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Management of Diabetes by Imaging and their Complications

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ABSTRACT

In the world, more than 400 million people are suffering from diabetes, while diabetes is one of the most widely spreading diseases, and will be the challenge in the future. The highest rate of diabetes is seen in adult (10.9%) in the middle east and north Africa region, while the greater number of diabetes (adult) patient are diagnosed in the western pacific region and has the highest number of spreading diabetes (37.5%). Many of the technologies are used for the treatment and diagnosis of diabetes but the perfect cure for diabetes is yet difficult to find. Treatment and the therapies available for diabetes are much expensive and less effective. Many of the patients have type 32 diabetes and a small percentage of people have type 1 diabetes. Different types of diabetes are compared in the term of the diagnosis criteria. Insulin production plays a vital role in the regulation of blood glucose in the body. Some of the defects in the beta mass cell and function are the major cause of diabetes 1 and diabetes 2.

Keywords: Diabetes, Beta-cell, Nuclear magnetic spectroscopy, Pancreas, ketoacidosis.

INTRODUCTION

Different types of diabetes are compared in the term of the diagnosis criteria. Insulin production plays a vital role in the regulation of blood glucose in the body. Some of the defects in the beta mass cell and function are the major cause of diabetes 1 and diabetes 2. Yet none of the therapies are available. None of the therapies are available to directly promote the improvement in the beta-cell mass or the functioning. Therefore there is a great need to improve the target therapies of the beta-cell. Beta-cell is located in the endocrine cells known as the islets. The pancreatic islet (mini-organs) containing the endocrine cells(contain the beta cell and the glucagon producing alpha cells).Most of the imaging techniques such as Magnetic resonance imaging, nuclear magnetic spectroscopy, positron emission tomography and are used for the quantitative detection and characterization of the beta cell (reference from the molecular imaging and beyond). Diabetes is a group of the disorder may occur when the blood glucose or the concentration of sugar in the body is high. Food provides us the blood sugar which is the main source of the energy. Pancreas secrets or make the insulin that helps the glucose from food to get into your cell and that can be used as energy. Sometimes your body or pancreas does not make enough insulin or not able to use that insulin well.

MATERIALS AND METHODS

The glucose remains in the blood and cant able to reach your cells. Some of the people call diabetes "a touch of sugar" These terms explain that diabetes is not present or it is a less serious case, but every case of the diabetes is serious (Figure 1).

Figure 1: Classification of diabetes.

Diabetes mellitus type-1

It causes due to autoimmune beta cell destruction of the pancreas that may lead to insulin deficiency. This type of diabetes also known as diabetes that depends on insulin or insulin-dependent diabetes. This type of diabetes mainly occurs in childhood age and may occur at any age even in the eighty and ninth decades of life. These types of diabetes usually come in contact faster in the infants and the children rather than the adults. In some of the children and the teenager may be the presence of the ketoacidosis at the first manifestation of the disease and some of them have a minor stage of hyperglycemia and that can be suddenly changed into chronic hyperglycemia and ketoacidosis in the presence of the different infection and the presence of stress. Many of the diabetes patients in type 1 diabetes depend on the daily intake of insulin for survival and maybe at the risk of ketoacidosis. The honeymoon phase means in which insulin secretion is rapidly decreased, no longer period of the normal glucose homeostasis and insulin release may be seen after a short diagnosis of type 1 (Figure 2).

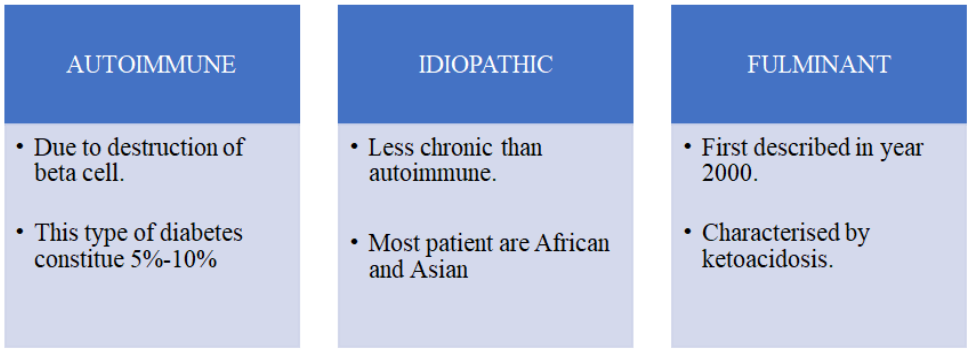


Figure 2: Different types of type-1 diabetes.

Diabetes mellitus type-2

Diabetes mellitus type-2 diabetes also known as diabetes which is not dependent on insulin. This diabetes occurs due to the resistance to insulin or insulin deficiency. This type of diabetes does not require insulin to survive. This diabetes may be caused by many of the different reasons. Patients with type 2 diabetes are having obesity and due to obesity, they may have some resistance to insulin. Ketoacidosis may occur in this type of diabetes.

Gestational diabetes

Only 5% of this type of diabetes occurs in women during pregnancy. This mostly occurs due to obesity in women. In this, there is a risk for both the mother and the child during the pregnancy. This may cause risks like cesarean and macrosomia shoulder dystocia and hyperbilirubinemia in the women or child during pregnancy (Figure 3).

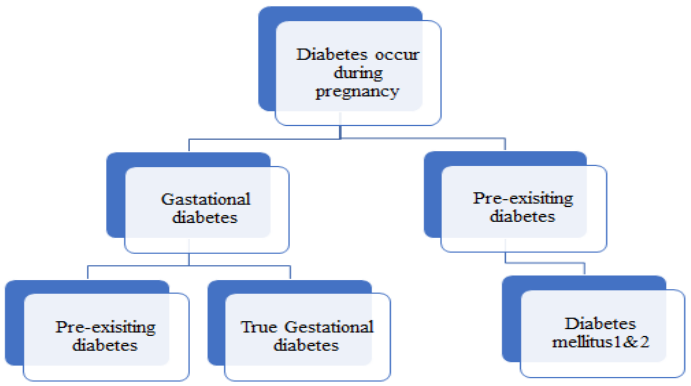


Figure 3: Hyperbilirubinemia in the women or child during pregnancy.

RESULTS AND DISCUSSION

Manganese analog of calcium ion (Ca^{2+}) enter into the beta cell through the voltage-dependent Ca^{2+} channel which leads to result in a strong signal of glucose-dependent in the beta islets and the cell lines (Table 1) (Figures 4 and 5).

Table 1: Marketed products available for diabetes.

Drug form	Generic name	Brand name	Drug class	Made by	Treating
Tablet	Metformin hydrochloride	Metformin	Biguanides	Takeda pharmaceuticals	Type-2
Injection solution	Insulin glulisine	Apidra	Insulin	Sanofi aventis	Type-1and 2
Tablet	Glimepiride	Amaryl	Sulphonylurea	Sanofi aventis	Type-2
Injection solution	Liraglutide	Victoza	Incretinmimetics (GLP-1 AGOINST)	Nova Nordisk Ltd	Type-2

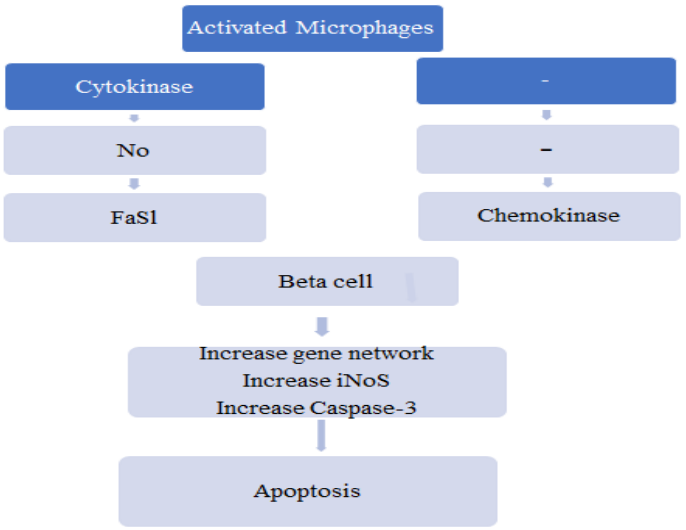


Figure 4: Mechanism of type-1 and type-2 diabetes T1dm.

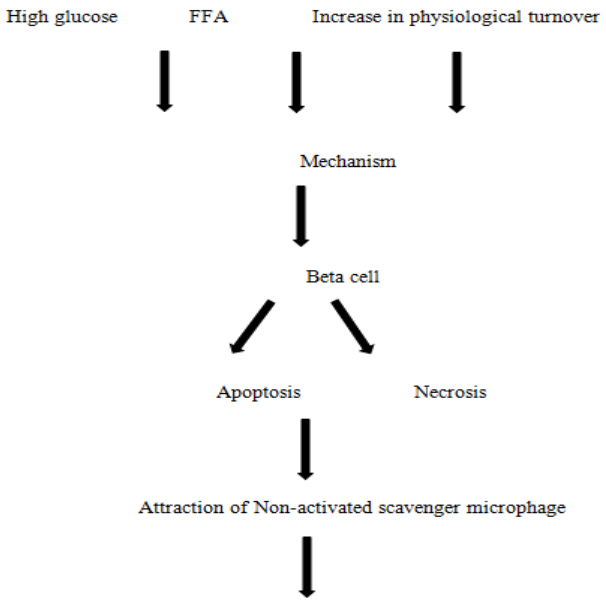


Figure 5: Imaging technologies used in diabetes.

MRI based on manganese contrast media

A concept study proves manganese enhance pancreatic signals on MRI images and can be used to distinguish between type 2 diabetes and normal-glycaemic patients. Manganese imaging can also help identify early changes that occur in the functioning of BCM during the beta cell destruction. The islets which varies in size (35 um -250 um) and which is distributed uniformly in the pancreas. Analysis and functioning of beta-cell islets mass

are challenging through MRI and CT. Sometimes a large dose of the Mn^{2+} or long exposure to the concentration of Mn_2^{+} may cause adverse effects such as (extrapyramidal dysfunction and may also cause temperature regulation malfunction).

Model: A mice having a high fat/high-sucrose diet (C57BI/6J).

Manganese based on PET probes

Positron emission tomography is the technique used to detect two coincident gamma rays which destroy the nearby present positron. PET has good imaging sensitivity as compared to the MRI Inherently not probing the anatomy but is used for probing physiological and these traces can target the specific tissue which can be used in the (clinical) analysis of the Beta Cell Mass functions. The radio manganese ($52Mn^{2+}$, t1/2: 5.6 d) is the tracer which used in the study of beta-cell noninvasively $52Mn^{2+}$ PET increase the beta-cell mass function of a model (ob/ob) of diabetes (type-2)

Model: Diabetes(type-1) mouse model in which STZ is induced.

Imaging of VMAT-2

Vesicular monoamine transporter 2 is the main source of circulating catecholamines (chromaffin cells) It is also expressed in the hematopoietic system and vesicular monoamine transporter 2 is primarily used for storage and release in synaptic terminals of various monoamine varieties (i.e., norepinephrine and serotonin). According to the previous studies it had been proved that Vesicular monoamine transporter 2 contains a high binding for the DTB2 dihydro-tetrabenazine which is an active metabolite of tetrabenazine (Figure 6).

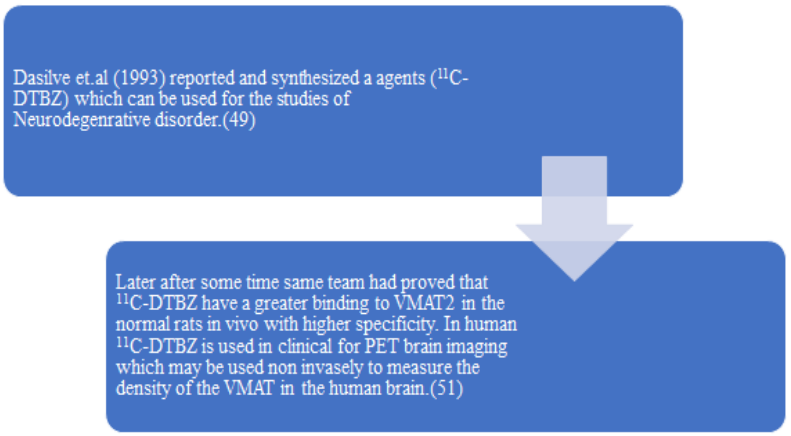


Figure 6: The studies of Neurodegenrative disorder.

After sometime (11C-DTBZ) had been used for the quantification analysis and functioning of beta cell mass in both the animals (rodents) and human. The disadvantage related to the agents is that's its half life 11C (t1/2:20 min) is short. This disadvantage can be overcome by labelling the agent with prolong live positron emitters so some of the compounds [18F-labelled] which are the analogues of DTBZ such as [18F-labelled] having the half-life of (t1/2=110 minute) [18F] Fluor propyl [FP]-DTBZ, [18F], [18F]-FE-DTBZ-d4[18F] fluoroethyl [FE]-DTBZ which had been discussed in the clinical and preclinical studies (Figure 7).

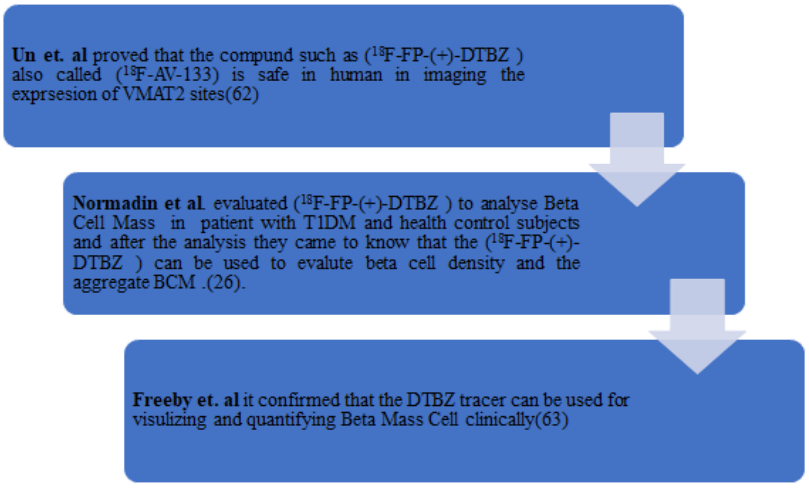


Figure 7: Safe in human in imaging the exprsesion of VMAT2 sites.

Disadvantages of VMAT2 targeting probes

Some of the studies proved that the (11C-DTBZ) and (18F-labelled) which are analog of DTBZ which are used for the imaging of the BCM are not suitable due to non-specific binding nature to the exocrine pancreas. Due to this reason, the VMAT2 targeting probe for imaging of beta cells has to be discontinued for some time.

Some Studies based on the Disadvantage of VMAT2

After some of the studies on the efficacy of the 11C-DTBZ and 18F-FB+(DTBZ) in targeting VMAT-2 and concluded that some of the latter tracers found which shows a non-invasive method to measure the beta mass cell. The author also reported that fast and high flow kidney cortex is a region: For imaging of beta mass cell in the animal model (rodents) because the variability uptake of tracer is less in the kidney cortex than the liver proved that the spleen has the lowest uptake of 18F-FP-(+)-DTBZ and is less affected by the radio metabolites and the partial volume effects and also suggested that the spleen can be the good practical reference region for measuring the beta mass cell using the F-FP-(+)-DTBZ PET.

The volume of the pancreas is smaller in the type 1 diabetes mellitus as compared to the non-diabetic patient. The small volume is the limitation of PET when imaging of the small structure of the single islets. The 90% of the beta-cell convey the VMAT-2 and 40% pancreatic polypeptide (Gamma cells) cells convey the VMAT-2. Overestimation of beta-cell measuring can be occurred because of binding (no-specially) of the F-FP-(+)-DTBZ to the polypeptide cells. The beta mass cell in the patient with type-1 diabetes is nearly to be depleted so the use of the agent like F-FP-(+)-DTBZ is lowered.

Imaging of (SUR-1) sulfonylurea receptor 1

The secretion of the insulin is mediated by membrane if the beta cell of the pancreas in the mammals or creatures. An increase in the calcium inflow, membrane depolarization, and insulin granule exocytosis caused due to increase in glucose level which causes inhibition of ATP-sensitive potassium channel in the plasma membrane. Hetero-octameric potassium channel having 4 inward rectifiers (k^+ channel) subunits and 4-sulfonylurea receptors subunits (SUR1, SUR2A, SUR2B). The symptoms of T2DM inpatient can be reduced by the use of SUR1, sulfonylurea which stimulates the secretion of the insulin in the absence of glucose. Sulfonylurea such as glibenclamide and tolbutamide had been a good candidate for beta-cell mass imaging.

Glibenclamide: Original molecule of glibenclamide shows a hepatic clearance and the liver uptake of radiolabelled glibenclamide was too high which was unstable for islet imaging. The novel glibenclamide is used for targeting pancreatic islet cells with high pharmacokinetics and biodistribution.

Studies: Schneider added a new moiety to the structure of glibenclamide and they synthesize a compound having high affinity show a high binding to sulfonylurea receptor-1 *in vitro* studies. In the *in vivo* studies, the compound (glibenclamide-glucose conjugate) showed that due to lower plasma protein binding its cause's fast clearance from the body circulation. The (glibenclamide-glucose conjugate) compound is used for developing other derivatives of glibenclamide for beta-cell imaging by targeting the sulfonylurea receptors. Repaglinide (medication is taken orally)-secretion of insulin by inhibiting the ATP-dependent potassium channel and also stimulating the Ca^{2+} channels of the beta-cell membrane Therefore, the Repaglinide also used for non-invasive Positron Emission Tomography imaging of beta cells.

Recently studies: Mitiglinide (novel) derivatives and reported that from all the compounds one of the compounds (+)-(S)-o-FMIT, had been accumulated in the pancreatic beta-cell and showed higher affinity towards sulfonylurea receptors by doing ex vivo autoradiography. From these studies, they also suggested that (+)-(S)-o-18F-FMIT may be the best candidate for beta-cell imaging (*In-vivo*) by the (PET) Positron Emission Tomography.

Imaging of glucagon-like peptide-1 receptor (GLP-1R)

Agonists of GLP-1R/GLP-1 pathway: After ingestion of food cause the secretion (GLP-1) in an intestinal cell which is an agonist of GLP-1R. Release and synthesis of the insulin in a glucose-dependent way is increased because of the activation of the Adenylyl cyclase pathway which leads to proliferation and neogenesis in the beta cell. For Imaging beta cells and treatment of diabetes, the peptide targeting GLP-1R is the best promising agent. The native peptide (GLP-1) endogenous is not suitable for imaging of beta-cell due to its degradation within a minute in (*in-vivo*) studies, so many studies had been made for the modification of GLP-1 to enhance its biological half-life and *In-vivo* efficacy. During the above studies, a stable compound is isolated from the salivary gland of (Lila Monster) Lizard(GLP-1R agonist) extended-4 (Exenatide) which binds to a domain (extracellular) of GLP-1R with a not comparable affinity.
Some of the uses of Exendid-4:

- As agonist (GLP-1R) for the T1DM (98-100).
- Used in nuclear medicines, fluorescence, and imaging of beta-cell mass (101-108).
- Used for determining Beta-cell mass (97-109).
- Exendid based Positron emission tomography and SPECT probes.

Studies made by Gotthardit and co-authors in this they synthesized an analog of (111In labeled) exendid-4 that is (111In-DTPA-Lys40-exendin-4) and analyzed its *in-vivo* efficiency in the rat and mice models. By imaging with SPECT *In-vivo* in the high resolution, they reported and suggested that uptake of the tracers in the pancreas, stomach, adrenal glands, lungs and the pituitary glands.

Further studies

Tested a probe Exendid for beta-cell imaging of the pancreas. Large amount concentration is found in the lungs and secondly in the pancreas (9-39) and this is a helpful probe for beta-cell imaging. After a while, the same author with his group had found a different probe exendin-4 suggested that this can be used for non-invasive visualization and measurement of beta-cell and beta mass cell with SPECT imaging. Recently studies showed that *in-vivo* injection of (111In-labelled) exendid-3 had shown some specific targeting to the beta-cell which can be used for quantification analysis and visualization (non-invasively) of beta mass cell in the pancreas of human, healthy person and rodents. Reported that it is difficult to analyze images of SPECT for pancreatic beta-cell imaging so for quantification analysis of beta mass cell a method should be developed so a solution for this had been made by developing a method in which a three-dimension printed Phantom images were used for the quantification of the pancreas. Show that lower in the uptake of 68 Ga-DO3A-VS-Cys40-exendin4 (68Ga-DO3A-exendid-4) in the rats (which are STZ induced diabetes rats) as compared to the non-diabetics rats. From the same group a study reported and suggested that accumulation in the pancreas of imaging agents had failed to distinguish a difference in diabetic and non-diabetic these studies show that GLP-1R is seen in the diabetes pancreas pig's cells in some of the amounts. It had seen that high retention of tracers was accumulated in the lung (bilateral) of diabetes pig and no uptake of the tracer was seen in the porcine liver so they suggested this tracer can be used as an alternative agent for imaging of glucagon-like peptide-1receptor expressing beta-cell implanted to the liver. All these studies and the studies given by Willekens. It can be learned that animal models show greater efficacy in targeting

beta-cell probes (*In-vivo*) studies for the quantification of the beta mass cells.

Molecular Imaging with beta cell-specific antibodies

The requirement of the beta-cell imaging may be done by the beta-cell antibodies and humanized high-affinity fragments when conjugation with the radioactive isotopes. From the reported study it had been suggested that radiolabelled monoclonal antibodies can be used for targeting the pancreatic beta-cell and this ability of the radiolabeled monoclonal antibodies to bind to the beta-cell and developing antibodies based imaging probes. It shows a promising treatment for the imaging and is also important for the analysis of the beta mass cell. On the beta cell surface, the transmembrane protein is express due to the stimulation of the pancreatic beta-cell proliferation and may be used for the pancreatic beta-cell mass as a potential marker. In the human and in animals model the author had suggested many strategies of imaging for targeting the beta cell by using mAb (8 mAb /9-mAb) which are specific to human TMEM2, some of the specificity of (8 mAb /9-mAb) for specific to human TMEM27 shows limitation for their use in the beta mass cell in the animals model in preclinical studies. An IC2 rat was discovered 30 years ago for the specific binding to the insulin granule. It has been now used for imaging off beta cells *in-vivo*.

Studies: Targeting of the beta cell. IC2 has been labeled with 111In after the conjugation with DTPA both for *in-vivo* and *in-vitro* studies for the specific targeting of 111In DTPA-IC2 to the surface of the beta-cell. The studies also reported and suggested that the uptake of agents like 125I-labelled IC2 found directly co-related with the beta mass cell in the normal and diabetic animals. Due to the large size of the probe, it shows slow blood clearance so it may not be used in the clinical studies for the human diagnostics. The antibodies with the single-chain show a high uptake in the pancreas and also shown an immediate blood clearance. Colleagues and Ueberberg they have shown that 125I-labelled single-chain antibodies can be used for the monitoring of the beta mass cell in the rats.

Studies: An antibody developed using the 125I that is (zinc transporter 8 ZnT8) and reported its affinity of binding to the pancreas and insulinomas was higher than (125I-labelled)exendid-4. These above studies and results show that the single chain and the antibodies are the best alternatives for beta-cell imaging.

Molecular imaging of insulitis

In type-1 diabetes mellitus, there is the destruction of the beta-cell in pancreatic islets of the Langerhans by the infiltration of lymphocytes. In type-1 diabetes mellitus, there is microvasculature alteration, Inflammatory Infiltration and autoimmune destruction of the beta-cell. In Type-1 diabetes, the occult phase is considered to be the microvasculature alteration and lymphocytes infiltration within around the pancreatic islets while the overt phase is considered to be the destruction of the beta-cell by the T cells. Molecular imaging of the insulitis may provide early information regards the destruction of the beta-cell completely. Some approaches such as the pancreas biopsy or the serum test which can be used for the detection of the insulin this test cannot be performed repeatedly due to its invasive use. This limitation can be overcome by the non-invasive technique for the quantification of the beta mass cell (Figure 8).

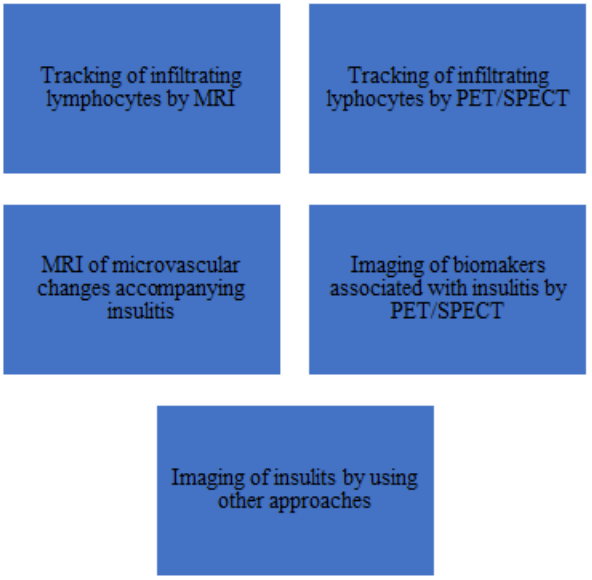


Figure 8: Tracking of infiltration lymphocytes by MRI.

In the initial phase of Type-1 diabetes mellitus, there is an infiltration of lymphocytes and slowly destroying the beta-cell into the islets. Therefor the non-invasive *in-vivo* method for visualizing of the infiltration of lymphocytes may be used for identifying the pre-diabetic patient. For the *In-vivo* tracking of lymphocytes, the MRI is one of the most used methods. The lymphocytes may be labeled as antigen-specific or antigen un-specific labeling strategies.

Studies: In the isolated and labeled lymphocytes from a Non-obese mouse (diabetes) with Cross-Linking of Iron-Oxide nanoparticle derivatives with translocation membrane signal (CLIO-TAT). After the intravenous, it has been clearly labeled that the cell used the MRI technique in the pancreatic of the cell. The limitation of this clinical is that the MR signals cannot be quantified and this doesn't allow tracking of recruitment of the autoreactive lymphocytes as these strategies of the labeling is not antigen-specific. It can be demonstrated successfully that tracking of the lymphocytes (*in-vivo*) in diabetes containing mouse model. A similar group after the studies had improved the method used by the antigen-specific magnetic labeling. In this, the above author and group had improved the method that super-magnetic nanoparticle was coated by the NOD relevant V7 peptide and some of the Major Complex Class-I (MHC-I) which allowed the CD^{8+} T cells which are antigen-specific which had been isolated from the transgenic mice (NOD), not from the T cell of healthy mice. The MRI used for successfully visualizing the inflammation of the islets of pancreases with the help of the auto reactive T cells.

This author used nanoparticles having negative surface charge (anionic magnetics nanoparticles) for effective labeling of T cells. The author used the MRI for monitor the population of the T cells in situ up to twenty days after the transfer into the NOD mice in this author suggested that cells (T) can be labeled in pancreatic lymph node and imaging can be done by a non-invasive technique in the Type-1 diabetes mellitus.

Tracking of Infiltration lymphocytes by PET/SPECT

The *In-vivo* imaging of the whole body is frustrating because of its lesser possibilities for labeling of lymphocytes with the required amount of the contrast agent for analysis by MRI technique due to its toxicity in higher concentration or its limited coupling efficiency. It is very hard to generate high MRI signals outside the body. In imaging technique such as PET and SPECT, the radiolabelled lymphocytes are enough for the *In-vivo* studies. In *ex-vivo* radiolabelling of cells in this the approach involves are 99mTe-hexamethyl propylene amine oxide, "In-oxine", In-tropolonate for the SPECT and 18F-FDG and 64cu 189 Zr-antibodies for the PET *in-vivo* (Figures 9 and 10).

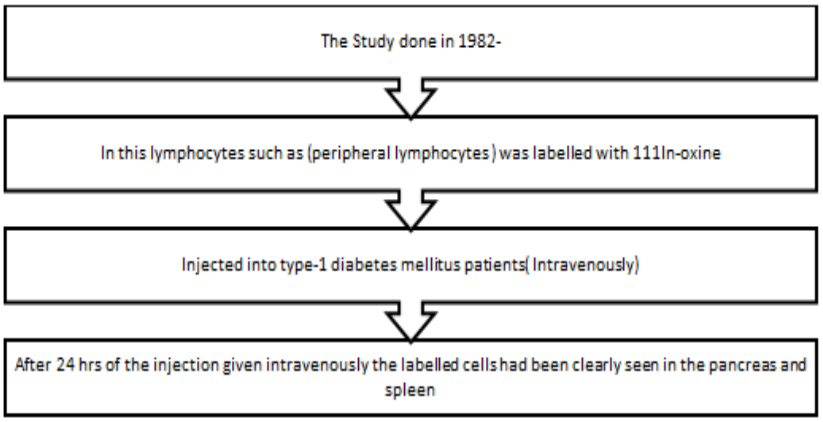


Figure 9: The lymphocytes tracking in diabetes has been seen in some of the studies.

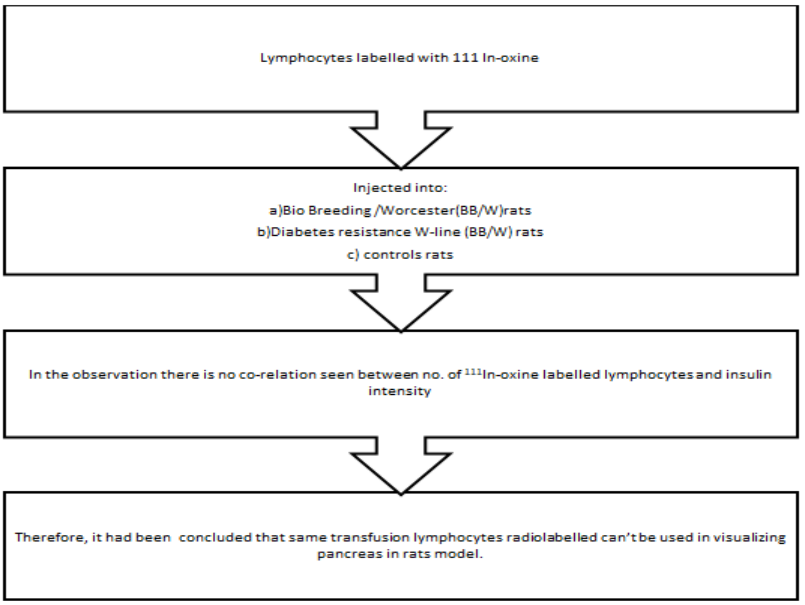


Figure 10: Lymphocytes labelled with 111 In-oxine.

The approach used in the above study was failed, the reason behind the failure of the approach was the use of radiolabelling of lymphocytes for *In-vivo* detection of the insulitis for more than 30 years ago and due to its low resolution of the SPECT imaging technique used in this studies.

MRI of the changes of microvascular in the insulitis (check it once)

The inflammation of the pancreas can be caused due to microvascular dysfunction which leads to alteration in the vascular volume, vascular permeability and the blood flow. Micro vascular abnormalities in the areas of the islets (pancreas) are the earliest symptoms and which can be earlier diagnosed and can be monitored in the type-1 diabetes mellitus (Figure 11).

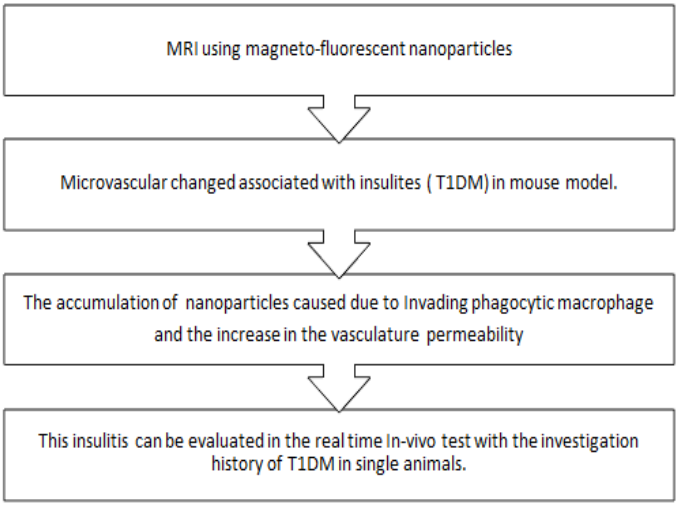


Figure 11: MRI using magneto-fluorescent nanoparticles.

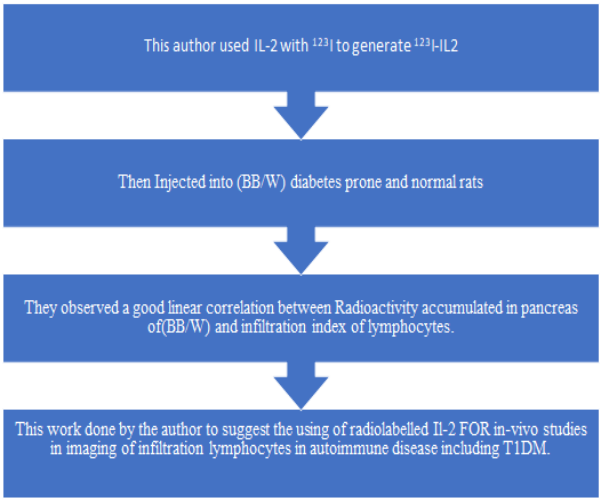
A similar study done for the non-invasively monitoring the autoimmune inflammation caused in the live mouse pancreas and the same MRI imaging technique was used, After the therapy of anti-CD3 performed in the NOD mice and had reported a reversal in diabetes. Using the contrast agent such as protected graft polymer which Is covalently linked to a gadolinium-diethylenetriaminepentaacetic acid residue which has been labeled with fluorescein isothiocyanate (PGC-GdDTPA-F) a non-invasive MRI had been performed for the microvascular change in the streptozotocin-induced mouse model, a high accumulation of the contrast agent seen in the pancreas of the animals having diabetes by the T1 weighted MRI imaging. For the studies of T1DM in the animal tested a clinical study was performed using MRI with ferumoxtran-10 to visualize the insulitis in the patient with the onset of diabetes. An MNP molecule was used with the dextran coating the size of the molecule was the same as the size of particle used in the animal's experiment.and the molecule ferumoxtran-10 was used for the detection of the occult lymph node in the prostate cancer by the non-invasive method. For the clinical studies of the MRI, it involves 10 patients with T1DM and about 12 non-diabetes patients. Upon the migration of the ferumoxtran-10 form the leaky vessels and the phagocytosis by the macrophage cell, it would be predicted that MRI would be used to detect the ferumoxtran. The MRI technique with the ferumoxtran-10 can be used to detect the T2 signals in the pancreatic parenchyma which may be used effectively for the visualization of the pancreas and to find the difference in the diabetic and non-diabetic patient. Later on, a similar group had demonstrated that the ferumoxytol an MNP approved by the FDA which has been used for the early marking of inflammation in the pancreas, the MRI technique can be used for the detection of the pancreatic inflammation. For the diagnosis and treatment of diabetes, the MRI-MNP can be used to advance the basic research. Example- MRI-MNP can be used as a sensitive prediction tool for the detection of diabetes in the NOD mouse model.

PET/SPECT imaging of biomarker associated with insulitis

The *In-vivo* imaging of the lymphocytes infiltration in the insulitis depends on the high sensitive imaging technique such as PET and SPECT because of the following reasons:

- In insulitis, there is very less amount of lymphocyte infiltration.
- The low number of biomarker is expressed in the lymphocytes.

For the molecular imaging of the insulitis, there are very few biomarkers. Interleukin-2(IL-2) is the most and widely studies biomarker. The IL-2 receptor is highly found on the surface of the T-lymphocytes in the chronic auto-immune disease. Radiolabelled IL-2 used for the In-vivo studies in the detection of the IL2-receptor. The 123I-IL-2 and 99m TC-IL-2 are the most widely used IL-2 imaging agents for the diagnosis of chronic autoimmune disease.



In later studies, the author tested the IL-2 both in the animals and in the patient with T1DM, this test has shown that the contrast media was highly up-taken by the pancreas and suggested that the 123I-IL2 agent can be used in the SPECT imaging of the infiltration lymphocytes which are been associated with Insulitis. After this studies the agent IL-2 was labeled with 99mTC to form 99mTc-IL-2.

IL-2 + 99mTC 99mTc-IL-2

Then the 99mTc-IL-2 was tested in about 40 newly diagnosed T1DM patient before and after the treatment, It has been seen that 31% of the patient had shown pancreatic accumulation of 99mTc-IL-2. The patient containing the (99mTc-IL-2) agent the requirement of the insulitis and inflammation of the pancreas caused was reduced by nicotinamide after 1-year treatment. This above study suggested and reported that the 99 mTc-IL-2 can be used to access the autoimmune phenomenon in the endocrine of the pancreas, Some of the recent studies shown that the 99 mTc-IL-2 can be used for SPECT imaging in the patient with LADA, pancreatic cancer, T1DM, T2DM. From the above study, it was reported that the 99 mTc-IL-2 SPECT imaging can be used to identify (CD^{25+}) lymphocytic infiltration in the patient having T1DM, T2DM, LADA, and pancreatic cancer, allowing the patients for non-invasive monitoring in the autoimmune diabetes condition. The large scale studies on this agent yet to be needed for the confirmation of finding. The SPECT IL-2 was labeled with 18F for the PET imaging of T lymphocytes to find-out the limited resolution of SPECT IL-2 these studies are not yet performed in the patients.

Imaging of glucose uptake by various tissue

Many Imaging technologies are used for studying the role of the blood flow and the perfusion in the glucose uptake by various tissue of the body including the tissue such as skeletal muscle and adipose tissue. The majority of the insulin-stimulated glucose uptake after the meal or the glucose load is done in the skeletal muscle. Some of the imaging techniques used to visualize the glucose uptake are Contrast-enhanced ultrasound technique which revealed that the skeletal muscle capillaries are rapidly opened by the insulin to take up the glucose. The decrease in the microvascular perfusion rate and the skeletal muscle capillaries density are reported in a human in diabetic condition and this is identified using various imaging techniques such as side stream dark-field Imaging, PET and ultrasound and tracers such as 15O-H_2O or 18F-fluorodeoxyglucose (18F-FDG). This imaging technique revealed that in healthy people there is an increase in the bronchial artery diameter and Blood flow in the skeletal muscle due to an increase in the insulin but it is not seen in an obese patient. This Imaging suggests that diabetes and glycose dysregulation can be caused due to cardio-vascular disease such as cardiac insufficiency and hypertension with reducing blood perfusion in tissue. This shows a reciprocal relationship between both diabetes and cardiovascular diseases. In the insulin resistance mice of skeletal muscle, it has been revealed that GLUT-4 translocation was impaired. In the imaging of GLUT4-GFP. The main glucose transporter In the liver is the GLUT-2 and the repression of the hepatic glucose uptake due to the deletion of the GLUT-2 from the liver but not the HGP in the mice. Some studies showed that translocation in hepatocytes and in regulating the GLUT expression insulin and glucose plays an important role. In an imaging study done by PET using 18F-FDG the uptake of the glucose rate is subject to encoding key upstream molecule of GLUT translocation and loss of function mutation, AKT2 was mainly reduced in the liver (16.1%), In BAT (29.7%) and skeletal muscle (36.4%). Some of the studies done using PET imaging with tracers shows:

- PET imaging using 18F-FDG, 15O-H_20, 11C-3-O-methyl glucose as tracer revealed that insulin glucose uptake in skeletal muscle was weak in the obese patient as compared to normal in the patient with newly T2DM.
- PET Imaging using 18F-FDG shown that Rosiglitazone,(TZD) Thia Zoli Dinedione, not the metformin shows increase insulin and stimulated glucose uptake in the skeletal muscle. The mass and the force of the skeletal muscle were reduced in the insulin-resistant patient and the patient having diabetes when demonstrated under imaging system such as MRI Dual-Energy X-ray Absorptiometry (DEXA). The loss in the skeletal muscle in a diabetes patient can be reduced with the help of insulin sensitizers such as the (TZDs) and metformin.

PET imaging using 18F-FDG or 15O-H_2O had shown that the (BMI) Body Mass Index is negatively been co-related with the uptake of the glucose in the skeletal muscle and the adipose tissue, and the weight loss may increase the glucose uptake and the insulin sensitivity in the skeletal muscle of the obese patient with or without diabetes. Resistance to insulin sensitivity in the obese mother can be an increase in skeletal muscle. The scanning of DEXA shows that in the patient with T2DM there is an increase in insulin sensitivity and mass muscle due to resistance to exercise. This above imaging finding suggested that moderate or medium physical exercise shows a beneficial effect on hyperglycemia by increasing or maintaining the mass muscle in a patient with diabetes. The main site for thermogenesis is BAT and reduces the activity of the BAT due to T2DM and obesity. Exposure to cold can activate the activity of BAT. The BAT activity was rapidly increasing when imaging through PET/CT using 18F-FDG and the activity of BAT also decrease gradually by rewarming. Due to exposure to cold which increases or improves glucose metabolism by stimulating the BAT activity in the human as reported by the PET/CT imaging with 18F-FDG studies.

Rosiglitazone and Pioglitazone the PPARg agonist have hypoglycaemic effects. The side effect caused due to PPARg is gain in the weight. From the study made using PET imaging 18F-FDG as a tracer, they suggested that the glucose in the subcutaneous adipose tissue was stored in the form of triglyceride, ameliorating hyperglycemia mainly in humans. The treatment with Rosiglitazone in T2DM patients shows an increase in adipose glucose uptake by using PET imaging with 18F-FDG or 15O-H_20 as a tracer. From these studies finding it shows that PPARg agonist mainly targets to adipose tissue for decreasing the glucose level while metformin shows hypoglycaemic effect by targeting the liver in the diabetes patient, so the non-invasive imaging technique of glucose uptake by various tissue in the combination with insulin level and fasting blood glucose may show strategies for effectively evaluating the risk of T2DM in high population.

Imaging of hepatic glucose production

There is an increase in the HGP due to fasting *via* glycogenolysis and gluconeogenesis after the stimulation od glucagon essential for maintaining the euglycemia. In the past year many imaging techniques were used to determine the HGP and the changes in the glycogenolysis and gluconeogenesis occur during diabetes in the human.

CONCLUSIONS

- 13C-MRS found that after the administration of galactose there is an increase in the HGP rate in humans by 3 fold in the first 15 mins and then returned to its baseline.
- 2H-13C-MRI founded that the HGP rate in the healthy human was observed to be 10.79mmol kg^{-1} min^{-1}+0.9mmol kg^{-1} min^{-1}.
- Shulman's group using 13C-MRI had determined the role of glycogenesis and glycogenolysis in the production of glucose in a healthy subject. The gluconeogenesis was 60% and the glycogenolysis was 40% during the first 12 of the fasting in healthy humans. The author also demonstrated that there was 64% of gluconeogenesis of overall glucose production during the 22 hours of the fasting in humans. There was an increase in about 82% to 96% in the glucogenesis during 114 hrs to 18 hrs period of fasting. In healthy women, there was 60% glycogenesis demonstrated by overnight fasting using the 2H-MRI. From the above studies overall it was concluded that glycogenesis leads to the production of glucose during long term fasting in humans.
- MRI with multiple tracers ([3-4-13C2]glucose, 2H_20 and [U-13C3] propionate) suggested and reported that there is a decrease in glycogenolysis and increase in hepatic gluconeogenesis by 3-d feeding of a high fast diet with affecting the production of glucose in the

human. The above finding provides direct evidence that an increase in HGP and hyperglycemia due to an increase in gluconeogenesis during over nutrition. The above study also provided the rationale that the metformin exerts hypoglycaemic effect by suppressing the HGP which leads to delay or prevention of the onset of the T2DM in the patient with pre-diabetes.

- 18F-FDG demonstrated that there is an improvement in the hepatic insulin resistance, suppressed HGP and enhancement in the HGO in males after the administration of the exenatide (GLP-1) receptor agonist. In the patient with Bariatric surgery by PET using 18F-FDG, they visualized that there is the reduction in the HGP after the 6 months of surgery.
- These above studies finding suggested that increase in the HGP is the event in the development of the fasting hyperglycemia in the human.

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