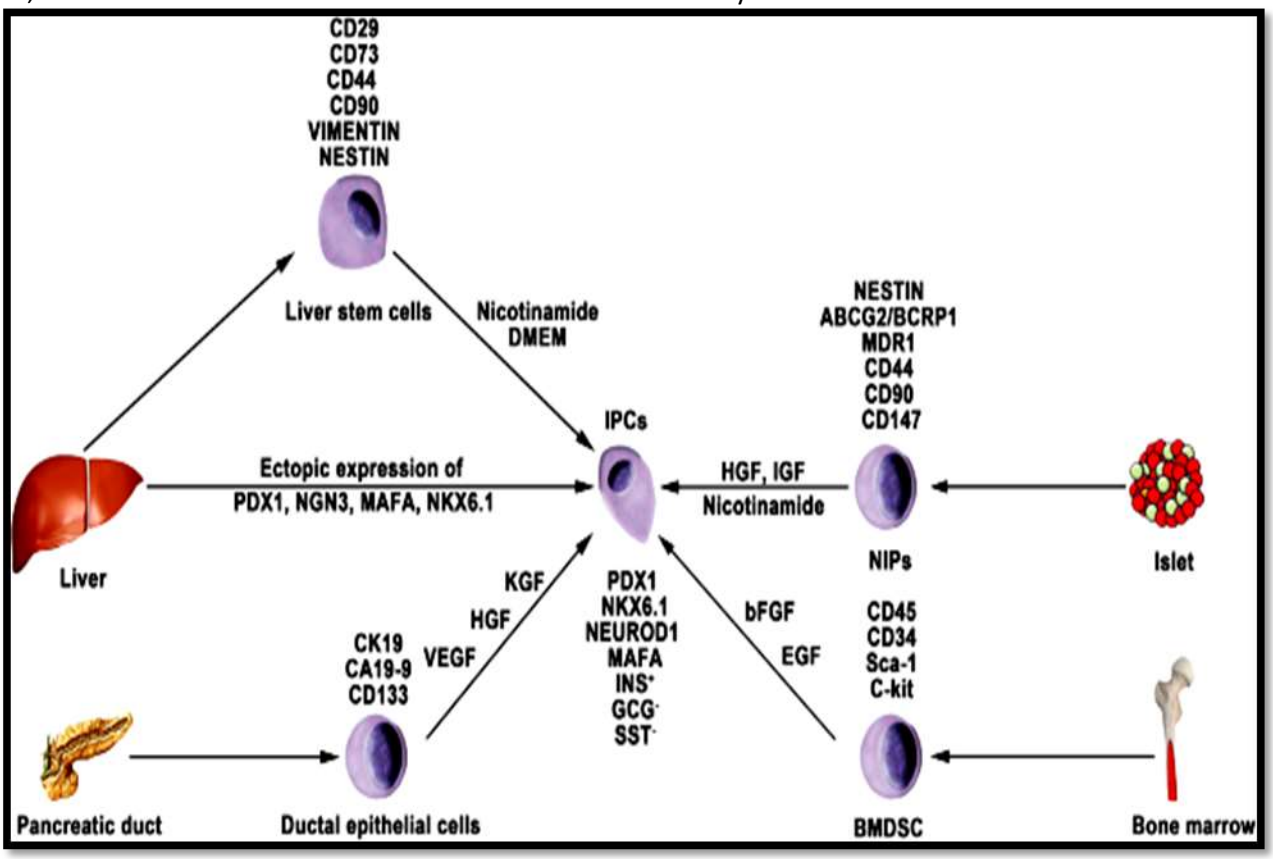

Fig:3 Producing IPCs using a person's own adult stem cells as the starting material. Adult pancreatic stem cells are a candidate for serving as a source of IPCs. Both adult islet NIPs and pancreatic ductal cells have been employed with great success in order to generate fully functional islet precursor cells (IPCs). Throughout the course of embryonic development, both the liver and the pancreas are derived from the same endoderm progenitors. IPCs can form when liver cells undergo transdifferentiation as a result of the ectopic synthesis of pancreatic transcription factors. It has been demonstrated that a certain subpopulation of highly pluripotent cells known as HLSCs are able to create IPCs when grown in vitro. Stem cells extracted from bone marrow can be used to create clusters of insulin-producing cells.

In rodent models, the beta cells that are located in the middle of the pancreatic islets are surrounded by alpha cells, delta cells, and pancreatic polypeptide (PP) cells[34]. Each of these cell types secretes hormones that help maintain a normal level of glucose in the blood. In mouse models of diabetes, alpha, delta, and PP cells intermix with beta cells inside the islet

core, which indicates an abnormal islet architecture. This architectural arrangement promotes homologous cell-cell interactions, which are important for optimal islet function. The severe compartmentalization seen in rodent islets is absent in human islets, which instead include a more even distribution of endocrine cell types across the islet and fewer heterologous cell-cell interactions. It has been discovered that the endocrine subtypes are not always distributed evenly across the mouse and human islets. In some instances, the human islets are more alpha (40%) and beta (50%) cell dominated than the mice islets[35]. There are some compositional and structural differences between mouse and human islets, and these differences have been linked to the functional differences that exist between mouse and human islets. There are some functional differences between mouse and human islets. As a result of the fact that human islets do not contain as many homologous beta cell interactions as murine islets do, the release of insulin in response to glucose stimulation is asynchronous in human islets. This finding suggests that beta-beta intercellular contacts are responsible for coordinating the homogenous and synchronous release of insulin in murine islets[36]. Single cell sorting and sequencing have shown encouraging results, which lend support to the concept that multiple beta cell subtypes exist in human islets.

Beta cell activity is also determined by communication with non-endocrine cell types that are present in the islet niche. These non-endocrine cell types include endothelial, perivascular, neuronal, and mesenchymal cells. Islets of the pancreas in particular are highly vascularized, and it is a commonly held opinion that beta cells start connections with endothelial cells in order to provide one-of-a-kind ultrastructural traits at their interface. The cytokine known as vascular endothelial growth factor A (VEGF-A), which is secreted by endocrine cells, is the initial factor that draws endothelial cells into an islet that is in the process of forming in the pancreas. Endothelial cells are responsible for the production and secretion of the islet basement membrane[37]. This membrane is assumed to play an important part in the development, survival, and function of beta cells. Endothelial cells also secrete other proteins. The research team led by Otonkoski discovered that human islets contained two basement membranes, one of which surrounded the endothelium and the other of which surrounded the beta cells. It stands to reason that beta cells produced from hESC may fare better in vitro if they were provided with a more realistic representation of the specialised interaction that takes place between beta cells and supporting cells in the natural environment in which beta cells reside.

Endothelial cells and pericytes, which are located in the mural layer of the vascular islet niche, are the two types of cells that can be found in this specialised environment. Pericytes are cells that wrap around the tubes that are made by endothelial cells[38]. They do this to provide structural support, to encourage the development of mature blood arteries, and to regulate the proliferation, survival, and function of endothelial cells. Pericytes also play a role in promoting the development of mature blood arteries. Pericyte loss in the adult rat islet results in lower insulin expression, total insulin content, and glucose-clearing, according to a study that utilised genetic ablation; however, the specific role of pericytes in normal islet function is still unknown.

Generation of Induced Pluripotent Stem Cells from Urine

The process of reprogramming, which refers to the transformation of somatic cells into induced pluripotent stem cells (iPSCs) using exogenous factors, has the potential to be used in personalised regenerative medicine. It also has the potential to produce useful in vitro models of human diseases or toxology, and it can be used in either of these applications. 3,4 Human iPSCs have been derived from a variety of different sources, including skin (keratinocytes and fibroblasts), extraembryonic

tissues, and cord blood. Reprogramming from various tissues has been achieved with varying frequency, demonstrating that the cells of origin are a significant contributing factor in the decision-making process. Researchers are now suggesting that iPSCs may maintain the epigenetic memory of their cells of origin in addition to accumulating additional defects[39]. It is crucial, for this reason, to determine all of the cell types from which iPSCs can be produced and to identify the benefits and drawbacks of each of these cell types. The ideal cell source would be one that was readily available, adaptable, and applicable everywhere (any age, sex, ethnic group, and body condition). Because neonatal tissues are not routinely kept in most countries, the former criteria eliminates them, while the later consideration eliminates many of the cell types that have been employed up to this point. It's possible that dermal fibroblasts are the type of cell that's used for reprogramming the most often. However, in order to accomplish this, a biopsy is necessary, and candidates are occasionally encouraged to decline the opportunity to donate tissue. In addition, the treatment should not be performed on patients who have burns or skin conditions that are potentially lethal, such as severe epidermolysis bullosa. Recent studies have shown that it is possible to reprogram cells from the peripheral blood without the need for CD34+ cell mobilisation. The technique is not too intrusive and just requires a tiny amount of blood to be drawn. However, the efficiency was modest (between 0.0008% and 0.1%), and the primary target is mature T cells carrying certain T cell receptor rearrangements[40]. This presents a limitation for some possible applications because of the nature of the target cells. In addition, there are some circumstances in which giving or receiving blood may be fraught with risk (for example, due to a person's religious beliefs), and the reprogramming may be troublesome for individuals who suffer from blood illnesses (such as haemophilia and leukaemia) or immunodepression (e.g., cancer and AIDS). During the course of our investigation into the best possible sources of tissue, we were able to derive human iPSCs from periosteal membrane, adipose stem cells, and extraembryonic tissues. Exfoliated renal tubular cells can be found in urine, and these cells were used to generate iPSCs, which we report here.

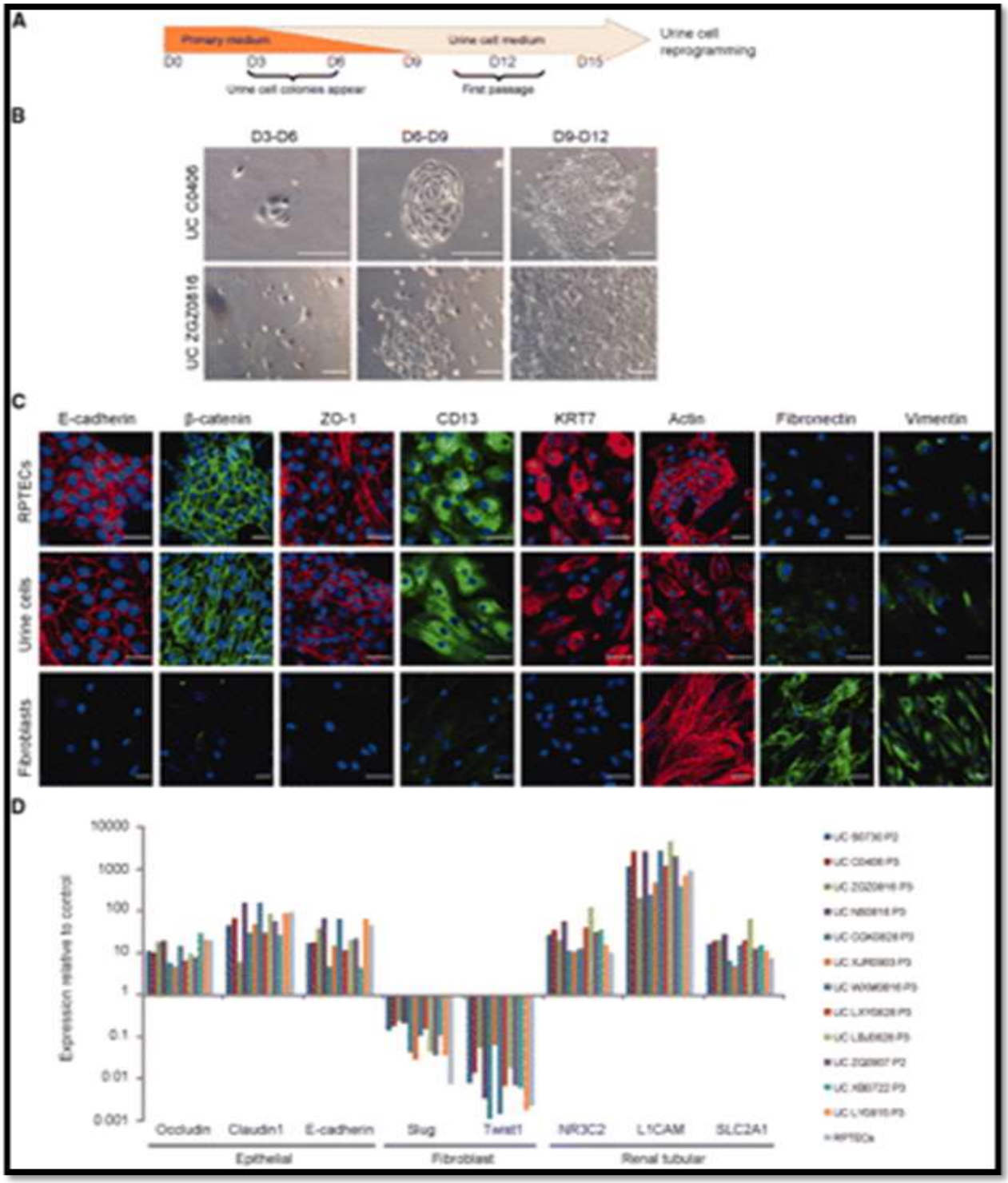

FIG: 4 Collecting and analysing urine cells. A. Strategy for collecting urine. Phase contrast (B) images of urine cells (UC) taken at varying time points following collection. The most dominant cells are those of type 1. Type 2 cells are listed last. D, day (also hereafter). The distance between the two scale bars is one hundred metres. Examining RPTECs, fibroblasts, and urine cells with confocal immunofluorescence microscopy for specific markers (C). E-cadherin, -catenin, zonula occludens-

protein 1 (ZO-1), and keratin 7 are junction markers; KRT7, keratin 7; scale bars, 40 m. All donor (D) cells used in this study were screened for the appropriate markers using quantitative real-time PCR, with the findings normalised to skin fibroblasts. The RPTECs were used as a benchmark to ensure consistent high quality. Group 2-transporter solute Specifically, proximal tubule of the kidney contains SLC2A1.

The kidneys include an extensive tubular network that, when combined, has a surface area that is more than that of the epidermis. The number of cells that have broken free from their cellular moorings in the tubular system and farther downstream regions of the urinary tract and are found in urine ranges anywhere from 2,000 to 7,000. (the ureters, the bladder, and the urethra). These cells, which will be referred to as urine cells from this point on, are not only unharmed but also completely functional, making them suitable for use in in vitro research. Not to mention, they may be gathered anywhere, without the need for any kind of medical intervention, and they can easily be multiplied. In addition, they have the capability of being quickly multiplied (fig:4 A). There were squamous cells (presumably from the urethra) and a few blood cells (mainly erythrocytes) in the beginning, but after three to six days, these were replaced by small colonies that expanded fast. It is likely that the squamous cells originated in the urethra. Because of the way these colonies looked, we were able to categorise them as either type 1 or type 2 (Fig4B). This finding is in line with results on the isolation of urine cells that were previously published in another setting[41]. Characteristics of an epithelial phenotype were shown by the growth of type 1 cells, which included becoming rounder and moving closer to their neighbours. Type 2 cells were the predominant variety because they were the most advanced in terms of length and distribution. In some of the samples, each colony was composed of only one of the two distinct types of cells, and in others, there was a mixture of the two. After the cell densities in each culture had been optimised, they were pooled together and then subdivided for the purposes of analysis and reprogramming. According to the results of immunofluorescence microscopy, the cell-cell connections in the areas that were rich in type 1 cells were properly created (fig 4 C). They also displayed other markers such as CD13, which is located in the renal proximal tubules, and keratin 7, an intermediate filament keratin that is also expressed by epithelial cells. Both of these keratins are detected in epithelial cells (fig 4C). The quantitative real-time PCR, often known as qPCR, offered up some more supporting evidence for an epithelial origin (Fig4D). Using fibroblasts and epithelial cells taken from the proximal renal tubule, controls for immunofluorescence and quantitative polymerase chain reaction were carried out. In Type 2 cell-enriched cultures, comparable immunofluorescence patterns were seen, but at a lower intensity and with a more diffuse distribution (data not shown); qPCR results were likewise consistent (Figure 4, C and D). In all instances, the fibronectin and vimentin stains were not very strong. Both of these proteins are associated with fibroblasts (Figure 4C). These data lend support to the hypothesis that both types of cells start from the epithelium. Furthermore, they imply that type 2 cells emerge from a process that involves partial epithelial dedifferentiation.
Immune modulation in stem cell therapy for T1DM.

Since it was initially introduced, SCT has gained popularity and been demonstrated to be useful in a number of new contexts for the management of common diabetic problems. This is due to the fact that it can reduce insulin resistance and improve glucose control. Research in these areas is centred on the complications of diabetes, such as diabetic

retinopathy (DR), diabetic neuropathy (DN), and diabetic nephropathy (DN), which develop in cells that are especially vulnerable to the chronic hyperglycemia exposure that is characteristic of diabetes. These complications include diabetic retinopathy (DR), diabetic neuropathy (DN), and diabetic nephropathy (DN) (DNP). Because around 80 percent of persons with type 1 diabetes are at risk for DR, this is an important concern[42]. Ischemia of the retina is caused by a chain reaction that begins with persistent, low-grade inflammation, continues with the degeneration of retinal endothelial cells, and is completed by a reduction in blood flow to the retina. This results in the retina not receiving enough blood. A paradoxical compensatory mechanism known as neovascularization is at work in the advanced stages of DR. This reaction results in the formation of weak vessels that eventually burst and cause more damage and, in many cases, blindness. Both nonproliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) are popular classifications of diabetic retinopathy patients. These classifications are based on the amount of visible neovascularization (PDR). Treatments for DR that are now considered to be the gold standard include laser photocoagulation, vitrectomy, corticosteroids, and antivascular endothelial growth factor therapy. The primary objective of these treatments is to arrest the progression of the disease[36]. The regeneration capabilities of SCT offer promise for a disease called DR, which does not currently have any treatments available. During the course of a clinical experiment that evaluated the efficacy and safety of autologous bone marrow MSCs, patients who suffered from both NPDR and PDR experienced an improvement in their visual acuity. More evidence of advancement might be seen in the early NPDR group. Although there were no significant adverse events or short-term reactions recorded, this trial had a small sample size (there were only 17 participants), and there was no control group. In addition, patients were only monitored for a maximum of six months to evaluate the drug's safety, which is not likely to be a long enough period of time to identify the incidence of immune-related or neoplastic complications. Results from these medicines have been proven to be encouraging in studies conducted on animals; nevertheless, additional research is required to discover whether or not they are safe and effective for use in humans[39,40]. Both induced pluripotent stem cells (NCT03403699) and autologous CD34+ cells derived from bone marrow are the focus of clinical research that is currently being conducted (NCT01736059). Both in the lab and in clinical trials involving humans, there has been encouraging study exploring the possibility of employing stem cells as a treatment for DR.

Research on DNP, which is the most prevalent cause of chronic kidney disease and is responsible for half of all cases of end-stage renal disease around the world, has also been conducted. DNP is the most common cause of chronic kidney disease. MSCs are an effective treatment for preventing DNP from occurring in the first place. MSCs were shown to play a function in the prevention of DNP in a study that used rats with type 1 diabetes. This role was in addition to the MSCs' ability to regenerate pancreatic cells[42]. The same primary investigator conducted a comparative murine trial seven years later to further prove the renoprotective effects of MSCs. The results of this trial showed that MSC-treated mice had reduced inflammatory factors and a "pro regenerative microenvironment" in the kidney, which preserved kidney function despite the presence of diabetes. Additionally, the results of this trial showed that MSC-treated mice had a "pro regenerative microenvironment" in the kidney. In the second study of its sort, it was discovered that mesenchymal stromal cells (MSCs) are advantageous in preventing the development of DNP by preventing damage to podocytes. Recent studies have suggested that mesenchymal stem cells (MSCs) could provide a

therapeutic solution for diabetic neuropathy (DNP). However, the majority of this research has been focused on the preventative aspect of care, which is less likely to reach the larger population of people with diabetes who are already experiencing DNP[43]. If additional research and clinical studies are carried out, patients who have already been diagnosed with DNP may benefit from these interventions, which aim to slow the progression of the disease and prevent the onset of kidney failure. However, this is only the case if the research and studies are finished[46].

Because of their capacity to regenerate, stem cells have been found to hold potential as a treatment for diabetic neuropathy (DN). In addition, stem cells have been demonstrated to aid in the healing of diabetic foot ulcers, which are a common complication of diabetic peripheral neuropathy[45]. It is estimated that sixty percent of all diabetic patients will get DN, despite the fact that there are now no treatments available for this prevalent and debilitating disorder. The condition known as diabetic neuropathy (DN) is associated with hyperglycemia, which sets off a cascade of neurodegeneration and loss of sensory function over the course of time. Ulcers of a serious nature could be brought on by this type of damage to the nervous system[44]. Even though it has been demonstrated in animal studies that MSC treatment can reduce the pathologic characteristics and symptoms of peripheral neuropathy, additional study is still required to describe the applicability of such treatments in human patients. People who have type 1 diabetes and suffer from complications such as diabetic neuropathy (DN) or diabetic foot ulcers may benefit from stem cell therapy in a fresh and exciting way that has the potential to improve their quality of life. In the end, SCT has the potential to be a promising treatment option for autonomic neuropathy caused by diabetes. Autonomic neuropathy is characterised by a number of symptoms, some of which include incontinence, diarrhoea, and a loss of erection. Autonomic neuropathy can also affect the digestive system. In a phase 1 clinical trial, four male subjects had autologous MSC transplants taken from their own bone marrow. These transplants were placed in the corpus cavernosum.

Conclusion

In this analysis, we are going to focus on the most recent studies that were published between the years 2000 and 2021 that address the following topics concerning diabetes mellitus in Latin America: prevalence; awareness; treatment; control; and adherence to recognised standards of care. During this time period, there were various surveys carried out to estimate the prevalence of the disease, and there was an ever-growing corpus of papers outlining the efficacy of therapy and care. In light of these frightening statistics, it is abundantly clear that additional research is required to determine the global burden of diabetes and to evaluate the success of current and historical efforts to create models of diabetes prevention and care that are efficient enough to serve all of the people in the region and are also sustainable enough to do so.

References

1. Weir GC, Bonner-Weir S. Islet beta cell mass in diabetes and how it relates to function, birth, and death. *Ann N Y Acad Sci.* 2013;1281:92–105.
2. Leibowitz G, Kaiser N, Cerasi E. Beta-cell failure in type 2 diabetes. *J Diabetes Invest.* 2011;2:82–91.
3. Butler AE, Janson J, Bonner-Weir S, Ritzel R, Rizza RA, Butler PC. Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. *Diabetes* (2003) 52:102–10. 10.2337/diabetes.52.1.102
4. Kumar, R., Saha, P., Keshamma, E., Sachitanadam, P., & Subramanian, M. (2022). Docking Studies of Some Novel Hetrocyclic Compound as Acat Inhibitors: A Meta Analysis. *Journal for Research in*

Applied Sciences and Biotechnology, *1*(3), 33-41.

5. Nyarko, R. O., Awuchi, C. G., Kumar, R., Boateng, E., Kahwa, I., Boateng, P. O., ... & Saha, P. (2022). Evaluation of Cafeteria Diet in Experimental Animal with Plant Extract of Calotropis procera for Obesity Parameter. *Journal for Research in Applied Sciences and Biotechnology*, *1*(3), 107-113.
6. Finegood DT, Scaglia L, Bonner-Weir S. Dynamics of beta-cell mass in the growing rat pancreas. Estimation with a simple mathematical model. *Diabetes* (1995) 44:249–56. 10.2337/diab.44.3.249
7. Amle, V. S., Rathod, D. A., Keshamma, E., Kumar, V., Kumar, R., & Saha, P. (2022). Bioactive Herbal Medicine Use for Eye Sight: A Meta Analysis. *Journal for Research in Applied Sciences and Biotechnology*, *1*(3), 42-50.
8. Huang C, Snider F, Cross JC. Prolactin receptor is required for normal glucose homeostasis and modulation of beta-cell mass during pregnancy. *Endocrinology* (2009) 150:1618 –26. 10.1210/en.2008-1003
9. Kumar, R., Keshamma, E., Paswan, S. K., Saha, P., Trivedi, U., Chourasia, A., & Otia, M. (2022). Alkaloid Based Chemical Constituents of Ocimum santum & Cinchona Bark: A Meta Analysis. *Journal for Research in Applied Sciences and Biotechnology*, *1*(2), 35-42.
10. Kumar, S., Yadav, S. P., Chandra, G., Sahu, D. S., Kumar, R., Maurya, P. S., ... & Ranjan, K. (2019). Effect of dietary supplementation of yeast (Saccharomyces cerevisiae) on performance and hemato-biochemical status of broilers.
11. Burke GW, Vendrame F, Virdi SK, et al. Lessons from pancreas transplantation in type 1 diabetes: recurrence of islet autoimmunity. *Curr Diabetes Rep.* 2015;15:1–9. Potter KJ, Westwell-Roper CY, Klimek-Abercrombie AM, Warnock GL, Verchere CB. Death and dysfunction of transplanted β-cells: Lessons learned from type 2 diabetes? *Diabetes.* 2014;63:12–19.
12. Singh, Y., Paswan, S. K., Kumar, R., Otia, M. K., Acharya, S., Kumar, D., & Keshamma, E. (2022). Plant & Its Derivative Shows Therapeutic Activity on Neuroprotective Effect. *Journal for Research in Applied Sciences and Biotechnology*, *1*(2), 10-24.
13. Nyarko, R. O., Roopini, R., Raviteja, V., Awuchi, C. G., Kumar, R., Faller, E. M., ... & Saha, P. (2022). Novel Sars-CoV-2 Variants & Therapeutic Effects. *Journal for Research in Applied Sciences and Biotechnology*, *1*(2), 25-34.
14. Nyarko, R. O., Roopini, R., Raviteja, V., Awuchi, C. G., Kumar, R., Faller, E. M., ... & Saha12, P. Novel Sars-COV-2 Variants & Therapeutic Effects.
15. Ahren B. Type 2 diabetes, insulin secretion and beta-cell mass. *Curr Mol Med.* 2005;5:275–286.
16. Saha, P., Kumar, A., Bhanja, J., Shaik, R., Kawale, A. L., & Kumar, R. (2022). A Review of Immune Blockade Safety and Antitumor Activity of Dostarlimab Therapy in Endometrial Cancer. *International Journal for Research in Applied Sciences and Biotechnology*, *9*(3), 201-209.
17. Heit JJ, Apelqvist AA, Gu X, et al. Calcineurin/nfat signalling regulates pancreatic beta-cell growth and function. *Nature.* 2006;443:345–349.
18. Nyarko, R. O., Kumar, R., Sharma, S., & Chourasia, A. (2022). Ayushmann Roy, and Purabi Saha.". *Antibacterial Activity Of Herbal Plant-Tinospora Cordifolia And Catharnthus Roseus*.
19. Saha, P. (2020). EVOLUTION OF TOLBUTAMIDE IN THE TREATMENT OF DIABETES MELLITUS. *Diabetes*, *2*, 10.
20. Kumar, R., & Saha, P. (2022). A Review on Artificial Intelligence and Machine Learning to Improve Cancer Management and Drug Discovery. *International Journal for*

Research in Applied Sciences and Biotechnology, *9*(3), 149-156.
21. Kumar, R., Jain, A., Tripathi, A. K., & Tyagi, S. (2021, January). Covid-19 outbreak: An epidemic analysis using time series prediction model. In *2021 11th international conference on cloud computing, data science & engineering (Confluence)* (pp. 1090-1094). IEEE.
22. KUMAR, A. (2019). The Scenario of Pharmaceuticals and Development of Microwave Assisted Extraction Techniques.
23. Jhala US, Canettieri G, Screaton RA, et al. Camp promotes pancreatic beta-cell survival via creb-mediated induction of irs2. *Genes Dev.* 2003;17:1575–1580.
24. Poitout V, Robertson RP. Glucolipotoxicity: Fuel excess and beta-cell dysfunction. *Endocr Rev.* 2008;29:351–366.
25. Prentki M, Nolan CJ. Islet beta cell failure in type 2 diabetes. *J Clin Invest.* 2006;116:1802–1812.
26. Butler AE, Janson J, Bonner-Weir S, et al. Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. *Diabetes.* 2003;52:102–110.
27. Saha, P., Nyarko, R. O., Lokare, P., Kahwa, I., Boateng, P. O., & Asum, C. (2022). Effect of Covid-19 in Management of Lung Cancer Disease: A Review. *Asian Journal of Pharmaceutical Research and Development*, *10*(3), 58-64.
28. Porat S, Weinberg-Corem N, Tornovsky-Babaey S, et al. Control of pancreatic beta cell regeneration by glucose metabolism. *Cell Metab.* 2011;13:440–449.
29. Daharia, A., Jaiswal, V. K., Royal, K. P., Sharma, H., Joginath, A. K., Kumar, R., & Saha, P. (2022). A Comparative review on ginger and garlic with their pharmacological Action. *Asian Journal of Pharmaceutical Research and Development*, *10*(3), 65-69.
30. Kumar, R., Saha, P., Kumar, Y., Sahana, S., Dubey, A., & Prakash, O. (2020). A Review on Diabetes Mellitus: Type1 & Type2. *World Journal of Pharmacy and Pharmaceutical Sciences*, *9*(10), 838-850.
31. Nyarko, R. O., Boateng, E., Kahwa, I., Boateng, P. O., & Asare, B. (2020). The impact on public health and economy using lockdown as a tool against COVID-19 pandemic in Africa: a perspective. *J Epidemiol Public Health Rev*, *5*(3).
32. KUMAR, R., SAHA, P., SARKAR, S., RAWAT, N., & PRAKASH, A. (2021). A REVIEW ON NOVEL DRUG DELIVERY SYSTEM. *IJRAR-International Journal of Research and Analytical Reviews (IJRAR)*, *8*(1), 183-199.
33. Kumar, R., Saha, P., Pathak, P., Mukherjee, R., Kumar, A., & Arya, R. K. EVOLUTION OF TOLBUTAMIDE IN THE TREATMENT OF DIABETES MELLITUS. *Jour. of Med. P'ceutical & Alli. Sci*, *9*.
34. Sakuraba H, Mizukami H, Yagihashi N, et al. Reduced beta-cell mass and expression of oxidative stress-related DNA damage in the islet of japanese type ii diabetic patients. *Diabetologia.* 2002;45:85–96.
35. Del Prato S, Bianchi C, Marchetti P. Beta-cell function and anti-diabetic pharmacotherapy. *Diabetes Metab Res Rev.* 2007;23:518–527.
36. UKPDS-group Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33).Uk prospective diabetes study group. *Lancet.* 1998;352:837–853.
37. Weinberg N, Ouziel-Yahalom L, Knoller S, Efrat S, Dor Y. Lineage tracing evidence for in vitro dedifferentiation but rare proliferation of mouse pancreatic beta-cells. Diabetes. 2007;56:1299–1304.
38. Bonner-Weir S. Life and death of the pancreatic beta cells. Trends Endocrinol Metab. 2000;11:375–378.

39. Kumar, S. (2022). A quest for sustainium (sustainability Premium): review of sustainable bonds. Academy of Accounting and Financial Studies Journal, Vol. 26, no.2, pp. 1-18
40. Allugunti V.R (2022). A machine learning model for skin disease classification using convolution neural network. International Journal of Computing, Programming and Database Management 3(1), 141-147
41. Dor Y, Brown J, Martinez OI, Melton DA. Adult pancreatic beta-cells are formed by self-duplication rather than stem-cell differentiation.[see comment]. Nature. 2004;429:41–46.
42. Teta M, Rankin MM, Long SY, Stein GM, Kushner JA. Growth and regeneration of adult beta cells does not involve specialized progenitors. Dev Cell. 2007;12:817–826.
43. Wang P, Fiaschi-Taesch NM, Vasavada RC, et al. Diabetes mellitus advances and challenges in human [beta]-cell proliferation. *Nat Rev Endocrinol.* 2015;11:201–212.
44. Takane KK, Kleinberger JW, Salim FG, Fiaschi-Taesch NM, Stewart AF. Regulated and reversible induction of adult human β-cell replication. *Diabetes.* 2012;61:418–424. Rankin MM, Kushner JA. Adaptive beta-cell proliferation is severely restricted with advanced age. *Diabetes.* 2009;58:1365–1372.
45. Kushner JA. The role of aging upon beta cell turnover. *J Clin Invest.* 2013;123:990–995.
46. Cano DA, Rulifson IC, Heiser PW, et al. Regulated beta-cell regeneration in the adult mouse pancreas. *Diabetes.* 2008;57:958–966.
47. Rohatgi N, Remedi MS, Kwon G, et al. Therapeutic strategies to increase human β-cell growth and proliferation by regulating mtor and gsk-3/β-catenin pathways. *Open Endocrinol J.* 2010;1:40–54.
48. Kulkarni RN, Mizrachi EB, Ocana AG, Stewart AF. Human beta-cell proliferation and intracellular signaling: Driving in the dark without a road map. *Diabetes.* 2012;61:2205–2213.