*https://doi.org/10.33472/AFJBS.6.2.2024.1172-1199*

African Journal of Biological Sciences

Research Paper Open Access

# Potential role of the mesenchymal stem cells as a therapeutic for T1DM in dogs: comprehensive review

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Article History

Volume 6, Issue 2, April 2024

Received:19 April 2024

Accepted: 10 June 2024

Published: 10 June 2024

*doi.org/10.33472/AFJBS.6.2.2024.1172-1199*

**Abstract: Background:** Diabetes mellitus (DM) is a chronic metabolic disease that characterized by persistent hyperglycemia and glucosuria. Type 1 diabetes is an autoimmune disease, mostly affects dogs and is manifested clinically by polyuria, polydipsia, polyphagia, and weight loss.The presence of characteristic clinical symptoms and glycemic profile tests, such as blood glucose concentration (BGC), insulin, c-peptide level, fructosamine (SFA), and hyperglycated haemoglobin concentration (HBA1c), are used to diagnose diabetes mellitus. One of the common therapeutic options accessible nowadays is insulin therapy. However, the majority of T1DM patients receiving insulin therapy are unable to keep their blood glucose levels within the normal range, and there is a risk of developing dangerous hypoglycemia. This led to look for other strategies for controlling blood glucose level. It is evident that the current standard therapy for diabetics fails to mimic the insulin secretion of healthy beta cells. As a result, exogenous insulin is more life-saving than curative. Therefore the two main strategies for treating type 1 diabetes mellitus reestablishing the insulin secretion mechanism and creating new islet β-cells. This new trial involves mesenchymal stem cells (MSCs), as they possess regenerative and immunomodulatory properties and can control immunological dysregulation that leads to beta cell death. Therefore, insulin-dependent diabetes mellitus in dogs may be treated with stem cell transplantation (IDDM). Though MSCs have been isolated from different sources, all show excellent improvement in the clinical cases.

**Keywords:** *diabetes; Mesenchymal stem cells; Dogs; and regenerative medicine*

**Introduction**

Dogs have historically been essential to helping us understand the pathogenesis and management of diabetes mellitus, along with the role of the pancreas in digestion, **Von Mering and Minkowski (1890)** shown that pancreatectomized dogs exhibit polydipsia and polyuria, which are correlated with the presence of glucose in the urine. By accident, they had produced an animal model of diabetes, which is still employed in certain research facilities today. This led them to the accurate conclusion that the pancreas has to produce an "antidiabetogenic factor," eventually identified as insulin, to allow the body to utilize glucose.

Strict blood glucose regulation is necessary for the body to carry out essential physiological processes. The mechanism involves the release of a complex network of hormones and neuropeptides, primarily sourced from the brain, pancreas, liver, gut, adipose tissue, and muscle tissues. By secreting by secreting the blood sugar-lowering hormone insulin and its antagonist, the glucagon hormone **(Bruyette, 2013 and Röder et al., 2016).**

The majority of patients with T1DM are unable to consistently keep their blood glucose levels within the normal range, even while using insulin. Additionally, there is a risk of serious hypoglycemia episodes, which limit the efficacy of diabetes treatment. Due to these problems, doctors and researchers are searching for other methods of regulating glucose levels **(McCall et al., 2010).**

**Madsen (20*0*5) and Noguchi (2009)** recently, it was reported that Exogenous insulin infusion is the current treatment for hyperglycemia, has been shown to help individuals with DM to control their blood sugar levels to some extent. It is imperative to maintain constant control over insulin injections since an excess of insulin can lead to hypoglycemia and in certain cases, coma, while insulin deficiency can result in the harmful effects of hyperglycemia in nearly each system of the body. Therefore, this standard trial for diabetic treatment fails to mimic the secretion of insulin by healthy pancreatic beta cells. From this point on, exogenous insulin is preventive rather than therapeutic.

Replacing new islets of pancreatic beta cells and rebuilding system of insulin secretion are the important and crucial strategies for type 1 diabetes treatment. As the pathogenesis of T1DM is marked by a gradual decrease in the pancreatic beta cells number and function. Although islet transplantation is a great way to treat type I diabetes mellitus, its clinical applicability is severely limited due to the limited number of potential donors, the challenging islet isolation and purification procedure, and immunological rejection **(Demeester et al., 2016 and Rickels and Robertson, 2019).**

Consequently, the cell transplantation methods to substitute pancreatic islets in the diabetes mellitus treatment has become has become very active.

**Xu et al. (2008) and Liu et al. (2013)** reported that stem cells are able to replace damaged cells in the body; therefore, they offer a promising treatment to replace the non-functional insulin-producing β cells of the pancreas.

**Anatomy and physiology of the Pancreas:**

The pancreas is a tiny but important organ that is located near to the stomach. It is composed of two major tissue types, the islets of Langerhans, which mainly regulate blood glucose levels by secreting insulin and glucagon directly into the bloodstream, and the acini, which secrete digestive juices into the duodenum to ensure correct digestion **(Qadri et al., 2015 and Mahadevan, 2019).**

The three main cell types found in the islets are beta, delta, and alpha cells. Beta cells, which make up roughly 60% of all islet cells, are mostly found in the centre of each islet. About 25% of the total cells are alpha cells. Conversely, 10% or so of the total are delta cells. Moreover, the islets and epsilon cells include modest populations of another type of cell called the pancreatic polypeptide cell (PP cell) **(Hall, 2011).**

**Da Silva Xavier (2018)** stated that glucagon, a peptide hormone known as the body's principal catabolic hormone, which raises blood levels of fatty acids and glucose, is released by alpha cells. The stated that glucagon, a peptide hormone known as the body's principal catabolic hormone, which raises blood levels of

fatty acids and glucose, is released by alpha cells. The insulin hormone that is released by beta cells lowers the blood's glucose levels. Delta cells release the somatostatin hormone, which prevents the secretion of both glucagon and insulin hormones. Epsilon cells release ghrelin hormone, which stimulates appetite, increases fat storage, and stimulates growth hormone release from the pituitary gland. Pancreatic polypeptide (PP) cells release pancreatic polypeptide, which is a satiety hormone that lowers gastric acid secretion, gastric output, and upper intestinal motility.

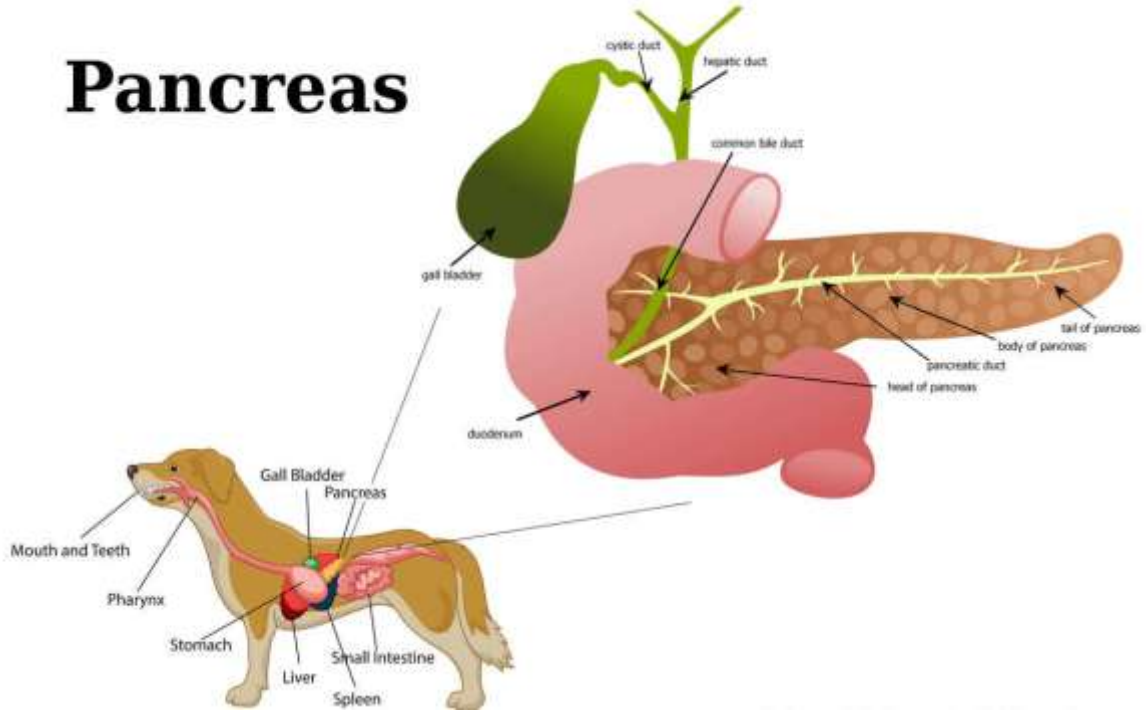


**Fig. 1Anatomy of pancreas in dogs**

The control of blood glucose level is a critical role of the pancreatic islets considering glucose acts as the primary metabolic fuel for the brain and central nervous system **(Campbell and Newgard, 2021).** Pancreas regulates blood glucose level by secreting endocrine hormones insulin and glucagon hormones through islets of Langerhans and also participates in digestion through the production and release of a variety of proenzymes or inactive precursors of enzymes by the acinar cells of exocrine pancreas, which are transported through the pancreatic ductal system to the duodenum to assist nutrient digestion **(Röder et al., 2016, Bastidas et al., 2017, Larsen and Grapin-Botton, 2017 and Westacott et al., 2017).**

Stimulation of insulin production is powerfully induced by postprandial rich energy-containing foods, mostly excess amounts of carbohydrates; moreover, insulin secretion is stimulated by the elevation of glucose level, amino acids, fatty acids, the level of the glucagon hormone, and the gastrointestinal tract **(Rorsman and Huising, 2018).**

**Hall (2011)** stated that insulin is a crucial anabolic hormone involved in the storage of extra energy. When there are too many carbohydrates, insulin motivates the body to store glycogen mostly in the muscles and liver. Any extra carbohydrates are then transformed by insulin into fat and stored in the adipose tissue. Insulin directly influences the uptake of amino acids by cells, their conversion into proteins, and the prevention of protein degradation. It regulates carbohydrate metabolism in the body and maintains the passage of glucose across the cell membrane.

Currently, the appropriate function of the pancreatic islets is required for metabolic homeostasis, and their dysfunction or the loss of functional beta cell mass is the key mechanism that leading to diabetes mellitus (DM) **(Cnop et al., 2005 and Campbell and Newgard, 2021).**

**Diabetes mellitus:**

Diabetes mellitus (DM) is a metabolic disorder that characterized by disturbances of carbohydrate, lipid and protein metabolism which result from defect in insulin secretion as Type 1, insulin inaction as Type 2 or both and associated with high mortality and morbidity **(Punthakee et al., 2018 and Poznyak et al., 2020).**

DM is one of the common endocrinopathy in dogs that affects middle-aged to older dogs, which manifested clinically by hyperglycemia, glycosuria and weight loss **(Abdullah et al., 2014 and Kumar et al., 2014).**

The incidence of diabetes has increased in dogs as in man. Alternatively this increase might be explained by the improvement in the diagnosis and management of diabetes, preference of certain breed by the owners and dependence on commercial feed, obesity **(Catchpole et al., 2005 and Davison, 2012).**

**Catchpole et al. (2005) and McCann et al. (2007)** indicated that the prevalence of DM is currently 1 in 500 dogs and 1 in 250 house cats. It usually affects canines between the ages of 5 and 12, but it is rare under 3 years of age.

DM causes in dogs appears to be multifactorial. Factors including, age, sex, obesity, neutering status, diet, and exposure to toxic chemicals/drugs that cause insulin resistance, immune-mediated destruction of islet cells **(Davison et al., 2008, Catchpole et al., 2013 and Nelson and Reusch, 2014).**

**Hoenig (2014) and Gilor et al. (2016)** reported that obesity as a risk factor for the development of DM in dogs is limited.

Some studies show that females are at increased risk compared to males, which may be due to progesterone and the diabetogenic effect of growth hormone, and castrated males are at increased risk compared to intact males **(Fall et al., 2007, Heeley et al., 2020 and Koren, 2022).**

Breeds showed high susceptibility to DM as the Samoyed, Tibetan Terrier, Cairn Terrier, and miniature schnauzers while others that have less susceptibility as the Boxer, Golden retrievers and German Shepherd **(Fall et al., 2007, Catchpole et al., 2013, Usui et al., 2015 and Yoon et al., 2020).**

Collectively, the more common risk factors for DM. Dogs more than 8 years of age, intact females, castrated male dogs, Border Terrier breeds in particular, and dogs having a concurrent diagnosis of hyperadrenocorticism or pancreatitis were all associated with increased odds of DM diagnosis. Variables associated with an increased hazard of death include dogs that were ≥ 10 years of age at diagnosis, entire, previously treated with glucocorticoids, having had a blood glucose level (BG) > 40 mmol/L at diagnosis, or dogs that did not start insulin treatment (**Hume et al., 2006).**

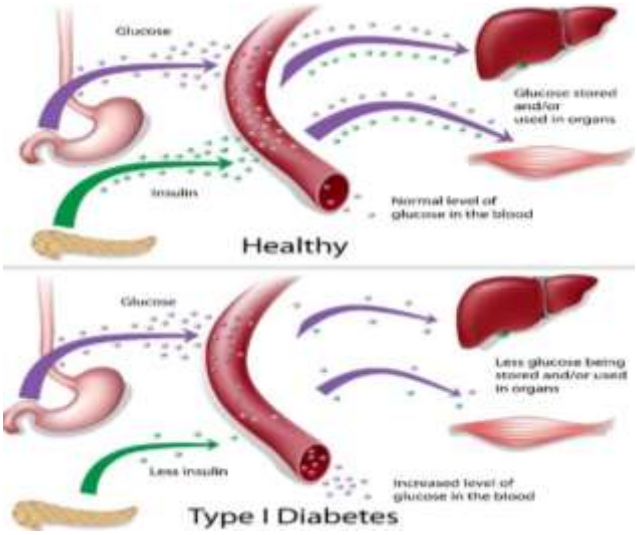


**Fig. 2 Pathophysiology of type1 diabetes**

**Classification and different types of diabetes mellitus:**

Nowadays, DM classification generally depends on both the aetiology and the disease pathogenesis rather than the clinical response to insulin treatment. According to this classification, diabetes can be divided into four main types: type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), gestational diabetes mellitus (GDM), and diabetes caused by or associated with certain specific condition **(Catchpole et al., 2008, American Diabetes Association, 2014 and American Diabetes Association, 2018).**

Previously, canine DM has been classified into insulin-dependent (IDDM), also known as Type 1, which is characterized by a lack of insulin production and depends mainly on external insulin for survival, or non-insulin-dependent (NIDDM), also known as Type 2, in which there is impairment in insulin production along with an poor response to insulin hormone. Although nearly all diabetic dogs require insulin therapy, unlike human beings, however, most diabetic dogs (>50%) are thought to have a disease similar to Type 1 DM in humans **(Feldman and Nelson, 1996 and Catchpole et al., 2005).**

**Type 1 diabetes mellitus:**

Type 1 diabetes is known as (IDDM)**,** the most common type of DM in dogs **(Plotnick and Greco, 1995 and Qadri et al., 2015).** It is a chronic autoimmune disease characterized by hyperglycemia owing to partial or complete insulin deficiency, which occurs due to the destruction of pancreatic islet beta cells **(SEARCH Study Group, 2004, Atkinson, 2014 and DiMeglio et al., 2018).**

The causes of IDDM in dogs are multifactorial and caused by a progressive loss of pancreatic beta cells. Although the exact cause is unknown, a number of disease processes are believed to be involved, including congenital beta cell hypoplasia, beta cell loss associated with exocrine pancreatic disease, immune-mediated beta cell destruction, and may be idiopathic **(Catchpole et al., 2005).**

**Nelson and Reusch (2014)** reported that IDDM in dogs is commonly characterized by permanent hypoinsulinemia, no increase in c-peptide level in response to insulin secretagogues, and an absolute requirement for exogenous insulin administration to avoid ketoacidosis**.**

**Zheng et al. (2018)** added that environmental factors as well play a role in IDDM susceptibility. Feed, Viruses, or environmental toxins may improve the progression of IDDM by inducing insulitis, an inflammatory infiltrate in the islets of Langerhans founded in the pancreas, or by activating the immune system.

**Pathophysiology of type 1 diabetes mellitus:**

IDDM develops through the stimulation of the immune system against beta cells and the autoimmune destruction of pancreatic beta cells, resulting in a deficiency of insulin secretion, which consequences in the metabolic derangements associated with IDDM. In addition to the loss of insulin secretion, impairment of the function of pancreatic alpha cells leads to excessive secretion of the glucagon hormone in IDDM patients **(Raju and Raju, 2010 and Saberzadeh-Ardestani et al., 2018)**.

Uncontrolled IDDM is characterised by hyperglycemia, which is due to the combination of both: elevation of hepatic glucose production through the conversion of liver glycogen into glucose, then hepatic gluconeogenesis; insulin deficiency weakens tissue utilization of glucose by adipose tissue and skeletal muscles; in addition, reduced glucose uptake by peripheral tissues in turn leads to a reduced rate of glucose metabolis **(Raju and Raju, 2010).** The authors added that when blood glucose exceeds the renal threshold, glucosuria occurs, which leads to polyuria due to osmotic diuresis, which is accompanied by a loss of water and electrolytes and the activation of the thirst mechanism (polydipsia). The negative caloric balance leads to an increase in appetite and food intake, which is known as polyphagia.

They also added that in hepatocytes, the majority of the acetyl COA is not oxidized by the TCA cycle but is metabolized into the ketone bodies (acetoacetate and beta-hydroxybutyrate). These ketone bodies are used for energy production by the brain, heart, and skeletal muscle. In IDDM, there is a production of excess ketone bodies that exceeds the body's ability to utilize them, leading to ketoacidosis.

**Chen et al. (2012)** stated that insulin disturbs protein metabolism, increasing the rate of protein synthesis and lowering the rate of protein degradation. Therefore, a lack of insulin accelerates the rate of proteolysis,

which in turn causes an increase in plasma amino acid level, muscle wasting, and poor wound healing. Hepatic lipidosis develops, and ketoacidosis can results secondary to enhanced ketone body production, immunological suppression and endothelial damage.

**Other types of diabetes mellitus:**

**Type 2 diabetes mellitus:**

Although obesity is becoming more common in dogs, there is no proof that insulin resistance causes beta cell malfunction and the subsequent DM in dogs, as it does in humans. Obese dogs show evidence of insulin resistance but compensated appropriately through increased insulin secretion, even after years of obesity-induced insulin resistance, DM does not appear to develop and majority of obese dogs retain euglycemia **(Verkest et al., 2012 and Gilor et al., 2016).**

About 80% of diabetic cats have a condition resembling type 2 DM in human. Type 2 diabetes is caused by insulin resistance, the inability of insulin-sensitive tissues to respond to insulin, which usually results from antagonism of insulin function by other hormones. Glucose intolerance related to obesity might contribute to insulin resistance, but obesity is not a primary cause of diabetes in dogs. Obesity, physical inactivity, and prior administration of glucocorticoids are common risk factors **(Rand, 2012 and Forcada et al., 2014).**

In type 2 diabetes the two main pathological defects are impaired insulin secretion through a dysfunction of the pancreatic beta cell and insulin resistance**,** inability of insulin-sensitive tissues to respond to insulin **(Holt, 2004 and Galicia-Garcia et al., 2020).**

**Gestational diabetes mellitus (GDM):**

GDM is the third form of diabetes mellitus, which is a type of insulin resistant diabetes (IRD), and may called diestrus-associated DM in dog **(Fall et al., 2008).**

This third form is because of insulin resistant effect of di-estrous phase in older female dogs, that it is associated by increasing the progesterone concentrations, which uniquely encourage the mammary glands to produce growth hormone which both are a potent inducer of insulin resistance, and it has been reported to resolve within days to weeks after parturition or termination of pregnancy **(Rucinsky et al., 2010, Mared et al., 2012, Kim et al., 2012 and Kumar et al., 2014).**

**Fall et al. (2008) and Kumar et al. (2014)** reported that GDM affects mainly middle-aged bitches in the latter half of gestation**.**

**Other specific types:**

Other specific types of diabetes include other forms in animals, including drug-induced diabetes (usually steroid use), endocrinopathies that antagonize insulin action (acromegaly, hyperadrenocorticism), or exocrine pancreatic disease. Chronic pancreatitis is the most common cause of canine diabetes in this category, accounting for approximately 30% of cases **(Rand, 2020).**

**Clinical signs of diabetes mellitus:**

**Durocher et al. (2008) and Qadri et al. (2015) reported that** clinical signs of diabetes mellitus (DM) such as polyuria, polydipsia, polyphagia, weight loss, persistent hyperglycemia, glycosuria, and ketonuria, and in rare cases, acute blindness due to cataract formation, are reported to be related to elevated blood glucose levels and the body's inability to use glucose as an energy source.

Clinical symptoms do not appear until blood glucose levels are high enough to cause glycosuria, which usually happens at 180–220 mg/dl in dogs and 220–270 mg/dl in cats **(American Diabetes Association, 2013).**

**1-polyuria and polydipsia:**

Are attributed to that relative or absolute insulin deficiency in DM that reduces blood glucose uptake by tissues like liver, muscle, and adipose tissues, leading to hyperglycemia .This hyperglycemia when exceeds the renal threshold for glucose, glucose remains in the ultrafilterate, then Glucosuria will typically develops and osmotic diuresis is stimulated. Polyuria occurs and then compensatory polydipsia. Renal threshold approximately 200 mg/dL in dogs (**Behrend et al., 2018 and Rand, 2020).**

**2-polphagia:**

Animals with uncomplicated DM may have an increased appetite. This is controlled by central mechanisms, including increased hunger triggered by nutrient loss predominantly glucose **(Rand, 2020).**

**3-Weight Change:**

**Rand (2020)** stated that untreated diabetic dogs, continue to lose weight despite an increased appetite and an increased intake because of their inability to utilize glucose, malassimilation of nutrients absorbed from the gut, and urinary loss of glucose and amino acids, which exacerbates weight loss.

**Ciobotaru (2013)** claimed that aberrant gluconeogenesis resulting from fatty and amino acids causes weight loss and muscular atrophy.

**Complication of diabetes mellitus:**

**Beam and correa (1999)** showed that it is widely accepted that the majority of diabetic dogs will develop cataract, but other consequences of moderate persistent hyperglycemia, e.g., retinopathy, vascular injury, and nephropathy, are not expected in this species.

Cataracts, Nephropathy, Urinary tract infection, Hyperadrenocorticism, dermatitis, pancreatitis, otitis are Common complications of DM in dogs. A metabolic condition that is prone insulin resistance may be further exacerbated by hypothyroidism **(Hess et al., 2000).**

**Diabetic ketoacidosis (DKA):** is one of the most severe and potentially life threatening diabetes copmlication. It occurs as a result of complete or partial insulin deficiency, and is typically characterized by hyperglycemia, ketosis, and acidosis **(Taylor et al., 2015).**

**Cataract:** this eye cataract seems because of the metabolism of glucose to its sugar alcohol "sorbitol" in the lens **(Varma, 1980).**Which has a higher osmotic pressure that absorbs and drainages water into the lens**.** It may also be due to non-enzymatic glycation of the lens matter **(Hashim and Zarina, 2011)**.Or oxidation stress **(Williams, 2008).** Eighty percent of the diabetic dogs suffer from cataract. This result is consistent with (**Wilkie et al., 2006, Miller and Brines, 2018 and Cantero et al., 2022).**

**Nephropathy:** There was a significant influence of DM on renal function. Animals with diabetes had much greater levels of urea and creatinine; these findings were corroborated by **Herring et al. (2014)** who reported that the prevalence of elevated urine protein-creatinine ratio (UPC) and microalbuminuria in urine of diabetic dogs was up to 55% and 73%, respectively.

**Yaribeygi et al. (2018), Umanath et al. (2018), Papachristoforou et al. (2020) and Sinha and Nicholas (2023)** stated that the main cause of end-stage renal disease is diabetes mellitus. The pathogenesis of diabetic kidney disease (DKD) related to hyperglycemia which causes various mechanisms and pathways, renal damage caused by several mediators contribute to the development of renal structural and functional changes, some of these mediators, such as proinflammatory cytokines, reactive oxygen species, protein kinase C, hemodynamic and hormonal disorders and advanced glycation end products.

**Urinary tract infection:**

Altered susceptibility to infection in patients with DM has been attributed to a depression in the function of polymorphonuclear leukocytes **(Szablewski and Sulima, 2017).**

**Complications of Diabetes Mellitus in Dogs and Cats:**

| **Common** | **Uncommon** |
|---|---|
| Iatrogenic hypoglycemia | Peripheral neuropathy (dog) |
| Persistent or recurring polyuria, polydipsia, weight loss | Diabetic nephropathy |
| | Significant proteinuria |
| Cataracts (dog) | Glomerulosclerosis |
| Lens-induced uveitis (dog) | Retinopathy |
| Bacterial infections, especially involving the urinary tract | Exocrine pancreatic insufficiency |
| | Gastric paresis |
| Chronic pancreatitis | Intestinal hypomotility and diarrhea |
| Recurring ketosis, ketoacidosis | Diabetic dermatopathy (i.e., superficial |

| | |
|---|---|
| Hepatic lipidosis<br>Peripheral neuropathy (cat)<br>Systemic hypertension (dog | necrolytic dermatitis) |

**(Nelson and Couto, 2019).**

**Diagnosis of diabetes mellitus:**

DM is diagnosed mainly by the presence of typical clinical signs such as; polyuria, polydipsia, polyphagia, and weight loss, as well as hyperglycemia and glycosuria with full laboratory assessment **(Ettinger and Feldman, 2010, Behrend et al., 2018 and Petersmann et al., 2018).**

**Clinical signs:**

Diagnosis of diabetes based on the presence of characteristic symptoms like polyuria, polydipsia, polyphagia and weight loss, in addition the presence of a persistently high level of blood glucose, and the presence of glucose in the urine and ketonuria **(Durocher et al., 2008).**

**Full laboratory evaluation:**

Blood glucose concentration, Urine analysis, Serum fructosamine (sFA) concentration measurement, a widely available, cost-efficient test, Hyperglycated hemoglobin concentration (HbA1c), C-peptide (**Behrend et al., 2018 and Del Baldo et al., 2020).**

***Blood glucose concentration:**

DM was diagnosed by finding persistent marked hyperglycemia .Which plasma glucose >250 mg/dl **(Herring et al., 2014).**

**Hyperglycemia:** The normal blood glucose level ranged from 60-130. It may rise to 250-300 mg/dl (13.6-16.5 mmol/l) after a large or high-calorie meal. However diabetes is the only common disease that will causes the blood glucose level to increase above 400 mg/dl (22 mmol/l). Some diabetic dogs will have a glucose level as high as 700- 800 mg/dl (44 mmol/l), although the most will be have range of 400-600 mg/dl (22-33 mmol/l) **(Cohen et al., 2009 and Kumar et al., 2014).**

Long-term hyperglycemia often leads to various microvascular and macrovascular diabetic complications, which are mainly responsible for diabetes-associated morbidity and mortality. Hyperglycemia serves as the primary biomarker for the diagnosis of diabetes **(Banday et al., 2020).**

Oral glucose tolerance used for DM diagnosis , that performed under fasting condition by adding 1 gm carbohydrate or starch per kg BWT, then administrated orally and measured every half an hour through two hours **(Briens et al., 2021).**

***Urine analysis:**

Urinalysis will reveal the presence of glucose, and sometimes also show the existence of protein, ketones, bacteria, and/or casts **(Behrend et al., 2018).**

Glucosuria means the presence of glucose in the urine .Which is manifested clinically when the blood sugar level exceeds the renal threshold level that is180 mg/dl **(Palmer et al., 2004, Nair and Wilding, 2010 and Hieshima et al., 2020).** Glucosuria usually develops when the blood glucose level surpasses approximately 200 mg/dL in dogs and 250-300 mg/dL in cats, what is called it exceed the renal threshold **(Behrend et al., 2018).**

Ketonuria suggests a change from the metabolism of carbohydrates into the breakdown of fats to supplies the body with enough energy. This shift is most closely known in small animal secondary to DM (**Qadri et al., 2015).**

**Serum fructoseamine concentration (**sFA)**:**

In addition to clinical observations, blood glucose curves, and glycated haemoglobin concentration (HbA1c), SFA concentration is a widely accessible and affordable test that is used to evaluate glycemic control in dogs with diabetes mellitus (**Behrend et al., 2018 and Del Baldo et al., 2020).**

Fructosamines are a class of blood proteins that have been glycated during circulation, primarily albumin. An elevated fructosamine level represents the mean blood glucose concentration over the previous 1-2 weeks, allowing for regular assessments to develop an ideal insulin treatment plan and track its effects. An elevated

fructosamine level suggests chronic hyperglycemia during the prior 1-2 weeks **(Reusch et al., 1993, Loste and Marca, 1999, Nelson, 2015 and Kuzi et al., 2023).**

Fructosamine has various limitations as a biomarker, due to its concentration is impacted by hypoalbuminaemia, hyperglobulinaemia, hyperlipidaemia, azotaemia, haemolysis and hypothyroidism **(Reusch and Haberer, 2001 and Zeugswetter et al., 2010).**

***Glycatedhemoglobin(**HbA1c)**:**

HbA1c is a group of glycated proteins that result from the irreversible non-enzymatic binding of hemoglobin in erythrocytes **(Reusch et al., 1993 and Pohanka, 2021).**

HbA1c readings in dogs can be used as an indicator for the average plasma glucose level during the preceding two to three months **(Mahaffey et al., 1984, Loste and Marca, 2001 and Kim et al., 2019).**

HBA1C falsely elevated levels can occur with diseases that prolong erythrocyte lifespan or are associated with a decrease in erythrocyte turnover, such as iron deficiency anaemia and splenic disorders. HbA1c level decreased in the pathological conditions that shorten erythrocyte lifespan or are associated with increased erythrocyte turnover, such as blood-loss anaemia, hemolytic anaemia, splenomegaly, and pregnancy **(Haberer and Reusch, 1998 and Welsh et al., 2016).**

Serum fructoseamine concentrations change more rapidly than do hyperglycated hemoglobin concentrations in response to alterations in insulin treatment, so for this cause serum fructoseamine concentration is considered better for assessment of glycemic control in diabetic dog **(Nelson, 2015).**

**Mikhaiel et al. (2022)** reported that dogs that have HbA1c ≥6.5 % were considered diabetic.

***C-peptide:**

C-peptide is produced in equal quantities to insulin and therefore is the best measure of endogenous insulin secretion; it indicates the effectiveness of beta cell function in diabetic patients **(Jones and Hattersley, 2013).**

C-peptide's physiology makes it appropriate for measuring insulin secretion. Given that the enzymatic cleavage of proinsulin yields equal quantities of both insulin and C-peptid **(Licinio-Paixao et al., 1986 and Polonsky et al., 1986).**

C-peptide plays a crucial clinical function in distinguishing between Type 1 and Type 2 diabetes, primarily in relation to the development of absolute insulin insufficiency in Type 1.Utility is greatest in long-standing diabetes as there may be a significant overlap between Type 1 and Type 2 diabetes at the time of diagnosis **(Iqbal et al., 2023).**

In type one diabetes insulin/C-peptide levels decrease rapidly, so the majority of patients with type 1 diabetes will have low C-peptide levels **(Palmer et al., 2004 and Besser et al., 2011).**

**Histopathological examination:**

**Nelson and Couto (2019)** reported that histopathological findings of renal tissue include membranous glomerulonephropathy as glomerular and tubular basement membrane thickening, the presence of sub endothelial deposits, glomerular fibrosis, and glomerulosclerosis. Who also mentioned that diabetic nephropathy is expressed as proteinuria, primarily albuminuria .As glomerular changes progress, glomerular filtration becomes progressively impaired, resulting in the development of azotemia and eventually uremia.

Non necrotic tubular degenerated tubules had swollen epithelum and had a foamy granular cytoplasm. Other showed moderate vacuolation and tubular necrosis, tubulointerstitial nephritis with inflammatory cell infilteration, and the tubular lumen had a dark necrotic debris (**Abdullaziz et al., 2022).**

The histopathological examination of pancreatic tissues of alloxan induced diabetic dogs showed severe congestion of blood vessels, perivascular and intestinal edema with inflammatory cells infiltration, coagulative necrosis of pancreatic acini and mononuclear cells infiltration between the pancreatic acini **(Watanbe et al., 2004 and Ismail et al., 2015).**

The author also added that histopathological findings of hepatic tissues of alloxan induced diabetic dogs showed severe cytoplasmic vacuolation of both hydropic and lipid types, multifocal areas of hepatic necrosis with mononuclear cells infiltration, widening of the hepatic sinusoids that replaced the necrotic hepatocytes,

hyperactivation of Kupffer cells and widespread moderate congestion. Additionally, the portal areas were moderately thickened by mononuclear cells infiltration.

**Treatment:**

The chief goals of treating diabetic patients are to improve clinical signs of diabetes and to avoid the complications, including hypoglycemia **(Fleeman and Rand, 2001).**

Treatment options are similar to those for human diabetics and include; insulin injections (usually administered twice a day at 12 h intervals), dietary modifications, exercise in dogs, correction of obesity, Oral hypoglycemic medications in cats **(American Diabetes Association, 2013).**

**Behrend et al. (2018)** showed that the treatment of clinical DM in the dogs, always requires exogenous insulin therapy**.**

The most common used insulin products in canine DM are isophane, lente and ultra-lente insulin. **(Monroe et al., 2005).**Lente (porcine zinc insulin suspension; Vetsulin) is mostly recommended as a first choice in treatment and commonly preferred for management of canine diabetes using a starting dose of 0.25 U/kg q 12 hr, the duration of action is near by 12 hr in most dogs, and the amorphous component of the insulin helps to minimize postprandial hyperglycemia **(Rucinsky et al., 2010 and Behrend et al., 2018).**

**Stem cell therapy**

**Therapeutic application of different types of stem cells**

**1- Embryonic stem cells (ESCs)**

ESCs emerge from the inner cell mass of blastocysts, which are pluripotent, self-regenerating cells and can be able to differentiate into any type of cell present in the three germinal layers. These are human embryonic cells that have been suggested as viable sources for cell transplantation and regenerative medicine due to their remarkable capacity to give rise to all somatic cell lineages (**Tobias et al., 2013 and Clevers, 2016).**

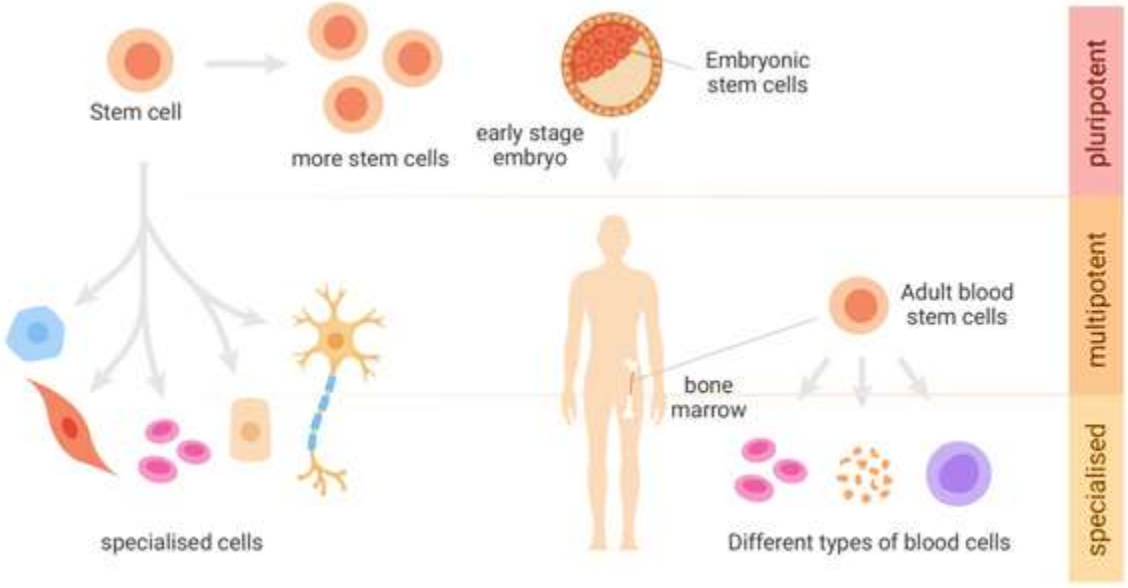


**Fig. 3 Different types of stem cells**

ESCs can be employed in the treatment of type 1 diabetes; the difference between the two types is that the undifferentiated form is characterised by the cell's capacity to adhere to the injured pancreatic tissue. The cell began to transdifferentiate into specialised beta cells in the conditioned microenvironment of the damaged pancreas, providing strong evidence for the theory that the pancreas secreted various factors in diabetes, including substances that attracted chemocollectors and stimulated stem cell development into specialised cells. These processes estimated the infused undifferentiated cells to the energy site in a manner similar to leukocyte migration (**Naujok et al.**, **2009**)**.**

However, the application of ESCs became restricted due to the development of teratoma and tumour formation, in addition to religious concerns about the methodology used for collecting these types of cells **(Lumelsky, 2001 and Nguyen et al., 2016)**. On the other hand, a number of research demonstrated that using ESCs to create IPCs was unsuccessful (**Sipione et al.**, **2004**)**.**

**2-Induced pluripotent stem cells (IPSCs).**

Induced pluripotent stem (iPS) cells are a new type of pluripotent stem cell using adult somatic cells with their genetic code altered to resemble that of embryonic stem (ES) cell **(Ye et al., 2013).**

**Takahashi et al. (2007)** revealed that adult somatic cells could potentially be reprogrammed to become induced pluripotent (iPSC) cells using just four necessary transcription factors. Similar to ESCs, It multiplied into endoderm, ectoderm, and mesoderm cells from the three germ layers (**Dimos et al.**, **2008**).

Transcription factors are required to transform mature fibroblasts into embryonic stem cells. These four factors are Yamanaka factors; they are c-Myc (also known as OSKM) and Sox2, Oct4, and Klf4. A few years later, human fibroblasts were also employed to create iPSCs using Yamanaka's OSKM formula (**Takahashi et al., 2007 and Lowry et al., 2008).**

Moreover, because ESCs are first separated from blastocysts that were not implanted, they are never of autologous origin; if injected into patients, this could result in immunological rejection. Therefore, the development of iPSCs has shown great potential because, in contrast to hESCs, iPSCs raise no ethical issues **(Wert and Mummery, 2003 and Taylor et al., 2011).**

IPSCs have become a viable substitute for hESCs, given the ethical and immunogenic issues they raise. This is due to the fact that adult somatic tissues are the source of iPSCs, whereas sources of hiPSCs, like blood, skin, and urine, are widely available. Furthermore, when hiPSCs are autologously implanted, immunological rejection can be prevented because they can be isolated from specific patients (**Felfly and Haddad, 2014, park et al., 2015 and Singh et al., 2015).**

***3*- Mesenchymal stem cell (MSCs)**.

Mesenchymal stem cells (MSCs) are multipotent stem cells that can self-renew and differentiate into several tissues. MSCs are reservoirs of trophic factors that stimulate intrinsic stem cells to heal injured tissues, regulate the immune system**,** have regenerative and immunomodulatory characters, and can regulate the immune dysfunction that leads to the destruction of beta cells. Thus, stem-cell transplantation may be used to treat dogs with insulin-dependent diabetic mellitus **(Rodríguez-Fuentes et al., 2021).**

Owing to these remarkable properties, MSCs are now acknowledged as one of the most promising cell sources for the treatment of degenerative diseases and damaged tissue **(Ezquer et al., 2017).**

Some researchers tried to change the name of MSCs to medicinal signalling cells because of their secretory function in the locations of diseases, injuries, and inflammations **(Caplan, 2017).**

MSCs isolated from AT, BM, and UC meet all of the minimal criteria listed by the ISCT, including morphology (plastic spindle shape), MSC surface markers (less than 2% negative for CD11, CD13, CD19, CD34, CD45, and HLR-DR; 95% positive for CD73, CD90, and CD105), and the capacity to differentiate into chondrocytes, osteocytes, and adipocytes **(Mohamed-Ahmed et al., 2018).**

Adult MSCs have the following common features: negative expression of CD14, CD34, and CD45, and positive expression of CD44, CD90, CD105 (SH2), and CD166 **(Silva-Carvalho et al., 2019).**

It could be differentiated into many cell types including insulin producing cells forming a cluster that response to glucose challenge in vitro secreting insulin (**Phadnis et al.**, **2011**)**.**

They show excellent potential for differentiation into a wide variety of tissue lineages, including as adipocytes, myocytes, osteoblasts, and chondrocytes found in cartilage, muscle, and fat. MSCs have been isolated from multiple tissues: bone marrow (BM), skeletal muscle tissue, adipose tissue (AT), synovial membranes, saphenous veins, dental pulp, periodontal ligaments, cervical tissue, Wharton's jelly, umbilical cords, umbilical cord blood, amniotic fluid, placentas, etc. are among the tissues from which MSCs have been extracted **(Squillaro et al., 2016 and Farkhad et al., 2021).**

**3.1. Bone marrow MSCs:**

Bone marrow stem cells are broadly considered hematopoietic stem cells and MSCs. Because these cells come from the same person, rejection issues may be reduced, potentially making this a type of T1D therapy **(Godfrey et al., 2012).**

BM has been highlighted as a promising source of MSCs containing various growth factors and cytokines that are potentially utilized towards regenerative procedures involving cartilage and bone **(Kim et al., 2020).**

One study looked at T1D patients with DKA and found BM-MSCs to preserve beta cell function in T1D patients, reducing levels of fasting and post-prandial C-peptide levels, with one patient achieving insulin independence for a period of three months **(Li et al., 2016).**

Lately, a study showed a rapid recovery and restoring for serum insulin level improving hyperglycemia in co-transplantation model of bone mononuclear cells with MSCs that suggested that both type of cells shared in regeneration and repairing of damaged beta cell when MSCs also, modulated the immune response that estimated in pancreatic islet that provide a synergistically effect that outcome form the combined transplantation (**Urbán et al.**, **2008**).

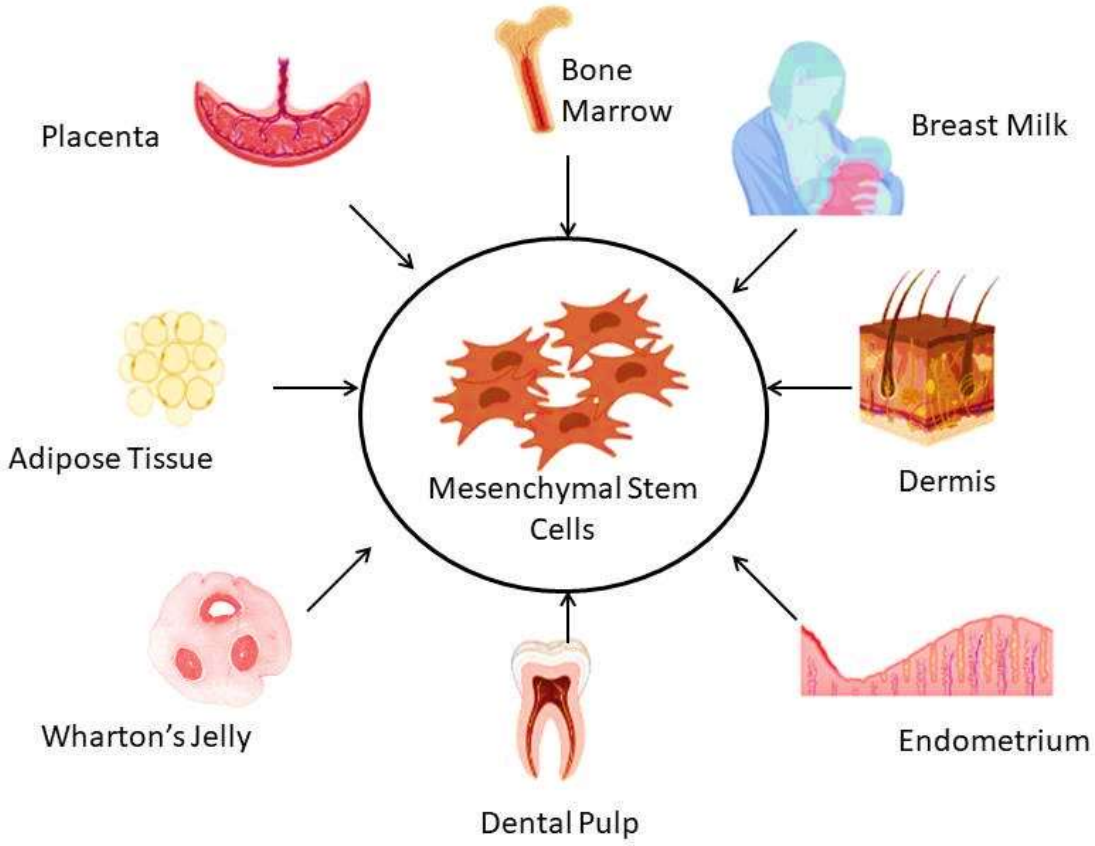


**Fig.4 Different sources of mesenchymal stem cells**

**3.2. Adipose tissue -MSCs:**

Adipose tissue-derived mesenchymal stem cells (ADSCs) are a group of cells that arise from the mesoderm during embryonic development. Amongst several types, subcutaneous adipose tissue seems to be the most clinically relevant source, being available in abundance for harvest, and its isolation only slightly invasive **(Minteer et al., 2013 and Lin et al., 2015).**

ADSCs possess great proliferation, differentiation, immunoregulatory properties, are easy to separate and culture, do not have ethical concerns, promote tissue regeneration, and are among the best resources for the treatment of type 1 diabetes mellitus **(Bateman et al., 2018 and Arora et al., 2020).**

Both BM-MSCs and UC-MSCs had a good ability to stick to the plastic disc and the typical morphology of fibroblasts **(Zhang et al., 2022).**

**3.3. Umbilical cord blood- MSCs (UCB-MSCs):**

Ethical problems are rarely raised when using UC-MSCs, which are isolated from umbilical cord that are typically disposed of as medical waste. Because the procedure of collecting UCs is non-invasive, ex vivo, and carries no danger of discomfort or infection, donors find it to be a more agreeable approach. Additionally, in vitro, UC-MSCs have higher proliferation capacity than BM-MSCs **(Kern et al., 2006 and Baksh et al., 2007).**

Cord blood is considered an additional necessary source of stem cells that have greater cellular potential and can be attained in a non-invasive way (**Ende et al.**, **2004**).

Interestingly, UC-MSCs were the most preferred MSCs for the remaining trials **(Hoang et al., 2022).**

Even though MSCs make up only about 10–7% of the cells in UC, due to their higher proliferation rate and rapid population doubling time allow these cells to rapidly replicate and increase in number during in vitro culture, so UC-MSCs have the fastest population doubling time compared to AT-MSCs and BM-MSCs in both conventional culture conditions and xeno- and serum-free environments **(Hoang et al., 2021).**

Many research proved that using umbilical cord blood mesenchymal stem cells became more effective in the treatment of type 1 or type 2 diabetes (**Yoshida et al.**, **2005**).

After receiving an allogenic UC-MSC transplant, recipients showed better control of blood glucose, a 50% rise in fasting C-peptide (FCP) at the 1-year follow-up, and even two years after the transplant, a 50% reduction in insulin usage **(Hu et al., 2013).**

Additionally, UC-MSC can be utilized to treat T1D chronic complications, such as neuropathy, DN, and retinopathy **(Wu et al., 2022).**

**3.4. Wharton's jelly MSCs**

Moreover, Wharton jelly, which a substance that found in the umbilical cord's matrix, possess multipotent, highly active mesenchymal stem cells that completely satisfy the requirements for mesenchymal stem cells. These cells also expressed a variety of embryonic stem cell markers, such as OCT4 **(Lo Iacono et al., 2017).**

However, because of their versatility and ability to differentiate into a wide variety of cell types that can produce insulin both in vivo and in vitro, these cells are thought to be among the best candidates for regenerative medicine due to their activity, noninvasive isolation method, and large donor pools. Together, these cells were able to effectively regulate hyperglycemia in type 1 diabetic patients during a prolonged research involving 29 patients(**Hu et al.**, **2012**).

**3.5. Hepatic stem cells:**

Since the liver and pancreas both originated from the endoderm, hepatic mesenchymal stem cells are considered to be one of the earliest possibilities for the production of insulin-producing cells. Remarkably, studies have demonstrated that even after prolonged culture, hepatic stem cells express the embryonic transcription factor of the pancreas, PDX1, without altering the degree of expression of these pancreatic marker genes (**Rossi et al., 2001 and Yang et al.**, **2002**).

Parallel to this, researchers were able to successfully generate insulin-producing cells from hepatic mesenchymal stem cells by transfecting the cells with an adenovirus that expressed pancreatic developmental markers including Pdx1, which increased the release of insulin (**Meivar-Levy and Ferber**, **2010**).

**3.6. Pancreatic stem cells:**

Pancreatic tissue contained two main parts: the exocrine element 90% and the endocrine element 10%. The endocrine element comprises nestin-positive cells that fulfil mesenchymal stem cell criteria and could be differentiated into specialized beta cells (**Zulewski et al.**, **2001**).

In a different investigation, the researchers showed that the pancreatic mesenchymal stem cells obtained from the pancreatic duct of diabetic and prediabetic mice were pluripotent. The cells transformed into glucose-responsive insulin-producing cells after being implantation which reduced type 1 diabetes hyperglycemia (**Bonner-Weir et al.**, **2000 and Xu et al., 2008)**. Then it was obviously explained by (**Bonner-Weir and Sharma**, **2006**) indicates the pancreatic progenitor cells are most likely found in the pancreatic ductal epithelium.

Furthermore, in a model of pancreatic duct ligation, the exocrine pancreatic component comprising acinar cells and secretory acini seemed to be regenerated pancreatic beta cells (**Xu et al.**, **2008 and Zhou et al., 2008**).

Progenitor cells exist in the pancreatic duct cells, where they differentiate and migrate to produce new islets during both organogenesis and regeneration. **Ramiya et al. (2000)** first described the generation of new islets from pancreatic duct epithelial cells in vitro, isolated from prediabetic adult NOD mice. These in vitro-grown islets contained alpha and delta cells, responded to in vitro glucose challenge and, once implanted into NOD mice, reversed insulin-dependent diabetes.

**Immunomodulatory effect:**

T1DM is a multifactorial condition which characterized by T cell-mediated autoimmune destruction of beta cells **(d'Annunzio et al., 2011).**

It has been determined that DM results from the invasion of the pancreas by macrophages and dendritic cells, which is followed by the infiltration of B cells, natural killer (NK) cells, and CD4 and CD8 T lymphocytes **(Willcox et al.**, **2009 and Odumosu et al., 2011).**

Beta cell death that happens over the inflammation course is most likely as a result of direct contact with activated macrophages and self-reactive T-lymphocytes, and exposure to soluble mediators released by these cells, such as pro-inflammatory cytokines, nitric oxide, and oxygen free radicals **(Eizirik and Mandrup-Poulsen, 2001 and Babon et al., 2016 ).**

There are two mechanisms by which MSCs exhibit a local immunosuppressive impact. 1. The paracrine action, or communication between cells 2.releasing a number of immunomodulatory cytokines, and in line with previous authors findings that diabetes was caused by an immunological malfunction, MSCs can treat diabetes by using their immunosuppressive processes.

MSCs have an immunosuppressive effect and release a range of cytokines, enhance the diabetic patient's microenvironment, target insulin-resistant tissue, treat islet damage, protect and regenerate islet beta cells, and lower blood sugar levels. . Because MSCs regulate the immune system, they can also successfully treat type 1 diabetes, which is related to the primary immunological mechanism of the disease. Almost half of the clinical trials on cell treatment for type 1 diabetes are looking at MSC therapy **(Huang et al., 2021).**

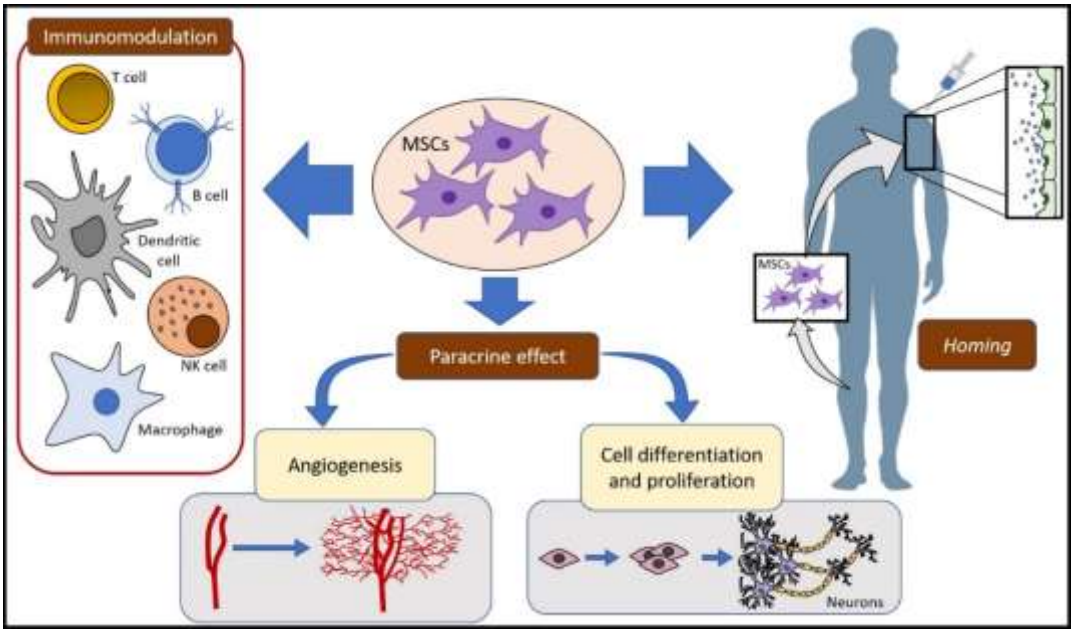


**Fig. 5 mechanism of action of MSCs**

Several in vivo and in vitro investigations demonstrated that MSCs could interact with T cells through a variety of adhesion markers, including CAM, ICAM-1, ALCAM, and LFA3, in addition to several integrin molecules, and might hinder the growth and functionality of T cells(**Le Blanc**, **2003 and Ramirez-Fernandez, 2021).** Furthermore, MSCs do not express MHC II and other co-stimulatory molecules including as CD80, CD86, CD40 and CD40L that elect T cell angry **(Götherström et al., 2004 and Dabrowska et al., 2021).** Additionally, MSCs supress T cells in G0/G1 phase that reflected by the stoppage of T lymphocytes proliferation (**Kim et al.**, **2007**)**.**

Regarding to inhibitory effect of MSCs on T lymphocytes **Selmani et al.** (**2008**) demonstrated that MSCs increase expression of CD4+CD25 (T regulatory lymphocyte) which in turn reduce the inflammatory process by suppressing CD8 T lymphocyte, Natural killer cells and dentritic cells.

Also, (**Sotiropoulou et al.**, **2006**) who discovered that MSCs secreted hepatocyte growth factor (HGF) to inhibit T cells and (**Beyth et al.**, **2005**) who reported that MSCs inhibit T cells proliferation through the secretion of IL10. Altogether the immunosupressive effect of MSCs on T cell could be referred to secretory activity of MSCs for endolamine (IDO) (**Frumento et al.**, **2002**), nitric oxide (NO) (**Sato et al.**, **2007**), HLAG (**La Rocca et al.**, **2009**), heme oxygenase 1 (**Chabannes et al.**, **2007**) and stromal cell-derived factor (SDF-1) (**Le Blanc et al.**, **2004**).

Conversely, the immune-suppressive function of MSCs may be explained by their suppression of denteritic cells. MSCs may prevent DC maturation, differentiation, and function (**Zhang et al.**, **2004**) through cell to cell interaction (**Zhang et al.**, **2004**), secretion of soluble factors (**Chen et al.**, **2007**), suppresing DC differentiation markers as CD80, CD86, CD40 and maturation marker CD83 (**Zhang et al.**, **2004**), decreasing secretory activity of DC for IL2, IL12, TNFα and increase secretion of IL10 (**Jiang et al.**, **2005**)**,** Also, MSCs could return mature DC to immature one (**Jiang et al.**, **2005**).

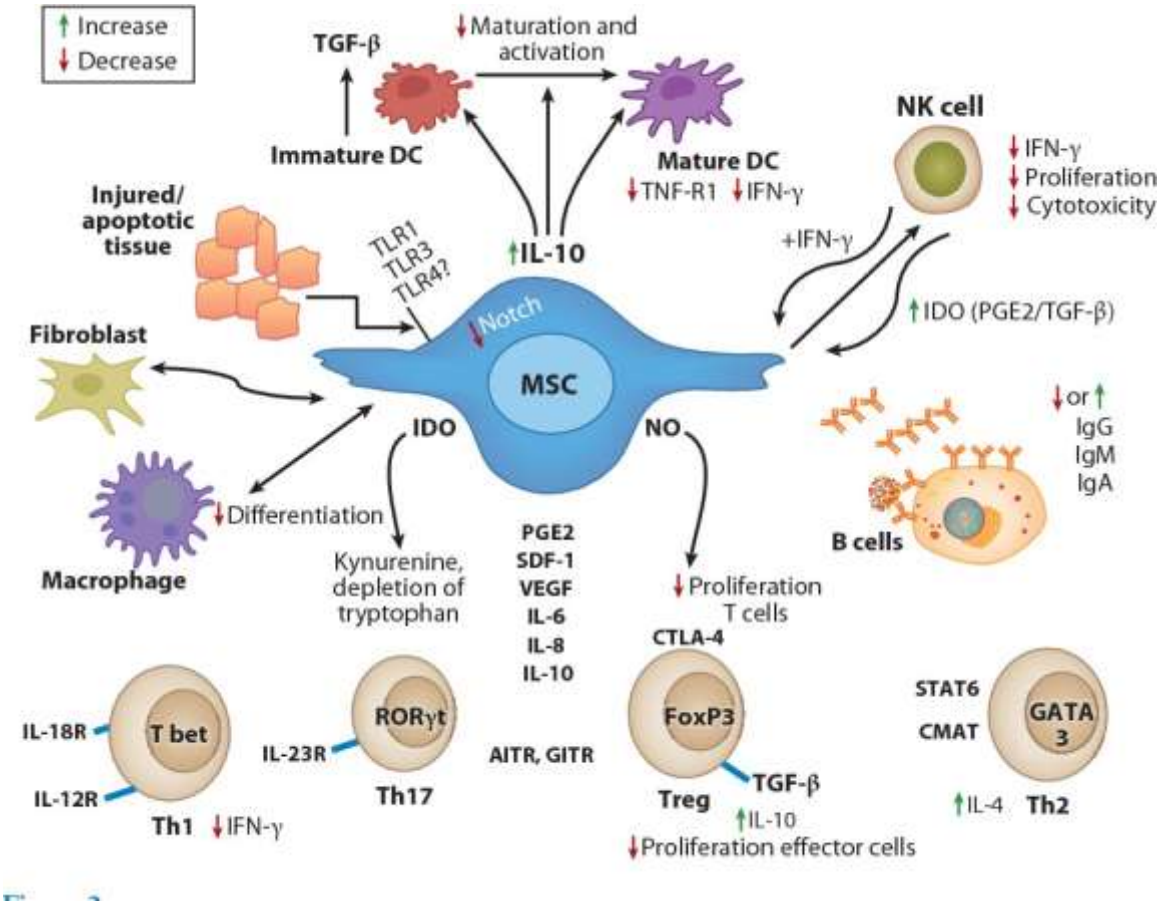


**Fig.6 Immunomodulatory activity of MSCs**

Similarly, MSCs cooperate with B lymphocyte to suppress B cells; proliferation, activation, immunoglobin secretion (**Deng et al., 2005**) and prevent B cell chemokine's receptors as CXCR4, CXCR5 and CCR7 expression (**Corcione et al., 2006**) through secretion of many soluble factors (**Hashemian et al., 2015**). On the same way, MSCs suppressed natural killer cells in a dose dependent manner (**Krampera et al., 2006).** Also, (**Rasmusson et al., 2003**) reported that MSCs could not be recognized by NK cells.

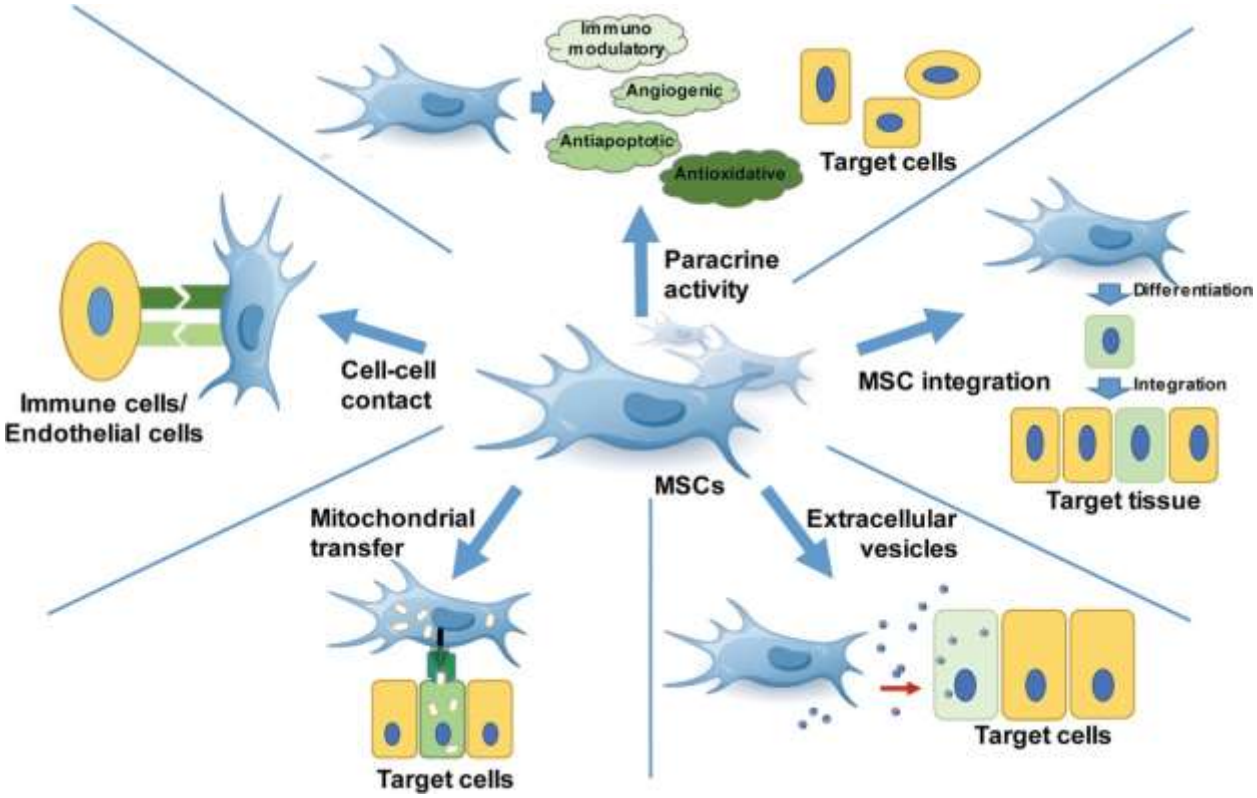


**Fig.7 Paracrine mechanism of MSCs**

**Differentiation into specialized tissue cells:**

(**Patel et al.**, **2013**) demonstrated that MSCs had the ability to differentiate and regenerate many types of cells as vasculature, tendon, bone, liver, kidney and nerve. Since many transplanted cells become apoptotic during the initial phase of the disease or migrate to the liver and lung, it is unknown exactly how much of the cells needed to be delivered to the wounded tissue in order to maintain and potentiate the various regenerative pathways.

Moreover, (**Kodama et al.**, **2009**) showed that the neogensis in the pancreatic beta islet was detected 2 to 3 weeks after infusion with the infused ESCs localized close to the neogenic pancreatic cells that endogenously expressed Ngn3 the revious mentioned evidence supported that stimulation of the internal repair mechanism.

Furthermore, many other reports suggested that MSCs in *vivo* differentiate into insulin secreting cells while infused undifferentiated into diabetic rodents models with bringing back hyperglycemia and regulating insulin secretion. It was shown that the undifferentiated MSCs may settle into the damaged pancreatic tissue and undergo transdifferentiation to become specialised cells that produce insulin **(Iskovich et al., 2012**).

**Transplantation of Undifferentiated mesenchymal Stem cell**

Infusion of undifferentiated MSCs based on Based on the MSCs' ability to migrate in response to certain chemokines released by injured tissue and interacting with particular receptors on their surface, including CCR1, CCR4, CCR7, CCR9, CCR10, CXCR1, CXCR3, CXCR4, CXCR5(**Granero-Molto et al.**, **2008**)**.** In total, the migratory activity of MSCs was effectively seen in radiation-induced acute renal failure, myocardial infraction, multi-organ failure, and brain ischemia(**Otto and Wright**, **2011**).

The exact type of stem cell tracking cytokine is still unknown, but new research has identified 39 chemokines with distinct roles in controlling stem cell trafficking (**Granero-Molto et al.**, **2008**)**.**

One of these chemokines was stromal derived factor (SDF-1), which was thoroughly studied for its role in MSC migration to damaged tissue as well as its expression on the surface of CNS and immune cells. It is in

charge of the stromal progenitor cells' migration into damaged tissue. It initially discussed the migration of MSCs in a rat model of myocardial infarction.(**Hiasa et al.**, **2004**).

Also, (**Meivar-Levy and Ferber**, **2010**) reported that SDF-1 increase MSCs homing to diabetic pancreas and enhance beta cell regeneration and insulin secretion in adiabatic patients.

Lipid lysophosphatidic acid LPA1 was another trafficking chemokine for MSCs that improve the migration of pulmonary resident MSCs in a LPA1 induced beta catenin activation (**Badri and Lama**, **2012**)**.**

Concerning the ability of MSCs to cross blood vessel and penetrate the damaged tissue MSCs likewise to leukocyte adhere to the endothelial of the blood vessel through several molecules as selectin-P, integrinβ1 and vascular cellular adhesion molecules1 (VCAM-1), then extravasted to infiltrate the damaged tissue. The migration process was enhanced with proapototic, inflammatory, angiogenic factors and growth factors such as; this process was controlled with many factors as interleukin (IL)-8, neurotrophin-3, TGF-□, IL-1□, TNF-□, platelet-derived growth factor, EGF, and SDF-1 (**Motaln et al.**, **2010**).

**Sohni and Verfaillie** (**2013**) reported that infused human MSCs could migrate to injured pancreatic tissue in the presence of many chemokine interacting with specific chemokines receptors on the surface of MSCs and persist in the damaged tissue for several weeks. Interestingly, (**Ezquer et al.**, **2012**) found that MSCs migrate and home to lymphatic system including pancreatic lymph node in diabetic rat model that suggested that the homed cells modulate and targeted immune system.

**Monitoring of diabetes mellitus:**

There are two types of diabetes monitoring techniques: indirect and direct. Assessing the amount of water consumed, detecting and measuring urine glucose, ketone bodies, and measuring glycosylated protein concentrations are some indirect methods of monitoring diabetes in dogs and cats. Though the direct ways include serial blood glucose measurements which are commonly referred as BG “curve” or continuous blood glucose monitoring through a subcutaneous probe **(Cook and dip, 2012).** Furthermore they stated that the majority of veterinarians favour routinely taking blood glucose directly over indirect ways because the indirect methods may fail to identify periods of hypoglycemia. However, logistical limitations on direct approaches may necessitate the use of indirect evaluations.

Since animals only drink water when they are thirsty not because it tastes good or is socially acceptable, hence fluid consumption inadvertently reflects BG status. **(Cook and dip 2012).**

Another indirect method of determining blood glucose status is urine glucose recognition, which also detects ketonuria **(Nelson, 2010).**

Serum fructosamine levels in dogs and cats offer a quantitative indirect measure of the regulation of diabetes **(Thoresen and Bredal, 1996 and Loste and Marka, 2001).**

Dogs and cats' glycosylated hemoglobin concentrations can also be measured, and the results offer important details about glycemic control over the preceding six weeks **(Elliott et al., 1997 and Loste and Mark, 1999).**

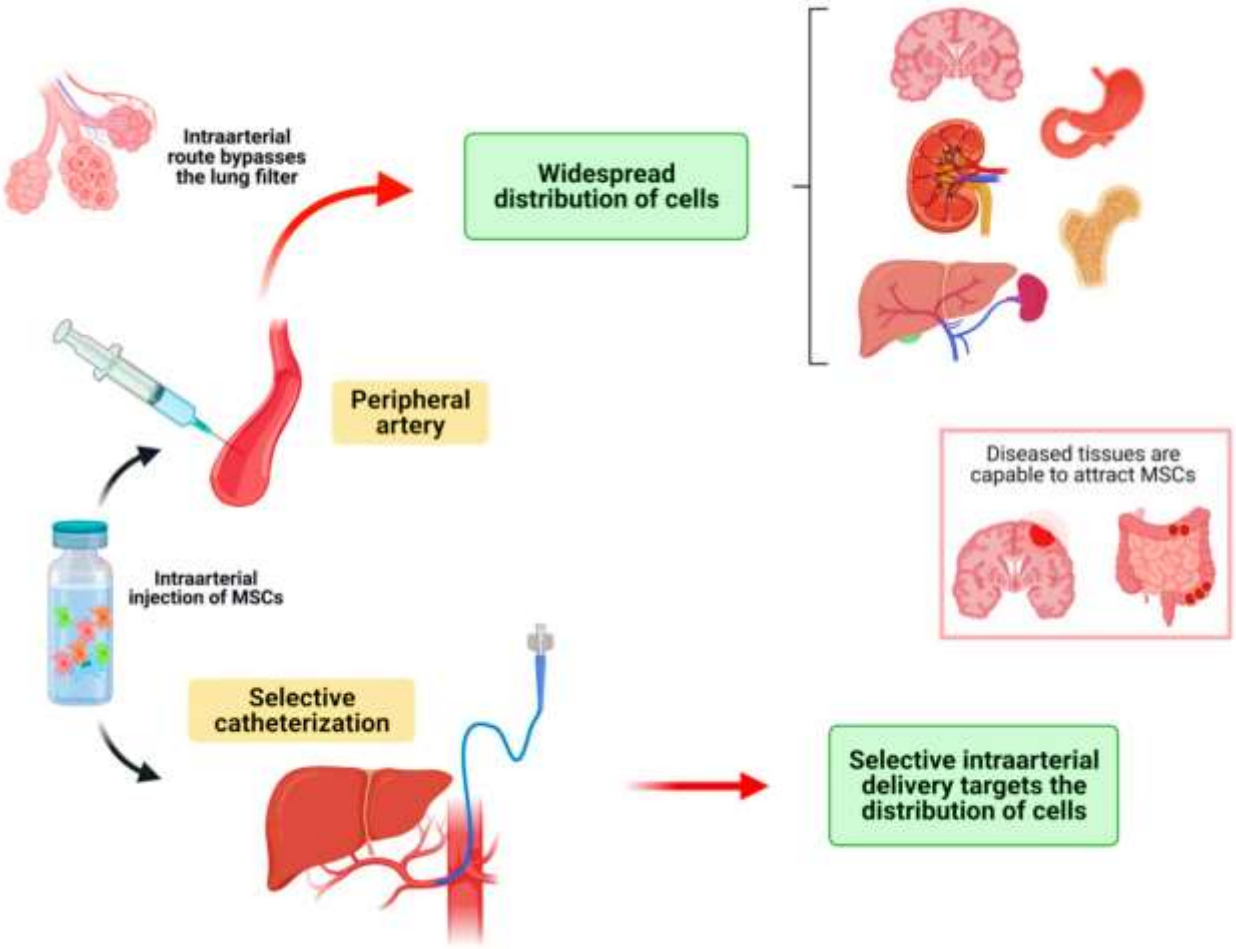


**Fig.8 different routes of MSCs administration**

**Induction of diabetes mellitus:**

Numerous animal models have been created over the years to study diabetes mellitus or evaluate medications that treat the disease. These models involve genetic engineering in multiple animal species, surgical techniques (pancreatectomy), and chemical methods (alloxan monohydrate, streptozotocin) to generate diabetes mellitus **(Srinivasan and Ramarao, 2007, Thatte, 2009 and Etuk, 2010).**

**Etuk (2010)** reported that chemical induction of diabetes mellitus seems to be the most frequently used method. It is capable of inducing both type I and type II DM with the correct dosage selection. The surgical and genetic methods require high technical skills, may be due to a high percentage of animal deaths, and consequently are rarely used.

Alloxan (ALX) is the most well-known drug for the induction of diabetes. Due to ALX is the most reliable, simple, and powerful reproducible method for diabetes mellitus induction, especially type 1, in experimental animals (**Viana et al., 2004).**

ALX emoly their diabetogenic effect when administered either intravenously, subcutaneously or intra-peritoneally **(Federiuk et al., 2004 and Lenzen, 2008).**

**Chemical structure of alloxan and mechanism of action:**

ALX (2, 4, 5, 6- tetraoxypyrimidine; 2, 4, 5, 6- pyrimidinetetrone) is a urea derivatives which produce selective necrosis of the beta cells of pancreatic islets. Additionally, it has been widely used to induce experimental diabetes in animals such as rabbits, mice, rats and dogs with different scores of disease severity by using different doses of alloxan **(Etuk, 2010 and Iranloye et al., 2011).**

This weak, hydrophilic product is about 1.5 minutes (at 37 °C) half-life. With a decrease in temperature, half-life decreases **(Lenzen, 2008).**

***Mechanism of action of alloxan:**

ALX causes diabetes by destructing the insulin-secreting cells of the pancreas leading to hyperglycemia**.** This seems to be due to two pathophysiologic pathways: (1) It can selectively prevent the secretion of glucose induced insulin by blocking glucokinase (2) it can produce reactive oxygen species (ROS) through cyclic redox reactions and dialuric acid **(Szudelski, 2001 and Lenzen, 2008).**

Alloxan's harmful effects on pancreatic beta cells include the oxidation of critical sulphydryl (SH) groups, glucokinase enzyme inhibition, free radical production, and disruptions in intracellular calcium homeostasis **(Dhanesha et al., 2012).**

ALX is predominantly accumulates in beta cells by the glucose transporter 2 (GLUT2) for making its toxicity to insulin-producing pancreatic beta cells. By the presence of intracellular thiols, ALX generates ROS which induce toxicity by its the product of its reduction and redox reaction, dialuric acid which establish a redox cycle with the formation of superoxide radicals. These radicals undergo dismutate to produce hydrogen peroxide. At the same time, with the action of ROS, there is a there is a massive increase in cytosolic calcium concentration that causes rapid destruction of pancreatic beta cells **(Marrif et al., 1995, Jorns et al., 1997 and Cheekati et al., 2017).**

This mechanism is because of the selective uptake of ALX through the GLUT2 transporter because of the structural resemblance to glucose **(Lenzen, 2008 and Viswanathaswamy et al., 2011).**

**<u>Phases of alloxan:</u>**

ALX induces a multiphasic blood glucose response after injection into an experimental animal, which is accompanied by corresponding inverse changes in the plasma insulin concentration followed by sequential ultrastructural beta cell changes ultimately leading to necrotic cell death. The first phase that comes into view within the first minutes after ALX injection is a transient hypoglycemic phase that lasts maximally for 30 minutes **(Wrenshall et al., 1950 and Lenzen, 2008).**

This first hypoglycemic phase has been noted to be the result of a transient stimulation of insulin secretion due to a temporary increase in ATP level resulting from the temporary effects of ALX inhibition of glucokinase that was confirmed by an increase of the plasma insulin concentration **(Kliber and Schindler, 1996 and Macdonald Ighodaro et al., 2017).**

The second phase begins shortly after an hour post administration showing a spike in the blood glucose level. There may be a decrease in plasma insulin. It is the first hyperglycemic phase which due to the first contact with the toxins by the pancreatic β cells lasts for a period of 2–4 hours. **(Mashi et al., 2019 (a) and Mashi et al., 2019(b)).**

Insulin secretion inhibition from the pancreatic beta cells activated by induction. The reason for their second phase diabetogenicity is their beta cell toxicity and ROS attack **(Kliber and Schindler, 1996).**

Hypoglycemia is the third phase, occurs 4-8 hours following injection of ALX ,that lasts for several hours. The flood insulin circulation results in extreme transitional hypoglycemia as a result of the ALX-induced secretion of granules and cell membrane rupture, ALX has also been linked to a hypoglycemic phase, which is accompanied by a significant influx of free Ca2+ into the cytosol of pancreatic islet beta cells, which in turn stimulates the secretion of insulin.**(Park et al., 1995 and Mashi et al., 2019 (a)).**

Full destruction of beta cells and loss of cell integrity occurs within 24-48 hours in the fourth stage of the diabetic process, which characterized by persistent hyperglycemia (**Jorns et al., 1997, Peschke et al., 2000 and Lenzen, 2008).**

The dose of ALX that required for inducing diabetes depends on the animal species, route of administration and nutritional status **(Sakata et al., 2012).**

**Num-Adom et al. (2022)** that DM was effectively induced by administering 100 mg/kg body weight of ALX via the saphenous vein.

**Mosallanejad et al. (2013)** reported that a single intravenous injection of ALX at a dose of 60 mg/kg body weight dissolved in normal saline was properly used for induction of DM.

**Abdullaziz et al. (2022)** reported that they using a single intravenous injection of 60 mg/kg body weight of ALX dissolved in 5 ml of saline (5%) to induce diabetes in dogs.

**Watanabe et al. (2004)** stated that they were inducing diabetic DM with a single intravenous injection of alloxan monohydrate diluted in physiological saline at a dosage rate of 50 mg/kg body weight.

In order to induce diabetic mellitus, 100 mg/kg body weight of ALX was injected into the saphenous vein after it had been reconstituted in cold normal saline to a concentration of 200 mg/ml **(Aluwong et al., 2016 and Esievo et al., 2021).**

**Kim et al. (2006)** demonstrated that an intravenous dose of 80–100 mg/kg body weight of ALX was administered immediately following the setup for DM induction. The ALX solution was prepared by dissolving alloxan monohydrates in normal saline at a concentration of 100 mg/ml.

**Sheweita et al. (2002)** stated that a single intravenous dose of 60 mg/kg body weight of ALX dissolved in normal saline was given to induce diabetes.

**Side effects of alloxan:**

Interestingly, certain liver lesions brought on by the toxic effects of STZ or ALX during the acute and sub-acute phases of treatment are also seen during the chronic stages of inducing diabetes. This implies that these lesions could be the consequence of either of these chemicals acting alone or of chronic hyperglycemia acting in concert with these other factors **(Remedio et al., 2011).**

**Lucchesi et al. (2013)** showed that IDDM altered the oxidative balance in the liver of alloxan-induced diabetic model over the longstanding, which was characterized by a significant increase in ROS in liver tissue and markedly reduced defense antioxidants.

**Lucchesi et al. (2015)** stated that the changes in blood liver enzymes (AST and ALT) and the morphological and ultrastructural lesions found in the livers of animals are closely correlated to DM-induced chronic stress in liver cells. Lesions were more severe in the longer experimental follow-up periods, especially in diabetic animals after 26 weeks of uncontrolled hyperglycemia.

During the first two weeks following the introduction of diabetes, systemic toxic effects of ALX and STZ are frequently detected. ALX shows a particularly narrow margin of safety between the diabetogenic and lethal dose, and deaths commonly occur as a result of diabetic ketoacidosis and/or kidney or liver failure. These facts highlight the importance of performing experimental observations of the liver after the acute or subacute phases of ALX **(Lucchesi et al., 2015).**

Several studies have revealed that ROS generated by ALX administration being the most common etiology for the destruction of vital organs of the body. Liver is one of the organs damaged by ROS **(Atawodi, 2011)** It was evident by increase in hepatic marker enzymes i.e. ALT, AST and ALP to the abnormal levels. But, these free radicals are also involved in the other tissue damage (liver and kidney etc.) which occurs in the progression of DM **(Mohamed et al., 2016).**

**Conclusion:** diabetes of the most devastating metabolic syndrome that had major health complications. Insulin and/or oral hypoglycemics fail to achieve tight glycemic control. Thus, replacing or regenerating the injured pancreas is the most convenient therapeutic approach. However, replacing the damage beta islet has several restrictions the most important of them are lack of the cadaveric donors and the body immune system transplant rejection. MSCs representing a promising therapeutic and regenerative tool for this syndrome.

**Conflict of interest:** the authors declare that there is no competing interest.

**Funding:** the current work did not receive any type of funding.

**Author contribution:** all the authors contributed equally.

## References:

Abdullah, N.; Attia, J.; Oldmeadow, C.; Scott, R. J.; and Holliday, E. G. (2014): The architecture of risk for type 2 diabetes: understanding Asia in the context of global findings. International journal of endocrinology, 2014, 1-21.

Abdullaziz, I. A.; Ismael, M. M.; Metwally, A. M.; El-Sayed, M. S.; Elblehi, S.S.; and El-Saman, A. E. (2022): New Insights on Alloxan Induced Canine Diabetes Mellitus in Relation to Updated Therapeutic Management Protocols. Alexandria Journal for Veterinary Sciences, 73(1).

Aluwong, T.; Ayo, J. O.; Kpukple, A.; and Oladipo, O. O. (2016): Amelioration of hyperglycaemia, oxidative stress and dyslipidaemia in alloxan-induced diabetic wistar rats treated with probiotic and vitamin C. Nutrients, 8(5), 151.

American Diabetes Association, (ADA). (2014): Diagnosis and classification of diabetes mellitus. Diabetes care, 37(Supplement_1), 81-90.

American Diabetes Association, (ADA). (2018): 2. Classification and diagnosis of diabetes: standards of medical care in diabetes. Diabetes care, 41(Supplement_1), 13-27.

American Diabetes Association: Standards of Care for Diabetes. (2013): Brief summary of screening and diagnosis of type 2 diabetes and its complications. Diabetes Care, 36, 11-61.

Arora, S.; Srinivasan, A.; Leung, C. M., and Toh, Y. C. (2020): Bio-mimicking shear stress environments for enhancing mesenchymal stem cell differentiation. Current Stem Cell Research & Therapy, 15(5), 414-427.

Atawodi, S. E. (2011): Evaluation of the Hypoglycemic, Hypolipidemic and Antioxidant Effects of Methanolic Extract of" Ata-Ofa" Polyherbal Tea (APolyherbal) in Alloxan-Induced Diabetic Rats. Drug Invention Today, 3(11).

Atkinson, M. A.; Eisenbarth, G. S.; and Michels, A. W. (2014): Type 1 diabetes. The Lancet, 383(9911), 69-82.

Babon, J. A. B.; DeNicola, M. E.; Blodgett, D. M.; Crèvecoeur, I.; Buttrick, T. S.; Maehr, R.; and Kent, S. C. (2016): Analysis of self-antigen specificity of islet-infiltrating T cells from human donors with type 1 diabetes. Nature medicine, 22(12), 1482-1487.

Badri, L.; and Lama, V.N. (2012): Lysophosphatidic acid induces migration of human lung-resident mesenchymal stem cells through the β-catenin pathway. Stem Cells 30, 2010–2019.

Baksh, D.; Yao, R.; and Tuan, R. S. (2007): Comparison of proliferative and multilineage differentiation potential of human mesenchymal stem cells derived from umbilical cord and bone marrow. Stem cells, 25(6), 1384-1392.

Banday, M. Z.; Sameer, A. S.; and Nissar, S. (2020): Pathophysiology of diabetes: An overview. Avicenna journal of medicine, 10(04), 174-188.

Bastidas-Ponce, A.; Scheibner, K.; Lickert, H.; and Bakhti, M. (2017): Cellular and molecular mechanisms coordinating pancreas development. Development, 144(16), 2873-2888.

Bateman, M. E.; Strong, A. L.; Gimble, J. M.; and Bunnell, B. A. (2018): Concise review: using fat to fight disease: a systematic review of nonhomologous adipose-derived stromal/stem cell therapies. Stem Cells, 36(9), 1311-1328.

Beam, and Correa. (1999): A retrospective-cohort study on the development of cataracts in dogs with diabetes mellitus: 200 cases. Veterinary Ophthalmology, 2(3), 169-172.

Behrend, E.; Holford, A.; Lathan, P.; Rucinsky, R.; and Schulman, R. (2018): diabetes management guidelines for dogs and cats. Journal of the American Animal Hospital Association, 54(1), 1-21.

Besser, R. E.; Shepherd, M. H.; McDonald, T. J.; Shields, B. M.; Knight, B. A.; Ellard, S.; and Hattersley, A. T. (2011): Urinary C-peptide creatinine ratio is a practical outpatient tool for identifying hepatocyte nuclear factor 1-α/hepatocyte nuclear factor 4-α maturity-onset diabetes of the young from long-duration type 1 diabetes. Diabetes care, 34(2), 286-291.

Beyth, S.; Borovsky, Z.; Mevorach, D.; Liebergall, M.; Gazit, Z.; Aslan, H.; Galun, E.; and Rachmilewitz, J. (2005): Human mesenchymal stem cells alter antigen-presenting cell maturation and induce T-cell unresponsiveness. Blood 105, 2214–2219.

Bonner-Weir, S.; and Sharma, A. (2006): Are there pancreatic progenitor cells from which new islets form after birth? Nat. Clin. Pract. Endocrinol. Metab. 2, 240–241.

Bonner-Weir, S.; Taneja, M.; Weir, G.C.; Tatarkiewicz, K.; Song, K.H.; Sharma, A.; and O'Neil, J.J. (2000): In vitro cultivation of human islets from expanded ductal tissue. Proc. Natl. Acad. Sci. U. S. A. 97, 7999–8004.

Briens, J. M.; Subramaniam, M.; Kilgour, A.; Loewen, M. E.; Desai, K. M.; Adolphe, J. L.; and Weber, L. P. (2021): Glycemic, insulinemic and methylglyoxal postprandial responses to starches alone or in whole diets in dogs versus cats: Relating the concept of glycemic index to metabolic responses and gene expression. Comparative Biochemistry and Physiology Part A: Molecular & Integrative Physiology, 257, 110973.

Bruyette, D. (2013): The Pancreas. The Merck Veterinary Manual. 8th ed. Merck Sharp & Dohme Corp., USA.**7**

Campbell, J. E.; and Newgard, C. B. (2021): Mechanisms controlling pancreatic islet cell function in insulin secretion. Nature reviews Molecular cell biology, 22(2), 142-158.

Cantero, F.; Leiva, M.; Gaztelu, L.; Cerrada, I.; Cardoso, R. V.; and Peña, T. (2022): Case Report: Urrets-Zavalia syndrome following cataract surgery in dogs: A case series. Open Veterinary Journal, 12(1), 138-147.

Caplan, A. I. (2017): Mesenchymal stem cells: time to change the name!. Stem cells translational medicine, 6(6), 1445-1451.

Catchpole, B.; Adams, J. P.; Holder, A. L.; Short, A. D.; Ollier, W. E.; and Kennedy, L. J. (2013): Genetics of canine diabetes mellitus: are the diabetes susceptibility genes identified in humans involved in breed susceptibility to diabetes mellitus in dogs?. The veterinary journal, 195(2), 139-147.

Catchpole, B.; Ristic, J. M.; Fleeman, L. M.; and Davison, L. J. (2005): Canine diabetes mellitus: can old dogs teach us new tricks?. Diabetologia, 48, 1948-1956.

Cheekati, R. R.; Rao, A. S.; and Vijayaraghavan, R. (2017): A histological study of alloxan-induced diabetes on experimental male Wistar rats. National Journal of Physiology, Pharmacy and Pharmacology, 7(12), 1329-1334.

Chen, L.; Zhang, W.; Yue, H.; Han, Q., Chen, B.; Shi, M.; and Zhao, R. C. (2007): Effects of human mesenchymal stem cells on the differentiation of dendritic cells from CD34+ cells. Stem cells and development, 16(5), 719-732.

Chen, R.; Corona, E.; Sikora, M.; Dudley, J. T.; Morgan, A. A.; Moreno-Estrada, A.; and Butte, A. J. (2012): Type 2 diabetes risk alleles demonstrate extreme directional differentiation among human populations, compared to other diseases. PLoS genetics, 8(4), 1002621.

Ciobotaru, E. (2013): Spontaneous diabetes mellitus in animals. Diabetes Mellitus-Insights and Perspectives. Croatia: InTech, 96-271.

Clevers, H. (2016): Modeling development and disease with organoids. Cell, 165(7), 1586-1597.

Cnop, M.; Welsh, N.; Jonas, J. C.; Jorns, A.; Lenzen, S.; and Eizirik, D. L. (2005): Mechanisms of pancreatic β-cell death in type 1 and type 2 diabetes: many differences, few similarities. Diabetes, 54(suppl_2), 97-107.

Cohen, T. A.; Nelson, R. W.; Kass, P. H.; Christopher, M. M.; and Feldman, E. C. (2009): Evaluation of six portable blood glucose meters for measuring blood glucose concentration in dogs. Journal of the American Veterinary Medical Association, 235(3), 276-280.

Cook, A. K.; and Dip. ACVIM-SAIM, Dip. ECVIM-CA. (2012): Monitoring methods for dogs and cats with diabetes mellitus. Journal of Diabetes Science and Technology, 6(3), 491-495.

Corcione, A.; Benvenuto, F.; Ferretti, E.; Giunti, D.; Cappiello, V.; Cazzanti, F.; and Uccelli, A. (2006): Human mesenchymal stem cells modulate B-cell functions. Blood, 107(1), 367-372.

d'Annunzio, G.; Russo, C.; Tallone, R.; and Lorini, R. (2011): Autoimmune disorders associated to type 1 diabetes mellitus in children and adolescents. In Autoimmune Disorders-Current Concepts and Advances from Bedside to Mechanistic Insights. IntechOpen.

Da Silva Xavier, G. (2018): The cells of the islets of Langerhans. Journal of clinical medicine, 7(3), 54.

Dabrowska, S.; Andrzejewska, A.; Janowski, M.; and Lukomska, B. (2021): Immunomodulatory and regenerative effects of mesenchymal stem cells and extracellular vesicles: therapeutic outlook for inflammatory and degenerative diseases. Frontiers in immunology, 11, 591065.

Davison, L. J. (2012): Canine diabetes mellitus. BSAVA Manual of Canine and Feline Endocrinology, 116-132.

Davison, L.; Walding, B.; Herrtage, M. E.; and Catchpole, B. (2008): Anti-insulin antibodies in diabetic dogs before and after treatment with different insulin preparations. Journal of veterinary internal medicine, 22(6), 1317-1325.

Del Baldo, F.; Magna, L.; Dondi, F.; Maramieri, P.; Catrina, O. M.; Corradini, S.; and Fracassi, F. (2020): Comparison of serum fructosamine and glycated hemoglobin values for assessment of glycemic control in dogs with diabetes mellitus. American journal of veterinary research, 81(3), 233-242.

Demeester, S.; Balke, E. M.; Van der Auwera, B. J.; Gillard, P.; Hilbrands, R., Lee, D.; and Keymeulen, B. (2016): HLA-A* 24 carrier status and autoantibody surges posttransplantation associate with poor functional outcome in recipients of an islet allograft. Diabetes Care, 39(6), 1060-1064.

Deng, W.; Han, Q.; Liao, L.; You, S.; Deng, H.; and Zhao, R.C.H. (2005): Effects of Allogeneic Bone Marrow-Derived Mesenchymal Stem Cells on T and B Lymphocytes from BXSB Mice. DNA Cell Biol. 24, 458–463.

Dhanesha, N.; Joharapurkar, A.; Shah, G.; Dhote, V.; Kshirsagar, S.; Bahekar, R.; and Jain, M. (2012): Exendin-4 ameliorates diabetic symptoms through activation of glucokinase. Journal of diabetes, 4(4), 369-377.

DiMeglio, L. A.; Evans-Molina, C.; and Oram, R. A. (2018): Type 1 diabetes. The Lancet, 391(10138), 2449-2462.

Dimos, J. T.; Rodolfa, K. T.; Niakan, K. K.; Weisenthal, L. M.; Mitsumoto, H.; Chung, W.; and Eggan, K. (2008): Induced pluripotent stem cells generated from patients with ALS can be differentiated into motor neurons. science, 321(5893), 1218-1221.

Durocher, L. L.; Hinchcliff, K. W.; DiBartola, S. P.; and Johnson, S. E. (2008): Acid-base and hormonal abnormalities in dogs with naturally occurring diabetes mellitus. Journal of the American Veterinary Medical Association, 232(9), 1310-1320.

Eizirik, D.L.; and Mandrup-Poulsen, T. (2001): A choice of death - The signal-transduction of immune-mediated beta-cell apoptosis. Diabetologia 44, 2115–2133.

Elliott, D.; Nelson, R. W.; Feldman, E. C.; and Neal, L. A. (1997): Glycosylated hemoglobin concentrations in the blood of healthy dogs and dogs with naturally developing diabetes mellitus, pancreatic beta-cell neoplasia, hyperadrenocorticism, and anemia. Journal of the American Veterinary Medical Association, 211(6), 723-727.

Ende, N.; Chen, R.; and Reddi, A.S. (2004): Transplantation of human umbilical cord blood cells improves glycemia and glomerular hypertrophy in type 2 diabetic mice. Biochem. Biophys. Res. Commun. 321, 168–171.

Esievo, K. A. N.; Num-Adom, S. M.; Adamu, S.; Ogbuagu, N. E.; Aluwong, T.; and Umar, I. A. (2021): Elevated serum sialic acids, a potent biomarker of alloxan-induced type 1 diabetes in dogs by ethanolic extract of Anogeissus leiocarpus. Journal of Diabetes & Metabolic Disorders, 20, 179-186.

Ettinger, S. J.; and Feldman, E. C. (2010): Veterinary internal medicine. Edn, 7, 2086-2088.

Etuk, E. U. (2010): Animals models for studying diabetes mellitus. Agric Biol JN Am, 1(2), 130-134.

Ezquer, F.; Bahamonde, J.; Huang, Y. L.; and Ezquer, M. (2017): Administration of multipotent mesenchymal stromal cells restores liver regeneration and improves liver function in obese mice with hepatic steatosis after partial hepatectomy. Stem cell research & therapy, 8, 1-18.

Ezquer, F.; Ezquer, M.; Contador, D.; Ricca, M.; Simon, V.; and Conget, P. (2012): The antidiabetic effect of mesenchymal stem cells is unrelated to their transdifferentiation potential but to their capability to restore Th1/Th2 balance and to modify the pancreatic microenvironment. Stem cells, 30(8), 1664-1674.

Fall, T.; Hamlin, H. H.; Hedhammar, Å.; Kämpe, O.; and Egenvall, A. (2007): Diabetes mellitus in a population of 180,000 insured dogs: incidence, survival, and breed distribution. Journal of veterinary internal medicine, 21(6), 1209-1216.

Fall, T.; Johansson Kreuger, S.; Juberget, Å.; Bergström, A.; and Hedhammar, Å. (2008): Gestational diabetes mellitus in 13 dogs. Journal of veterinary internal medicine, 22(6), 1296-1300.

Farkhad, N. K.; Mahmoudi, A.; and Mahdipour, E. (2021): How similar are human mesenchymal stem cells derived from different origins? A review of comparative studies. Current stem cell research & therapy, 16(8), 980-993.

Federiuk, I. F.; Casey, H. M.; Quinn, M. J.; Wood, M. D.; and Ward, K. W. (2004): Induction of type-1 diabetes mellitus in laboratory rats by use of alloxan: route of administration, pitfalls, and insulin treatment. Comparative medicine, 54(3), 252-257.

Feldman, E. C.; and Nelson, R. W. (1996): Feline reproduction. In canine and feline endocrinology and reproduction. WB Saunders, Philadelphia, 996, 74-768.

Felfly, H.; and Haddad, G. G. (2014): Hematopoietic stem cells: potential new applications for translational medicine. Journal of stem cells, 9(3), 163.

Fleeman, L. M.; and Rand, J. S. (2001): Management of canine diabetes. Veterinary Clinics of North America: Small Animal Practice, 31(5), 855-880.

Forcada, Y.; Holder, A.; Church, D. B.; and Catchpole, B. (2014): A polymorphism in the melanocortin 4 receptor gene (MC4R: c. 92C> T) is associated with diabetes mellitus in overweight domestic shorthaired cats. Journal of Veterinary Internal Medicine, 28(2), 458-464.

Frumento, G.; Rotondo, R.; Tonetti, M.; Damonte, G.; Benatti, U.; and Ferrara, G.B. (2002): Tryptophan-derived catabolites are responsible for inhibition of T and natural killer cell proliferation induced by indoleamine 2,3-dioxygenase. J. Exp. Med. 196, 459–468.

Galicia-Garcia, U.; Benito-Vicente, A.; Jebari, S., Larrea-Sebal, A.; Siddiqi, H.; Uribe, K. B.; and Martín, C. (2020): Pathophysiology of type 2 diabetes mellitus. International journal of molecular sciences, 21(17), 6275.

Gilor, C. S. J. M.; Niessen, S. J. M.; Furrow, E.; and DiBartola, S. P. (2016): What's in a name? Classification of diabetes mellitus in veterinary medicine and why it matters. Journal of veterinary internal medicine, 30(4), 927-940.

Godfrey, K. J.; Mathew, B.; Bulman, J. C.; Shah, O.; Clement, S.; and Gallicano, G. I. (2012): Stem cell-based treatments for Type 1 diabetes mellitus: bone marrow, embryonic, hepatic, pancreatic and induced pluripotent stem cells. Diabetic Medicine, 29(1), 14-23.Kim, G. B., Seo, M. S., Park, W. T., & Lee, G. W. (2020). Bone marrow aspirate concentrate: its uses in osteoarthritis. International journal of molecular sciences, 21(9), 3224.

Götherström, C.; Ringdén, O.; Tammik, C.; Zetterberg, E.; Westgren, M.; and Le Blanc, K. (2004): Immunologic properties of human fetal mesenchymal stem cells. Am. J. Obstet. Gynecol. 190, 239–245.

Granero-Molto, F.; Weis, J.A.; Longobardi, L.; and Spagnoli, A. (2008): Role of mesenchymal stem cells in regenerative medicine: Application to bone and cartilage repair. Expert Opin. Biol. Ther. 8, 255–268.

Haberer, B.; and Reusch, C. E. (1998): Glycated haemoglobin in various pathological conditions: investigations based on a new, fully automated method. Journal of small animal practice, 39(11), 510-517.

Hall, J. E. (2011): Guyton y hall. Elsevier Health Sciences Spain.

Hashemian, S.J.; Kouhnavard, M.; and Nasli-Esfahani, E. (2015): Mesenchymal Stem Cells: Rising Concerns over Their Application in Treatment of Type One Diabetes Mellitus. J. Diabetes Res. 2015, 1–19.

Hashim, Z.; and Zarina, S. (2011): Advanced glycation end products in diabetic and non-diabetic human subjects suffering from cataract. Age, 33, 377-384.

Heeley, A. M.; O'Neill, D. G.; Davison, L. J.; Church, D. B.; Corless, E. K.; and Brodbelt, D. C. (2020): Diabetes mellitus in dogs attending UK primary-care practices: frequency, risk factors and survival. Canine Medicine and Genetics, 7, 1-19.

Herring, I. P.; Panciera, D. L.; and Werre, S. R. (2014): Longitudinal prevalence of hypertension, proteinuria, and retinopathy in dogs with spontaneous diabetes mellitus. Journal of veterinary internal medicine, 28(2), 488-495.

Hess, R. S.; Saunders, H. M.; Van Winkle, T. J.; and Ward, C. R. (2000): Concurrent disorders in dogs with diabetes mellitus: 221 cases (1993–1998). Journal of the American Veterinary Medical Association, 217(8), 1166-1173.

Hiasa, K.I.; Ishibashi, M.; Ohtani, K.; Inoue, S.; Zhao, Q.; Kitamoto, S.; Sata, M.; Ichiki, T.; Takeshita, A.; and Egashira, K. (2004): Gene transfer of stromal cell-derived factor-1α enhances ischemic vasculogenesis and angiogenesis via vascular endothelial growth factor/endothelial nitric oxide synthase-related pathway: Next-generation chemokine therapy for therapeutic neovascularization. Circulation 109, 2454–2461.

Hieshima, K.; Sugiyama, S.; Yoshida, A.; Kurinami, N.; Suzuki, T.; Ijima, H.; and Jinnouchi, H. (2020): Elevation of the renal threshold for glucose is associated with insulin resistance and higher glycated hemoglobin levels. Journal of Diabetes Investigation, 11(3), 617-625.

Hoang, D. M.; Pham, P. T.; Bach, T. Q.; Ngo, A. T.; Nguyen, Q. T.; Phan, T. T.; and Nguyen, L. T. (2022): Stem cell-based therapy for human diseases. Signal transduction and targeted therapy, 7(1), 1-41.

Hoang, V. T.; Trinh, Q. M.; Phuong, D. T. M.; Bui, H. T. H.; Ngan, N. T. H.,; Anh, N. T. T.; and Hoang, D. M. (2021): Standardized xeno-and serum-free culture platform enables large-scale expansion of high-quality mesenchymal stem/stromal cells from perinatal and adult tissue sources. Cytotherapy, 23(1), 88-99.

Hoenig, M. (2014): Comparative aspects of human, canine, and feline obesity and factors predicting progression to diabetes. Veterinary Sciences, 1(2), 121-135.

Holt, R. I. (2004): Diagnosis, epidemiology and pathogenesis of diabetes mellitus: an update for psychiatrists. The British Journal of Psychiatry, 184(S47), 55-63.

Hu, J.; Li, C.; Wang, L.; Zhang, X.; Zhang, M.; Gao, H.; and Wang, Y. (2012): Long term effects of the implantation of autologous bone marrow mononuclear cells for type 2 diabetes mellitus. Endocrine journal, 59(11), 1031-1039.

Hu, J.; Yu, X.; Wang, Z.; Wang, F.; Wang, L.; Gao, H.; and Wang, Y. (2013): Long term effects of the implantation of Wharton's jelly-derived mesenchymal stem cells from the umbilical cord for newly-onset type 1 diabetes mellitus. Endocrine journal, 60(3), 347-357.

Hume, D. Z.; Drobatz, K. J.; and Hess, R. S. (2006): Outcome of dogs with diabetic ketoacidosis: 127 dogs (1993–2003). Journal of veterinary internal medicine, 20(3), 547-555.

Iqbal, S.; Alrashdi, A. M.; Jayyab, A. A.; and Reverté-Villarroya, S. (2023): The predictive ability of C peptide in distinguishing type1 diabetes from type 2 diabetes: A Systematic Review and Meta-Analysis. Endocrine Practice.

Iranloye, B. O.; Arikawe, A. P.; Rotimi, G.; and Sogbade, A. O. (2011): Anti-diabetic and anti-oxidant effects of Zingiber officinale on alloxan-induced and insulin-resistant diabetic male rats. Nigerian journal of physiological sciences, 26(1).

Iskovich, S.; Goldenberg-Cohen, N.; Stein, J.; Yaniv, I.; Fabian, I.; and Askenasy, N. (2012): Elutriated stem cells derived from the adult bone marrow differentiate into insulin-producing cells in vivo and reverse chemical diabetes. Stem Cells Dev. 21, 86–96.

Ismail, Z.B.; Hananeh, W.; Alshehabat, M.; Daradka, M.; and Ali, J. (2015): Short-term clinical and pathological alterations associated with a single intravenous injection of alloxan monohydrate in dogs. Human and Veterinary Medicine Bioflux, 7(2), 70-74.

Jiang, X.-X.; Zhang, Y.; Liu, B.; Zhang, S.-X.; Wu, Y.; Yu, X.-D.; and Mao, N. (2005): Human mesenchymal stem cells inhibit differentiation and function of monocyte-derived dendritic cells. Blood 105, 4120–4126.

Jones, A. G.; and Hattersley, A. T. (2013): The clinical utility of C-peptide measurement in the care of patients with diabetes. Diabetic medicine, 30(7), 803-817.

Jorns, A.; Munday, R.; Tiedge, M.; and Lenzen, S. (1997): Comparative toxicity of alloxan, N-alkylalloxans and ninhydrin to isolated pancreatic islets in vitro. Journal of endocrinology, 155(2), 283-294.

Kern, S.; Eichler, H.; Stoeve, J.; Klüter, H.; and Bieback, K. (2006): Comparative analysis of mesenchymal stem cells from bone marrow, umbilical cord blood, or adipose tissue. Stem cells, 24(5), 1294-1301.

Kim, G. B.; Seo, M. S.; Park, W. T.; and Lee, G. W. (2020): Bone marrow aspirate concentrate: its uses in osteoarthritis. International journal of molecular sciences, 21(9), 3224.

Kim, J. M.; Chung, J. Y.; Lee, S. Y.; Choi, E. W.; Kim, M. K.; Hwang, C. Y.; and Youn, H. Y. (2006): Hypoglycemic effects of vanadium on alloxan monohydrate induced diabetic dogs. Journal of Veterinary Science, 7(4), 391-395.

Kim, J.-A.; Hong, S.; Lee, B.; Hong, J.W.; Kwak, J.-Y.; Cho, S.; and Kim, C.-C. (2007): The inhibition of T-cells proliferation by mouse mesenchymal stem cells through the induction of p16INK4A-cyclin D1/cdk4 and p21waf1, p27kip1-cyclin E/cdk2 pathways. Cell. Immunol. 245, 16–23.

Kim, N. Y.; An, J.; Jeong, J. K.; Ji, S.; Hwang, S. H.; Lee, H. S.; and Kim, Y. (2019): Evaluation of a human glycated hemoglobin test in canine diabetes mellitus. Journal of Veterinary Diagnostic Investigation, 31(3), 408-414.

Kim, S. Y.; Sharma, A. J., and Callaghan, W. M. (2012): Gestational diabetes and childhood obesity: what is the link?. Current Opinion in Obstetrics and Gynecology, 24(6), 376-381.

Kliber, J.; and Schindler, I. (1996): Recrystallization/precipitation behaviour in microalloyed steels. Journal of materials processing technology, 60(1-4), 597-602.

Kodama, M.; Tsukamoto, K.; Yoshida, K.; Aoki, K.; Kanegasaki, S.; and Quinn, G. (2009): Embryonic stem cell transplantation correlates with endogenous neurogenin 3 expression and pancreas regeneration in streptozotocin-injured mice. J. Histochem. Cytochem. 57, 1149–1158.

Koren, D. (2022): Growth and development in type 1 diabetes. Current Opinion in Endocrinology & Diabetes and Obesity, 29(1), 57-64.

Krampera, M.; Cosmi, L.; Angeli, R.; Pasini, A.; Liotta, F.; Andreini, A.; and Annunziato, F. (2006): Role for interferon-γ in the immunomodulatory activity of human bone marrow mesenchymal stem cells. Stem cells, 24(2), 386-398.

Kumar, P.; Kumari, R. R.; Kumar, M.; Kumar, S.; and Chakrabarti, A. (2014): Current practices and research updates on diabetes mellitus in canine. Veterinary World, 7(11).

Kuzi, S.; Mazaki-Tovi, M.; Ahmad, W. A.; Ovadia, Y.; and Aroch, I. (2023): Clinical utility of serum fructosamine in long-term monitoring of diabetes mellitus in dogs. Veterinary Record, 192(2), no-no.

La Rocca, G.; Anzalone, R.; Corrao, S.; Magno, F.; Loria, T.; Lo Iacono, M.; and Farina, F. (2009): Isolation and characterization of Oct-4+/HLA-G+ mesenchymal stem cells from human umbilical cord matrix: differentiation potential and detection of new markers. Histochemistry and cell biology, 131, 267-282.

Larsen, H. L.; and Grapin-Botton, A. (2017, June): The molecular and morphogenetic basis of pancreas organogenesis. In Seminars in cell & developmental biology, Academic press 66, 51-68.

Le Blanc, K. (2003): Immunomodulatory effects of fetal and adult mesenchymal stem cells. Cytotherapy 5, 485–489.

Le Blanc, K.; Rasmusson, I.; Gotherstrom, C.; Seidel, C.; Sundberg, B.; Sundin, M.; Rosendahl, K., Tammik, C.; and Ringden, O. (2004): Mesenchymal Stem Cells Inhibit the Expression of CD25 (Interleukin-2 Receptor) and CD38 on Phytohaemagglutinin-Activated Lymphocytes. Scand. J. Immunol. 60, 307–315.

Lenzen, S. (2008): The mechanisms of alloxan-and streptozotocin-induced diabetes. Diabetologia, 51(2), 216-226.

Li, L.; Hui, H.; Jia, X.; Zhang, J.; Liu, Y.; Xu, Q.; and Zhu, D. (2016): Infusion with human bone marrow-derived mesenchymal stem cells improves β-cell function in patients and non-obese mice with severe diabetes. Scientific reports, 6(1), 37894.

Licinio-Paixao, J.; Polonsky, K. S.; Given, B. D.; Pugh, W.; Ostrega, D.; Frank, B. F.; and Rubenstein, A. H. (1986): Ingestion of a mixed meal does not affect the metabolic clearance rate of biosynthetic human C-peptide. The Journal of Clinical Endocrinology & Metabolism, 63(2), 401-403.

Lin, H. P.; Chan, T. M.; Fu, R. H.; Chuu, C. P.; Chiu, S. C.; Tseng, Y. H.; and Lin, S. Z. (2015): Applicability of adipose-derived stem cells in type 1 diabetes mellitus. Cell transplantation, 24(3), 521-532.

Liu, X.; Wang, Y.; Li, Y.; and Pei, X. (2013): Research status and prospect of stem cells in the treatment of diabetes mellitus. Science China Life Sciences, 56, 306-312.

Lo Iacono, M.; Anzalone, R.; La Rocca, G.; Baiamonte, E.; Maggio, A.; and Acuto, S. (2017): Wharton's jelly mesenchymal stromal cells as a feeder layer for the ex vivo expansion of hematopoietic stem and progenitor cells: a review. Stem Cell Reviews and Reports, 13(1), 35-49.

Losate, A,; and Marca, M. C. (1999): Study of the effect of total serum protein and albumin concentrations on canine fructosamine concentration. Canadian Journal of Veterinary Research, 63(2), 138.

Loste, A.; and Marca, M. C. (2001): Fructosamine and glycated hemoglobin in the assessment of glycaemic control in dogs. Veterinary Research, 32(1), 55-62.

Lowry, W. E.; Richter, L.; Yachechko, R.; Pyle, A. D.; Tchieu, J.; Sridharan, R.; and Plath, K. (2008): Generation of human induced pluripotent stem cells from dermal fibroblasts. Proceedings of the National Academy of Sciences, 105(8), 2883-2888.

Lucchesi, A. N.; Cassettari, L. L.; and Spadella, C. T. (2015): Alloxan-induced diabetes causes morphological and ultrastructural changes in rat liver that resemble the natural history of chronic fatty liver disease in humans. Journal of diabetes research, 2015.

Lucchesi, A. N.; Freitas, N. T. D.; Cassettari, L. L.; Marques, S. F. G.; and Spadella, C. T. (2013): Diabetes mellitus triggers oxidative stress in the liver of alloxan-treated rats: a mechanism for diabetic chronic liver disease. Acta Cirurgica Brasileira, 28, 502-508.

Lumelsky, N. (2001): Differentiation of Embryonic Stem Cells to Insulin-Secreting Structures Similar to Pancreatic Islets. Science (80-. ). 292, 1389–1394.

Macdonald Ighodaro, O.; Mohammed Adeosun, A.; and Adeboye Akinloye, O. (2017): Alloxan-induced diabetes, a common model for evaluating the glycemic-control potential of therapeutic compounds and plants extracts in experimental studies. Medicina, 53(6), 365-374.

Madsen, O. D. (2005): Stem cells and diabetes treatment. Apmis, 113(11-12), 858-875.

Mahadevan, V. (2019): Anatomy of the pancreas and spleen. Surgery (Oxford), 37(6), 297-301.

Mahaffey, E. A.; Buonanno, A. M.; and Cornelius, L. M. (1984): Glycosylated albumin and serum protein in diabetic dogs. American Journal of Veterinary Research, 45(10), 2126-2128.

Marrif, H. I.; Ali, B. H.; and Hassan, K. M. (1995): Some pharmacological studies on Artemisia herba-alba (Asso.) in rabbits and mice. Journal of ethnopharmacology, 49(1), 51-55.

Mashi, J. A.,; Atiku, M. K.; Shehu, D.; Idris, R. I.; Said, A. M.; Dangambo, M. A.; and Babandi, A. (2019 b): Comparative study of different solvents extract of Persea americana leaf on alloxan induced hyperglycemic rats. Asian J. Biol. Sci, 12, 67-72.

Mashi, J. A.; Atiku, M. K.; Bala, M.; Sa'id, A. M.; Idris, R. I.; Babandi, A.; and Babagana, K. (2019 a): Hypoglycaemic and Hypolipidemic Properties of Ethyl Acetate Fraction of P. americana Leaf in Alloxan-Induced Diabetic Rats. International Journal of Biochemistry, Biophysics & Molecular Biology, 3(3), 45.

McCall, M. D.; Toso, C.; Baetge, E. E.; and Shapiro, A. J. (2010): Are stem cells a cure for diabetes?. Clinical Science, 118(2), 87-97.Madsen, O. D. (2005). Stem cells and diabetes treatment. Apmis, 113(11-12), 858-875.

McCann, T. M.; Simpson, K. E.; Shaw, D. J.; Butt, J. A.; and Gunn-Moore, D. A. (2007): Feline diabetes mellitus in the UK: the prevalence within an insured cat 0population and a questionnaire-based putative risk factor analysis. Journal of Feline Medicine and Surgery, 9(4), 289-299.

Meivar-Levy, I.; and Ferber, S. (2010): Adult cell fate reprogramming: converting liver to pancreas. Methods Mol. Biol. 636, 251–283.

Mikhaiel, M.; Nasr, M.; Bakeir, N.; Beder, N.; Elshafey, B.; and Saleh, A. (2022): Prevalence, Clinical Picture, and Risk Factors Associated with Diabetes Mellitus in Dogs in Alexandria Governorate, Egypt. Damanhour Journal of Veterinary Sciences, 9(1), 7-15.

Miller, E. J.; and Brines, C. M. (2018): Canine diabetes mellitus associated ocular disease. Topics in companion animal medicine, 33(1), 29-34.

Minteer, D.; Marra, K. G.; and Rubin, J. P. (2013): Adipose-derived mesenchymal stem cells: biology and potential applications. Mesenchymal stem cells-basics and clinical application I, 59-71.

Mohamed, J.; Nafizah, A. N.; Zariyantey, A. H.; and Budin, S. (2016): Mechanisms of diabetes-induced liver damage: the role of oxidative stress and inflammation. Sultan qaboos university medical journal, 16(2), 132.

Mohamed-Ahmed, S.; Fristad, I., Lie, S. A.; Suliman, S.; Mustafa, K.; Vindenes, H.; and Idris, S. B. (2018): Adipose-derived and bone marrow mesenchymal stem cells: a donor-matched comparison. Stem cell research & therapy, 9, 1-15.

Monroe, W. E.; Laxton, D.; Fallin, E. A.; Richter, K. P.; Santen, D. R.; Panciera, D. L.; and Shinn, J. S. (2005): Efficacy and safety of a purified porcine insulin zinc suspension for managing diabetes mellitus in dogs. Journal of veterinary internal medicine, 19(5), 675-682.

Mosallanejad, B.; Avizeh, R.; Varzi, H. N.; and Pourmahdi, M. (2013): A comparison between metformin and garlic on a nlloxan-induced diabetic dogs. Comparative Clinical Pathology, 22, 169-174.

Motaln, H.; Schichor, C.; and Lah, T.T. (2010): Human mesenchymal stem cells and their use in cell-based therapies. Cancer 116, 2519–2530.

Nair, S.; and Wilding, J. P. (2010): Sodium glucose cotransporter 2 inhibitors as a new treatment for diabetes mellitus. The Journal of Clinical Endocrinology & Metabolism, 95(1), 34-42.

Naujok, O.; Francini, F.; Picton, S.; Bailey, C.J.; Lenzen, S.; and Jörns, A. (2009): Changes in gene expression and morphology of mouse embryonic stem cells on differentiation into insulin-producing cells in vitro and in vivo. Diabetes. Metab. Res. Rev. 25, 464–476.

Nelson, R. W. (2010): Canine diabetes mellitus In: Ettinger SJ, Feldman EC, eds. Textbook of Veterinary Internal Medicine: Diseases of the Dog and Cat. Seventh Edition ed. St. Louis: Saunders Elsevier, 1449-1474.

Nelson, R. W. (2015): Canine diabetes mellitus. Canine and feline endocrinology, 213-257.

Nelson, R. W.; and Couto, C. G. (2019): Small Animal Internal Medicine-E-Book: Small Animal Internal Medicine-E-Book. Elsevier Health Sciences.

Nelson, R. W.; and Reusch, C. E. (2014): Animal models of disease: classification and etiology of diabetes in dogs and cats. Journal of endocrinology, 222(3), 1-9.

Nguyen, M. T.; Okina, E.; Chai, X.; Tan, K. H.; Hovatta, O.; Ghosh, S.; and Tryggvason, K. (2016): Differentiation of human embryonic stem cells to endothelial progenitor cells on laminins in defined and xeno-free systems. Stem Cell Reports, 7(4), 802-816.

Noguchi, H. (2009): Pancreatic islet transplantation. World journal of gastrointestinal surgery, 1(1), 16.

Num-Adom, S. M.; Adamu, S.; Aluwong, T.; Ogbuagu, N. E.; Umar, I. A.; and Esievo, K. A. N. (2022): Ethanolic extract of Anogeissus leiocarpus ameliorates hyperglycaemia, hepato-renal damage, deranged electrolytes and acid-base balance in alloxan-induced diabetes in dogs. Scientific African, 16, 1183.

Odumosu, O.; Payne, K.; Baez, I.; Jutzy, J.; Wall, N.; and Langridge, W. (2011): Suppression of dendritic cell activation by diabetes autoantigens linked to the cholera toxin B subunit. Immunobiology, 216(4), 447-456.

Otto, W.R.; and Wright, N.A. (2011): Mesenchymal stem cells: From experiment to clinic. Fibrogenes. Tissue Repair 4.

Palmer, J. P.; Fleming, G. A.; Greenbaum, C. J.; Herold, K. C.; Jansa, L. D.; Kolb, H.; and Steffes, M. W. (2004): C-peptide is the appropriate outcome measure for type 1 diabetes clinical trials to preserve β-cell function: report of an ADA workshop, 21–22 October 2001. Diabetes, 53(1), 250-264.

Papachristoforou, E.; Lambadiari, V.; Maratou, E.; and Makrilakis, K. (2020): Association of glycemic indices (hyperglycemia, glucose variability, and hypoglycemia) with oxidative stress and diabetic complications. Journal of diabetes research.

Park, B. H.; Rho, H. W.; Park, J. W.; Cho, C. G.; Kim, J. S.; Chung, H. T.; and Kim, H. R. (1995): Protective mechanism of glucose against alloxan-induced pancreatic β-cell damage. Biochemical and biophysical research communications, 210(1), 1-6.

Park, B.; Yoo, K. H.; and Kim, C. (2015): Hematopoietic stem cell expansion and generation: the ways to make a breakthrough. Blood research, 50(4), 194.

Patel, D.M.; Shah, J.; and Srivastava, A.S. (2013): Therapeutic potential of mesenchymal stem cells in regenerative medicine. Stem Cells Int.

Peschke, E.; Ebelt, H.; Brömme, H. J.; and Peschke, D. (2000): 'Classical'and 'new'diabetogens—comparison of their effects on isolated rat pancreatic islets in vitro. Cellular and Molecular Life Sciences CMLS, 57, 158-164.

Petersmann, A., Nauck, M.; Müller-Wieland, D.; Kerner, W.; Müller, U. A.; Landgraf, R.; and Heinemann, L. (2018): Definition, classification and diagnosis of diabetes mellitus. Experimental and clinical endocrinology & diabetes, 126(07), 406-410.

Phadnis, S.M.; Joglekar, M. V.; Dalvi, M.P.; Muthyala, S.; Nair, P.D.; Ghaskadbi, S.M.; Bhonde, R.R.; and Hardikar, A.A. (2011): Human bone marrow-derived mesenchymal cells differentiate and mature into endocrine pancreatic lineage in vivo. Cytotherapy 13, 279–293.

Plotnick, A. N.; and Greco, D. S. (1995): Diagnosis of diabetes mellitus in dogs and cats: Contrasts and comparisons. Veterinary Clinics: Small Animal Practice, 25(3), 563-570.

Pohanka, M. (2021): Glycated hemoglobin and methods for its point of care testing. Biosensors, 11(3), 70.

Polonsky, K. S.; Licinio-Paixao, J.; Given, B. D.; Pugh, W.; Rue, P.; Galloway, J.; and Frank, B. (1986): Use of biosynthetic human C-peptide in the measurement of insulin secretion rates in normal volunteers and type I diabetic patients. The Journal of clinical investigation, 77(1), 98-105.

Poznyak, A.; Grechko, A. V.; Poggio, P.; Myasoedova, V. A.; Alfieri, V.; and Orekhov, A. N. (2020): The diabetes mellitus–atherosclerosis connection: The role of lipid and glucose metabolism and chronic inflammation. International journal of molecular sciences, 21(5), 1835.

Punthakee, Z.; Goldenberg, R.; and Katz, P. (2018): Definition, classification and diagnosis of diabetes, prediabetes and metabolic syndrome. Canadian journal of diabetes, 42, 10-15.

Qadri, K.; Ganguly, S.; Praveen, P. K. S.; and Wakchaure, R. (2015): Diabetes mellitus in dogs and its associated complications: A review. Int. J. Rec. Biotech, 3(4), 18-22.

Raju, S. M.; and Raju, B. (2010): Regulation of blood glucose and diabetes. Illustrated medical biochemistry. 2nd Edition. Jaypee Brothers Medical Publishers Ltd. New Delhi. India, 445-56.

Ramirez-Fernandez, O. (2021): A review from mesenchymal stem-cells and their small extracellular vesicles in tissue engineering. Instituto de Ingeniería y Tecnología.

Ramiya, V. K.; Maraist, M.; Arfors, K. E.; Schatz, D. A.; Peck, A. B.; and Cornelius, J. G. (2000): Reversal of insulin-dependent diabetes using islets generated in vitro from pancreatic stem cells. Nature medicine, 6(3), 278-282.

Rand, J. (2012): Feline diabetes mellitus. In BSAVA manual of canine and feline endocrinology, 133-147. BSAVA Library.

Rand, J. S. (2020): Diabetes Mellitus in Dogs and Cats. Clinical Small Animal Internal Medicine, 93-102.

Rasmusson, I.; Ringdén, O.; Sundberg, B.; and Le Blanc, K. (2003): Mesenchymal stem cells inhibit the formation of cytotoxic T lymphocytes, but not activated cytotoxic T lymphocytes or natural killer cells. Transplantation 76, 1208–1213.