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STEM CELL TREATMENT FOR TYPE 1 DIABETES MELLITUS

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Abstract:

Diabetes is one of the leading causes of morbidity and mortality affecting around 350 million people worldwide. Replacement of B cells is an attractive anticipation for diabetes treatment, but treatment options are rather limited. Even in the face of challenges, there is hope in cells that produce insulin from human pluripotent stem cells. So far, the most effective protocols have produced cells that mimic insulin and have very similar molecular properties to cells that secrete true insulin. However, these cells show little sensitivity to glycosylation and are a promising problem to be solved in the coming years. This review summarizes the latest progress in obtaining insulin-ex- pressing cells from different progenitor sources and highlights the major pathways and genes involved in diabetic patients.

Objective: *The purpose of the study was to know the Type 1 Diabetes Mellitus treatment with stem cells and its outcome.*

Study Design: *A prospective Study.*

Place and Duration: *The Study was held in the Endocrinology Department of Services Hospital, Lahore for the period of two years from January 2015 to January 2017.*

Methods: *Inclusion criteria were patients of both sexes, aged 12 to 60 years, with a diagnosis of type 1 DM during the previous 6 weeks confirmed by measurement of serum levels of anti–glutamic acid decarboxylase (anti-GAD) antibodies, BSR levels, GTT and HbA1C.*

Results: *Clinical trials embedding mesenchymal undifferentiated cells into type 1 diabetes patients exploit two resources these cells have. Right off the bat, they have the strength to repair beta cells, and on the other hand they have the ability to tweak the safe framework by avoiding the reactions promoting the immune system response and action on pancreatic beta cells. Stem cells are pieces of a human body normally, and they have the special capacity to discover and repair the place of harm inside the framework. For results to completely create, it as a rule takes up to four months after the immature stem cells are infused into human life form amid treatment.*

Conclusion: *Functional restoration of existing β-cells, transplantation of stem cells or stem cell-derived β-like cells might provide new opportunities for treatment. However, the use of stem cells to generate a renewable source of β-cells for diabetes treatment remains challenging, largely due to safety concerns. Current differentiation protocols that use viral vectors to generate induced β-cells result in low numbers of functional β-cells, and possible unexpected genetic modifications.*

Key words: *Diabetes mellitus; Stem cells; Insulin; Cell therapy.*

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INTRODUCTION:

Diabetes mellitus is a heterogeneous, abnormality which is caused bythe body imbalance forinsulin production.Diabetes mellitus has four sub-types; type 1, Type 2, & gestational diabetes and other referred to as pre-diabetic state. The three major sub-types incident mostly.(Diabetes, 2010). Type 1 is caused by the complete loss of insulin production. It occurs in children mostly which have long life time complications, if not managed properly. Type 2 has less severity than type 1 as the patients produce little amount of insulin and can be managed by diet and exercise but have the same complications as of type 1. Gestational diabetes by its name referred to as pregnancy diabetes which is mostly diminishes after delivery. Insulin plays the key role with the occurrence or absence of disease. As insulin signals to many tissues for maintenance of glucose level and different hormones balance in the body. Insulin done this by binding to its receptors. Any imbalance in insulin binding and its secretion cause metabolic processes and many hormones actions get disturbed, eventually causing diabetes mellitus. In type 1 the insulin action is hindered by destruction of body's own beta cells of pancreas thus have symptoms like hunger, thirst, excess of urination, fatigue etc., which will lead to serious complications of retinopathy, neuropathy and eventually to amputation.(Aguayo-Mazzucato& Bonner-Weir, 2010). Diagnosis of Type 1 is done by conducting different tests, one of the most important of which is HbA1C, other tests include fasting glucose test, random plasma test and oral glucose test. After the diagnosis further tests to learn the extent of disease is determined. These might include lipid profile, vitamin D levels, ketones test depending on the patient's condition. Treatment is done on the basis of test values. Insulin doses are adjusted which are different for every patient on its meal timings, physical activities, carbohydrates intake, and body response to medications and doses has been used. Many methods for advance treatments has been in application which include insulin pump, insulin inhaler, or may be pancreas transplant in developed countries. But due to rapid progress in technology stem cell therapy has now been in process to successfully introduce in the patient's body to produce insulin same as pancreatic cells produce. However, research is still be in work for a proper and effective result.

Types of diabetes mellitus

Type 1 diabetes also called insulin juvenile onset diabetes or insulin dependent (IDDM) as it mostly occur in childhood. The main reason of Type 1 diabetes is the complete deficiency of insulin production by beta cells of pancreas which leads to some serious and long term complications of eyes, kidneys, heart and even to amputation.(Wallis et al., 2016) (A. Zumla,Raviglione, Hafner, & Fordham von Reyn, 2013).

Type 2 another name is"non-insulin dependent diabetes mellitus" (NIDDM), which occur by the body cells to resist to insulin or insufficient production of insulin. It is an adulthood occurring disease, happens due to sedentary lifestyle and mostly obesity considered while it is not proper for every case. Its symptoms also include hunger, thirst, frequent urination, similar the symptoms of type 1. It can be treated with medicines taken orally, by exercise and diet control, but reach to totally insulin injections if not treated properly.(A. Zumla, Raviglione, et al., 2013)

Gestational diabetes mostly occurs in the pregnant ladies due to high glucose level in the body. It is treated during pregnancy time with the diet management and may retain if properly not treated during pregnancy. (D 'ambrosio et al., 2015).

Table1: Different types of Diabetes; Onset, Causes, Other terms, Symptoms, Treatment.

Types	Onset	Cause	Other terms	Symptoms	Treatment
Type 1	In youth	Loss of insulin production by beta cells	"juvenile-onset diabetes or insulin dependent diabetes mellitus (IDDM)"	Polyuria, polyphagia, polydipsia & weight loss	Insulin injections
Type 2	In adults	Insulin resistance by *B*-cells	"Adult-onset diabetes or non-insulin dependent diabetes mellitus (NIDDM)" "Non-insulin	Mainly overweight& other symptoms as Type 1	Exercise, oral medications
Gestational diabetes mellitus	Pregnant ladies	Insulin resistance by pregnancy hormones	Gestational diabetes mellitus	Baby put on weight	Usually goes after pregnancy

Other sub-types are intermediate state between the normal glucose level and higher occurrence of diabetes susceptibility. They are considered as pre-diabetic states and may develop to diabetes mellitus with increased risk. They are categorized as; impaired fasting glucose and impaired glucose tolerance. (Van Boogaard, Kibiki, Kisanga, Boeree, & Aarnoutse, 2009).

Prevalence and incidence

The categorization, tests and treatment of diabetes mellitus were arranged by the "National Diabetes Data Group of the USA" and the second "World Health Organization Expert Committee on Diabetes Mellitus" in 1980's. More than 230 million people has been effected by diabetes mellitus and this figure will double by the year 2030. The World Health Organisation and American diabetes Associationgiven the stats for the type 1 diabetes mellitus cases about 5–10% occurring worldwide.(A. I. Zumla et al., 2014)

According to the diabetes national survey of Pakistan, most importantly the age factor of increasing act as a prominent risk.. Currently 7.1 million Pakistani are suffering from diabetes. (Nasiruddin, Neyaz, & Das, 2017).Type 1 diabetes Treatment requires continuous injections of insulin, monitoring of blood glucose, diet planning, exercise and care of long term diabetes complications. Insulin produce by beta cells of the pancreas has major role in controlling the sugar level of patient. Still many developments and advancements are occurring to cure this disease. (Park et al., 2003).

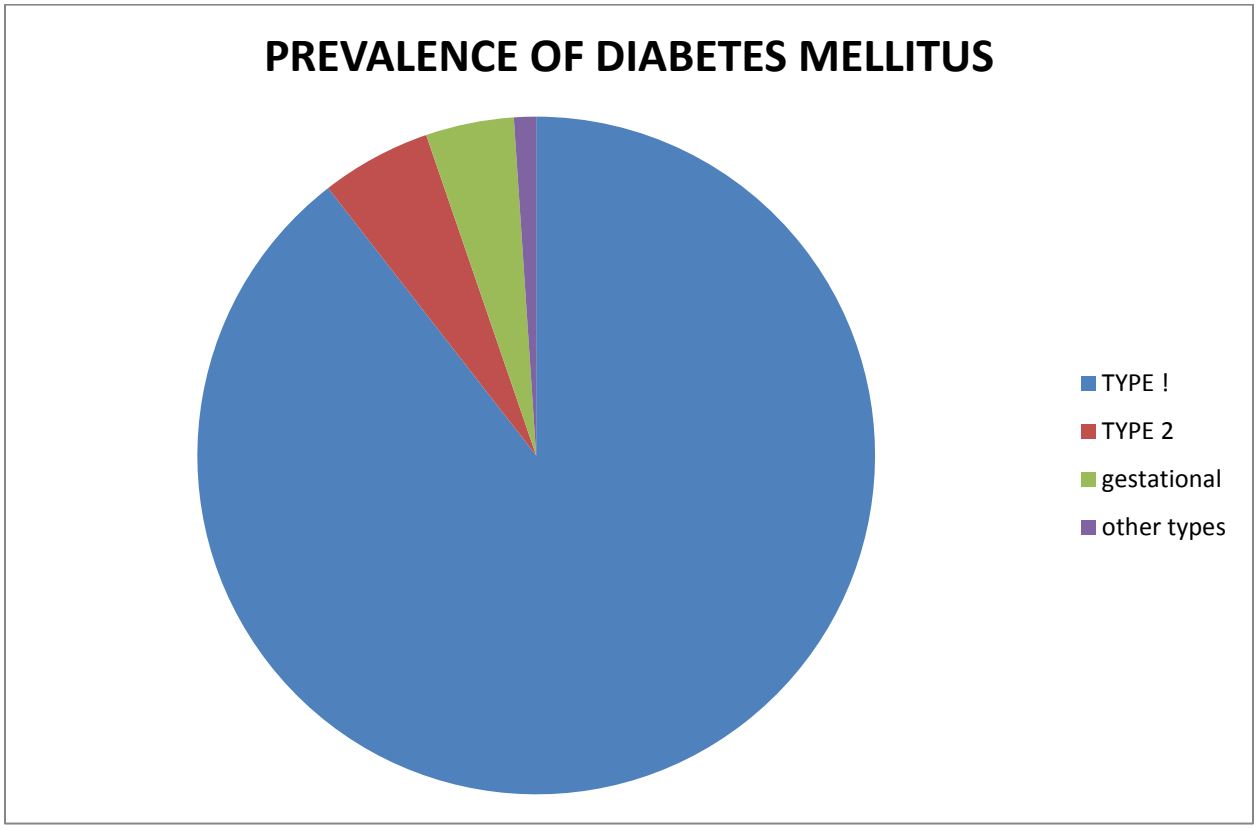

Figure 1: **prevalence of types of diabetes mellitus in which type 1 in (blue) indicates more prevalence than type 2 (Red), Gestational (Green) & Other types (violet).**

INSULIN ROLE

The cellular processes of body will be initiated by insulin when it binds to its ligand-binding and tyrosine kinase glycoprotein receptor 1 . (Am J Physiol.1994)present mainly in skeletal muscles liver and adipose) tiisues.which trigger the uptake of glucose and converting into glycogen for future energy source.and also inhibit the conversion of glycogen to glucose to maintain the glucose homeostasis. (Ginsberg & Spigelman, 2007

Structure of insulin

Insulin is a polypeptide hormone. It is stored in the beta cells of pancreas and release on the stimulation of glucose thus lowers the blood glucose level. (Casadevall& Ph, 2017).The gene responsible for producing human insulin is present on chromosome 11. The human insulin molecule consists of two polypeptide chains, the A-chain and the B-chain. The A-chain consist of 21 amino acids while the B-chain consist of 30 amino acids.The two chains are linked by three disulfide bridges. Insulin molecule is a three dimensional structure (tertiary structure). The molecular weight of insulin is 6000Da.(Lewis et al., 2003).

Synthesis of insulin

The production of insulin by the islets of beta cells of pancreas which are present in clusters forms appearing as small islands).After the fed state, glucose, fatty acids and amino acids from food circulate in the blood stream. (Villemagne et al., 2012). These molecules especially glucose from capillaries released into pancreatic tissues where itstimulate the beta cells to produce insulin which is stored. The mRNA give the message to the beta cell to produce protein for insulin. The first formed is known as preproinsulin. Preproinsulin is then sent to endoplasmic reticulum where it is assembled as proinsulin. Pyrazinamide. (A.Zumla, Nahid, & Cole, 2013).

Proinsulin consist of alpha unit, C-peptide (connecting-peptide) and the beta unit. This proinsulin is further sent to golgi apparatus where C-peptide is removed from proinsulin and the two units alpha and beta are joined together by disulfide bridges. Now this molecule with C-peptide removed consisting of two amino acid chains (alpha and beta) is known as insulin. (Mitra, 2012). Insulin is packed in vesicles in golgi apparatus which is bud off on maturing. This insulin and C-peptide on higher glucose concentration is then secreted from the cell to blood stream and travel to target tissues. The three main target tissues of insulin are liver, skeletal muscles and adipose tissues. (Mitchison, 2006).

These tissues on activation by insulin help to store glucose as energy source for future use. (Larijani et al., 2012).

Insulin receptor

The membranes of target tissues surfaces are covered with insulin receptors. The structure of insulin receptors are almost same in the tissues. Insulin receptor consist of two alpha sub-units of molecular weight ¬135,000 which reside on the surface of target tissue cell. The insulin molecule will bind on the these alpha units. The two beta sub-units of molecular weight ¬90,000 are embedded in the cell membrane. Insulin receptor is also known as tyrosine kinase enzyme which attaches the phosphate group to inner domains of target proteins in the cell by taking it from ATP. (Steven Jacobs, Pedro cuatrecasas,1981).

This enzyme has beta sub-units in the cellular matrix. It is mostly auto phosphorylated having attached phosphate groups. When the phosphate groups are not attached it is in inactive form. Two subunits of alpha and beta are attached to each other by disulfide bridges.

Insulin when binds to the extracellular units of receptors (alpha units), the beta units which have phosphate groups will phosphorylate the target proteins (IRS-1 and IRS-2) inside the cell. These target proteins are involved in the extracellular effects of insulin. (Yu et al., 2012).

On contrary, with the target protein activation, insulin binding to receptors also send signals for the glucose transporters to reach at the membrane surfaces of tissues (translocation of GLUT proteins) . These transporters allow the glucose to enter in the cells and store there for future use. GLUT 2 are present in liver cells while GLUT 4 are transported in muscleandadipose tissues cell surface for fat and protein absorption respectively.(Koheal.2013).

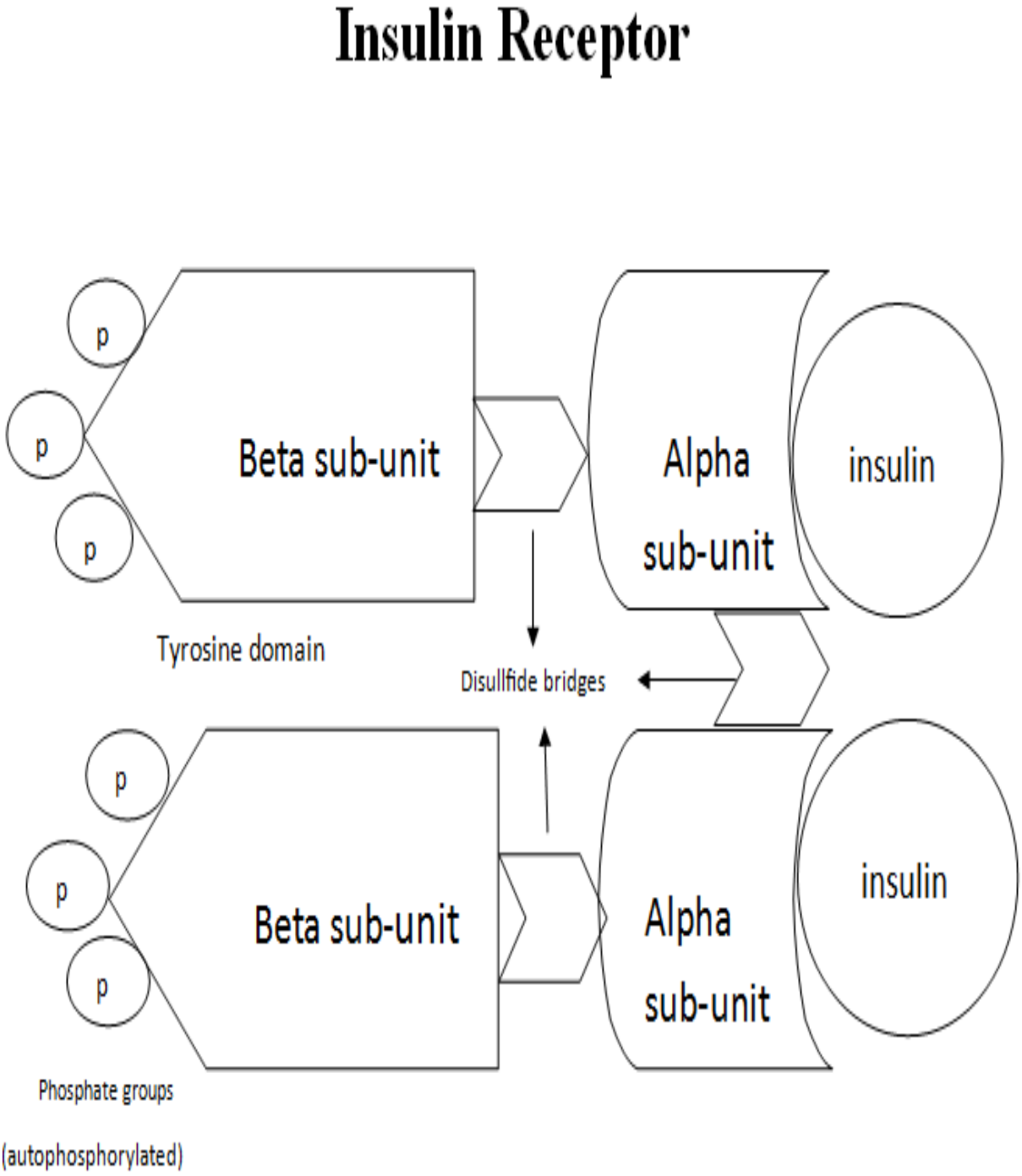

Figure2: insulin receptor (IR) a glycoprotein consist of 2*a* & 2*B* subunits joined by disulphide bridges, *a sub-units present onextracellular membrane for binding insulin, B sub-unit consisting of tyrosine kinase domain which is autophosphorylated& trigger substrates (IRS-1) for other chemical responses.(Communication and Cell Signalling Book Reference: p.20-21)*:

Molecular secretion of insulin

The auto-phosphorylation of receptor (tyrosine kinase) and phosphorylation of target proteins (IRS-1 & IRS-2) will be provided by K+ ion channels present in the beta cells. K+ channels are ATP sensitive. They remain open and the K+ ions move outside of the cell forming negative concentration of cell. (Schuppan and Afdhal, 2008).When glucose concentration is higher in blood it will move through GLUT transporters into the cell which is then metabolize to ATP. This ATP has potential to close the K+ ion channels. Thus negative charge is less as K+ will remain in the cell. The higher concentration in cell will cause the Ca2+ ions channel to open. The Ca2+ ions move in and trigger the vesicles containing insulin to be released. cell. (Perkins, 2007)

Metabolic processes of insulin

The target proteins of insulin when attached by phosphate group the cause many metabolic processes in body to occur. Insulin action can also be lowered or inhibit by the different hormones present in body other than the insulin receptors of muscles, liver and fat tissues which resist insulin production and its other metabolic processes. Saltiel, A. R., & Kahn, C. R. (2001).

Promotion effects

Insulin Increases the **gene expression** of growth hormone. It also increases**glucose absorption**by expanding the glucose transporter rateover the cell layer in fat tissue and muscle

a) **Carbohydrate digestion**:It builds the glycolysis rate in muscle tissues and fat tissuesand also fortifies the rate of glycogen storage in various tissues, including adipose tissue, muscle and liver. It likewise diminishes the rate of glycogen breakdown in muscle and liver (restrains the rate of glycogenolysisand gluconeogenesis)..

b) **Lipid digestion**:It diminishes the lipolysis rate in fat tissue and henceforth brings down the plasma unsaturated fat level. Thus, empowers unsaturated fat and triacylglycerol union in tissues. It also builds the rate of low-thickness lipoprotein arrangement in the liver which in case transport the cholesterol combination in liver. It expands the take-up of triglyceride from the blood into fat tissue and muscle and diminishes unsaturated fat oxidation in muscle and liver.

c) **Protein digestion**:It builds the rate of transport of some amino acids into tissues,italso expands the rate of protein blend in muscle, fat tissue, liver, and different tissues,

Table 2: insulin promotion & insulin inhibition processes

Insulin promotes	Insulin inhibits
Glucose → glucose 6-phosphate→ glycogen	Glycogen ×→ glucose
Glucose→ acetyl CoA→TAG	Fatty acids ×→Acetyl coA
Ribose activity → protein	Protein ×→ amino acid
Glucose transporters→ glucose absorption	High level glucose ×→ little absorption

Action of insulin in Type 1 patients

The action of insulin in type 1 patients is hindered by the body's immune cells thus type is referred to as autoimmune disease. In this case the immune system of the patient kills or mistakenly attacks its own beta cells (insulin producing cells) of pancreas. The clusters of beta cells present in the form of islets shrinks and unable to produce insulin. Some of the beta cells if remain intact may produce little amount of insulin. This insufficient or loss of insulin production the patient cannot regulate blood glucose properly and level of glucose rise in the body. This high level glucose will damage many tissues in the body and cause many other complications.

Symptoms

- **Increased hunger**

As the glucose is not absorbing properly by cells which are useful for their proper working, in this case body will demand more food for energy consumption.

- **DisproportionateThirst**

When more water is loss from body by urination, you will need more water to replace loss liquid. Dry mouth and pale skin is the result of severe thirst.

- **Excessive urination**

As insufficient insulin production promotes less glucose uptake in blood, thus more glucose in kidney will take more water from body to dilute more glucose and does not retain this water.

- **Blurred vision**

One of the Main symptom which is caused due to eye muscles being pulled and unable to focus properly.

- **Abdominal pain**
- **Weakness**

As body cells are not gaining enough glucose (an energy source) the tissues and muscles will not work properly and you feel tired and restless.

- **Weight loss**

In absence of insulin production, body cells not getting glucose for energy will breakdown other stored energy sources (fats & proteins) and gradually the weight loss.

- **Late wound healing**

Abnormal glucose level in body suppress the healing of wound on time.

- **Irritability**

Itchy skin, in this case skin become more sensitive and severity cause rashes

Feeling of

- **Mood changes**
- **Swollen gums of teeth**

LONG TERM COMPLICATIONS

Diabetic ketoacidosis

Diabetic ketoacidosis is otherwise called DKA, it happens for the most part in individuals as of now have diabetes, it is because of contamination, or unseemly insulin measurement, or the diabetic patient missed the insulin infusion. Diabetes grows step by step by the joined impact of three biochemical changes with the end goal that hyperglycemia, acidosis, ketosis. At the point when the body not gets enough insulin, you can't utilize glucose viably. Without glucose body utilizes fats and proteins from fat tissues and muscles to get its vitality. Other hormonal uneven characters likewise happen. these fats and protiens are changed over into glucose or to ketones by liver. At the point when a lot of measure of ketones develop in the blood, it makes the blood acidic, causing diabetic ketoacidosis with its indications of lack of hydration, over the top pee and heaving predominantly.

DIABETIC RETINOPATHY

The main cause of visual abnormality seen mostly in young-adults of 20-74 age in created nations is retinopathy realized by diabetes. The heart and circulatory framework issues said above reason veins in the eye to debilitate and every so often burst. At the point when veins develop back, they become back anomalous (and conceivably end up shut off by miniaturized scale blood clusters). These strange vessels can get inside the retina and eyeball, and make the retina segregate.

Keeping up a heart-solid way of life can enhance the dangers of eye harm and retinopathy. Moreover, anybody with diabetes ought to have a full eye exam done.

Factors affecting type 1 diabetes mellitus

Many factors have been supposed to be considered as environmental triggers. These may include virus infection, toxins, dietary factors such as Vitamin D deficiency, consumption of cow's milk etc. new evidences showed that enterovirus trigger beta cell cell destruction by having same epitope as protein of beta cell and thus trigger self tolerance and autoimmunity.(Hans.K, et al 2002). Cow's milk protein (casein hydrolysate) presence in infants has been reported as increased risk for genetically occurring diabetes. Trials had done on infants who had given cow's milk during 6-8 first life months had more chance than who has given breast milk. The increased risk is due to the fatty acids present in formula milk which trigger the islet autoimmunity. (M-Rewers 2016*).*

Vitamin D play a protective role in immune system regulation as it regulates the metabolic pathway and immune system to diabetes. Studies revealed that daily average sunshine hours had positive effect on decrease risk of diabetes. While it is not reported for taking dietary vitamin D for risk reduction. Seasonal variations such as birth in summer rather in winter may play effective role as production of vitamin D to sun exposure.(IWeets, et al)

Toxins are the main agents for activating the autoimmune response in susceptible diabetics genetically. The chemical compounds and N-nitroso compounds like nitrosamine, nitrates, nitrites present in food and water causes the pancreatic beta cell destruction. Reports have been revealed that families using food or water containing higher amount of nitrates have increased risk of type 1 diabetes children than the families with controlled amounts of nitrates.(M. Rewers, 2016).

Genetics

Type 1 the polygenic disorder include nearly 40 loci for the cause of disease.(NEnglJ Med, 2009).Chromosome 6 mainly with HLA complex is playing the critical role for disease suspect, as they are responsible for presenting antigens being processed into small fragments (peptides). The HLA has two main classes; HLA 1 & HLA 2. The latter is putatively involved in type 1 susceptibility. These are present on antigen presenting cell. The HLA genes with the combination of alleles i.e." DRB1*0401-"DQB1*0302 and DRB1*0301-DQB1*0201" combination will cause more chances for type 1 and "DRB1*1501 and DQA1*0102-DQB1*0602" has less chance of type 1 to occur and responsible for insulin resistance. Class 2 genes(DQ, DR, DP) haplotypes have strongest association with the onset of disease.(Abner Louis Notkins, 2007). Environmental and physiological triggers (vitamin D and viral infections) may also stimulate the genes to be susceptible for type 1 diabetes mellitus.(JD Cooper, et al).

Other genes which are also associated with disease occurrence include;

- *SH2B3*
- *ERBB3*
- *CLEC16A*
- *IL18RAP*
- *PTPN2*
- *CCR5*

(Patrick Concannon, et al. 2009)

Autoimmune

Autoimmunity is considered as the main factor to recognize type 1 patients from other diabetics. The autoantibodies should be present many months or years before the disease onset aided by the environmental factors and genetics. Three main types of autoantigens had been viewed in the patients of type 1 diabetes, first being glutamic acid isoform glutamic acid decarboxylase (GAD65), the second being either islet antigen-2 or the ZnT8 transporter, (M Rewers, et al) and the third major autoantigen is insulin.(SC Kent, et al). Of these autoantigens, autoantibodies are being produced in which they recoginize their conformational epitopes and change their catalytic activity. These autoantibodies are not pathogenic itself but they must be produced in sufficient amount for type 1 diabetes onset. (M Rewers, et al).The study showed that autoantibodies concentration decrease with the age i.e. in the prediabetics the autoantibodies concentration in sera is more than those with older diabetes. Destruction of beta cells has been identified as the main factor for onset of type 1 diabetes which present proinsulin as autoantigen thus, destroyed by different pathways (apoptosis,necrosis).(Abner Louis Notkins, 2002)

Diagnosis

Diagnosis of Type 1 diabetes can be done by different methods which include fasting tests like HbA1C, fasting blood glucose test, random blood glucose test, urine examination (lipid profile, ketones concentration) and in some cases the test of autoantibodies and the differences of vitamin D levels (MichealF.Holick) present in the body. HbA1C called glycosylated hemoglobin due to binding of glucose to red blood cells containing called hemoglobin. As red blood cells die approximately after 3 months, so this test is conducted after 3 months to check the concentration of glucose during these 120 days.American Diabetes Association set their reference values for determination of diabetes to incorporate glycated hemoglobin (A1C; a test that midpoints 5.5% and pre-diabetic may have the range between 5.5-6.5%. Fasting sugar test is normally taken after fasting overnight from almost 8-9 hrs. except intake of water. The normal range of fasting glucose must be less than 100 mg/dL above this or equal to this considered as pre-diabetic. More than 126mg/dl will have diabetes and should be tested further for confirmation. Random glucose test or plasma test sometimes does not give the best results as it is tested after random eating. Although its normal range after 2 hrs. of fed state should in between 140-200mg/dL. Another test called oral glucose test can be conducted for confirmation. It is done by taking glucose orally after first conducted fasting sugar test. Despite, endeavors to institutionalize conclusion of type 1 analysis, the causes and typology stay indistinct. (Federica Colomboa, et al, 2016). Fasting plasma glucose include Especially among grown-ups, conclusion of type 1 versus type 2 diabetes can be testing. Around 5– 15% of grown-ups determined to have compose 2 diabetes may really have type 1 ailment with islet autoantibodies present;36 if so, maybe as numerous as half of real kind 1 diabetes cases are misdiagnosed as sort 2, implying that the quantity of instances of sort 1 infection is endlessly disparaged. Precise determination of this issue is significant for ideal care and staying away from complexities, and accurately taking note of diabetic ketoacidosis at conclusion of type 1 malady speaks to a key window for survival(Atkinson, Eisenb arth, & Michels, 2014).

TABLE 4:Type1 Tests; HbA1C (Glycosylated haemoglobin), Fasting plasma glucose, random plasma glucose reference values; normal and occurrence ranges

Reference value	HbA1C (%)	FPG (mg/dL)	RPG (mg/dL)
Normal value	4.5-5.5	<90	<140
Occurrence	6.5 or <6.5	>126	>200

A universal board of trustees of diabetes specialists has as of late reexamined the analytic assesment for distinguishing Type 1 diabetes human patients. Finding is presently in light of any of the three criteria that take after: Exemplary side effects of diabetes (excessive urination, disappropiate thirst, undefined weight reduction, obscured vision) and an arbitrary blood sugar convergence of ≥200 mg/dL (11.1 mmol/L). Fasting plasma glucose of ≥126 mg/dL (7.0 mmol/L) after an overnight (no less than 8 h) quick. Post stack plasma glucose of two hours of ≥200 mg/dL (11.1 mmol/L) amid a standard 75-g oral

glucose resilience test. Experts set that without unequivocal high blood sugar with intense metabolic disturbance, analysis might be affirmed day by any of the three techniques on a resulting. (Zhang et al., 2012).

Despite the fact which was demonstrated earlier that glucose resistance stays ordinary until the clinical initiation of diabetes, beta-cell capacity and discharge of insulin diminishes notwithstanding amid the preclinical period. It is roughly estimated that 90% of mass of beta-cells must be obliterated before plain hyperglycemia occur. Analytic apparatuses other than blood sugar estimations incorporate HbA1C the screening for, which has led the fruitful results in the underlying assessment of the patient and in the appraisal of adequacy of helpful measures. The significant type of glycohemoglobin is hemoglobin A1C, which specifically mirrors the level of blood glucose focus over the first 8 to 12 wk, making it a compelling device to evaluate incessant diabetic control. In specific conditions, estimations of insulin or C peptide levels and also levels of counter-administrative hormones (development hormone, glucagon, cortisol, and epinephrine) may demonstrate valuable also. (Zhao et al., 2012).

Tests after diagnosis

After confirmation of diabetes other tests been conducted to know the exact condition of patient to which extent the diabetes had effected. The test then gives the values if the values are abnormal or high than normal range it is to be treated before adverse complications. These tests may include A1C test, lipid profile, vitamin D levels, urine test to check ketones.

HbA1C test is used for diagnosis as well as for treating diabetes repeated after every 3 months on the onset of disease. Lipid profile is done in order to check the cholesterol, triglycerides and other high density and low density lipoproteins. As these components are involved in the occurrence of other diseases such as stroke, atherosclerosis leads to thickening and blockage of arteries and eventually to heart attack. Thus normal values should be maintained. Range of cholesterol less than 200mg/dL is good as it helps in other body structure and function. High density lipoproteins (HDL) are good cholesterol as it helps in the removal of excess cholesterol but its value should be maintained i.e. less than 35mg/dL. Low and very low density lipoproteins are same and considered as bad cholesterol as it has more cholesterol quantity and values more than 130mg/dLcause blockage of arteries.

Table 5: Lipid profile

Tests	Units	Reference value
Total lipids	mg/dL	400-1000
Triglycerides	mg/dL	Upto 50
Cholesterol H.D.L L.D.L V.L.D.L	mg/dL mg/dL mg/dL mg/dL	≤ 200 ≤ 35 ≤ 130 7-25

The differences of vitamin D levels (Micheal F.Holick,2007) present in the body may exist with respect to gender, age, season, geographic Latitude and ethnic groups. However, its normal range should not be less than 20ng/ml and not be more than 100ng/ml.

Table 6: differences in Vitamin D levels

Reference ranges	values	units
Vitamin D deficiency	<20	ng/ml
Vitamin D sufficiency	21-30	ng/ml
Vitamin D desirable	31-100	ng/ml
Vitamin D intoxication	>100	ng/ml

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Treatment

Treatment of Type 1 diabetes includes many methods in a manageable way to control its adverse effects and circumstances. Methods for treatment includes self-monitoring glucose level by glucometers, continuous glucose monitors (CGMs), insulin injections, insulin pump, proper meal planning, exercise, proper eye, foot and dental checkup.Intensive therapy treatment has long advantageous consequences for the danger of cardiovascular malady in patients with type 1 diabetes. Intensive diabetes treatment went for accomplishing close normoglycemia diminishes the danger of microvascular and neurologic difficulties of type 1 diabetes.Type 1 diabetes is related with no less than a 10-crease increment in cardiovascular infection as contrasted and an age-coordinated non-diabetic populace. Intensive therapy treatment comprised of at least three day by day infusions of insulin or treatment with an outside insulin pump, with dosage changes in view of no less than four self-observed glucose estimations every day. Every day glucose objectives were 70 to 120 mg for each deciliter (3.9 to 6.7 mmol per liter) before dinners and escalated levels of under 180 mg for every deciliter (10.0 mmol per liter) after suppers. The objective for glycosylated hemoglobin was under 6.05 percent. (Larijani et al., 2012)

The auto-antigens present in diabetes mellitus patients can be tested as a difference between Type 1 and Type 2. Insulin and (GAD) isoform of glutamic corrosive decarboxylase (GAD) are major auto-antigens in patients with type 1 diabetes. Addition of GAD-alum may increase the protection of remaining insulin expression in patients with late beginning of Type 1 diabetes, in spite of the fact that it didn't change the insulin necessity.(Johnny Ludvigsson, et al.)

The cases of ideas and gadgets that may be keys to this transformative advance incorporate enhanced gadgets for home blood-glucose observing and routine assurance of HbA1c; improvement of a progression of insulin analogs; (eg, Humalogue and Aspart insulin),which are readily absorbed in the body (SK Garg, et al.) presentation of the primary sensors for constant glucose checking; and. advancement of treatments; such that pancreas transplantation and more recently with islet transplantation (AM Shapiro, et al) went for postponing or reducing complexities. (Meehan, 2003).

Types	Start working	Peak action	Duration of action	Example
Rapid-acting insulin	After 15 min.	About 1 hr.	2-4 hrs.	insulin glulisine (Apidra), insulin lispro (Humalog) and insulin aspart (Novolog).
short-acting insulin	After 30 min.	About 2-3hrs.	3-6hrs.	insulin glargine (Lantus), insulin detemir (Levemir),insulindegludec (Tresiba).
Intermediate-acting insulin	After 2-4hrs.	About 4-12hrs.	12-18hrs.	(regular) insulin Humulin R &Novolin R.
Intermediate-acting insulin	After several hours	Steady effect	24hrs.	insulin NPH (Novolin N, Humulin N).

Stem cell therapy

.The utilization of regenerative cells (stem cells) prescription possess extraordinary guarantee for the cure of numerous sicknesses, which also include type 1 diabetes mellitus (T1DM). Any type of regenerative stem cell can be used for the treatment of (T1DM) should address the requirement for β-cell substitution, and control of the immune system action on insulin producing beta cells. The preparation of β cells in lab reasonable for transplantation to reconstruct a practical β-cell mass has made use of regenerative cells from various sources, and in addition organ-particular facultative stem cells mainly from the pancreatic and liver tissues. The best conventions created up till now have cells that produce insulin and have qualities at molecular level that nearly look like true blue insulin-discharging cells; be that as it may, these cells are do not response to glucose, a trademark which might be used in future prespective. The use of umbilical rope or stromal cells of mysenchyma, blood to regulate the insusceptible reaction is as of now on trial basis; notwithstanding, authoritative outcomes are yet in consideration. This Centers for review around new techniques to acquire cells which may produce insulin from various forebear features the primary mechanism and

qualities required, and in addition the diverse methodologies for the regulation of the resistant reaction in patients with T1DM. (Song et al., 2015).
Clinical trials embedding mesenchymal undifferentiated cells into type 1 diabetes patients exploit two resources these cells have. Right off the bat, they have the strength to repair beta cells, and on the other hand they have the ability to tweak the safe framework by avoiding the reactions promoting the immune system response and action on pancreatic beta cells.(Yu et al., 2012).

Stem cells are pieces of a human body normally, and they have the special capacity to discover and repair the place of harm inside the framework. For results to completely create, it as a rule takes up to four months after the immature stem cells are infused into human life form amid treatment. fibrosis. (Schuppan and Afdhal, 2008). Over the span of that time, a patient notification consistent new changes. Since these stem cells originate from patient's own body, there is additionally no danger of dismissal or symptoms. The entire strategy is fast, easy, basic and safe, and it is finished inside just couple of hours. This approach advances beta cell work, in this manner lessening or taking out the prerequisite for exogenous insulin. (Yao et al., 2012).

Stem Cell Therapy program has been built to treat an assortment of conditions, one of which include a treatment in which a patient gets 200 – 300 million undeveloped cells. (Yu et al., 2012). This amount of the re-established plain cells covers day by day misfortunes, as well as surpasses them by a large number of times, restoring right around 15 – 20 year's worth. This makes side effects of a malady enhance and the entire body and the majority of the organs end up more advantageous and restored, in light of the fact that the new and dynamic cells supplant the old and harmed ones. (Margini et al., 2014).

Advantages of therapy by stem cells
Side impacts and dismissal free (patient's own one of a kind undifferentiated organisms from the belly and additionally bone marrow are utilized). Avoidance of any unfavorably susceptible and resistant responses (patient's own cells suit chromosomal and hereditary structure). (Petersen, 2012).Does not require general anesthesia. No danger of pollution by transmissible infections. No oncological entanglements as grown-up undifferentiated organisms in the correlation with embryonic cells are somewhat develop. Procedure is brisk and basic. Little amount of cells are removed from bone marrow or potentially fat tissue. Mix of the two can regularly demonstrate the best outcomes. The timeframe between getting lipoaspirate and infusion of the enacted foundational microorganisms is just a couple of hours.(Pai et al., 2008).Autologous Adult immature microorganisms are better finished embryonic undifferentiated cells, since they don't require development of a few months and originate from patient's own body, which is the reason there is no danger of symptoms after the treatment. (Terai et al., 2006).

CONCLUSION:

Clinical trials embedding mesenchymal undifferentiated cells into type 1 diabetes patients exploit two resources these cells have. Right off the bat, they have the strength to repair beta cells, and on the other hand they have the ability to tweak the safe framework by avoiding the reactions promoting the immune system response and action on pancreatic beta cells. Stem cells are pieces of a human body normally, and they have the special capacity to discover and repair the place of harm inside the framework. For results to completely create, it as a rule takes up to four months after the immature stem cells are infused into human life form amid treatment. Functional restoration of existing β-cells, transplantation of stem cells or stem cell-derived β-like cells might provide new opportunities for treatment. However, the use of stem cells to generate a renewable source of β-cells for diabetes treatment remains challenging, largely due to safety concerns. Current differentiation protocols that use viral vectors to generate induced β-cells result in low numbers of functional β-cells, and possible unexpected genetic modifications.

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