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CASE STUDY

ARTIFICIAL PANCREAS SYSTEM: AN EFFECTIVE APPROACH FOR TREATMENT OF DIABETIC COMPLICATIONS (DIABETIC NEPHROPATHY)

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ABSTRACT;

Diabetes mellitus along with diabetic complication (diabetic nephropathy) is well documented. There are few studies regarding Artificial pancreas treatment, which is the only FDA approved treatment for safe and effective way to stop and to reverse the chronic life shortening complications of diabetes. Here our main motto is to report such a case, who was presented with diabetic complication (particularly diabetic nephropathy) and undergoing treatment with artificial pancreatic system & to explain briefly with what mechanism does the artificial pancreatic system is effective in treatment or controlling the diabetic complications.

Key words: Diabetes mellitus, diabetic nephropathy, artificial pancreas treatment.

INTRODUCTION;

DIABETES MELLITUS;

Diabetes mellitus is a group of metabolic diseases in which a person has high blood sugar, either because the pancreas does not produce enough insulin, or because cells do not respond to the insulin that is produced¹.

There are three main types of diabetes mellitus (DM).

Type 1 DM results from the body's failure to produce insulin, and currently requires the person to inject insulin or wear an insulin pump. This form was previously referred to as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes".

Type 2 DM results from insulin resistance, a condition in which cells fail to use insulin properly, sometimes combined with an absolute insulin deficiency. This form was previously referred to as non insulin-dependent diabetes mellitus (NIDDM) or "adult-onset diabetes".

The third main form, gestational diabetes, occurs when pregnant women without a previous diagnosis of diabetes develop a high blood glucose level. It may precede development of type 2 DM.

The main symptoms associated with diabetes mellitus are loss of weight, polyuria (frequent urination), polydipsia (increased thirst), and polyphagia (increased hunger)².

The main complications associated with diabetes mellitus are³:

- Coronary heart disease, which can lead to a heart attack

- Cerebrovascular disease, which can lead to stroke
- Retinopathy (disease of the eye), which can lead to blindness
- Nephropathy (disease of the kidney), which can lead to kidney failure and the need for dialysis
- Neuropathy (disease of the nerves), which can lead to, among other things, ulceration of the foot.

Diabetic nephropathy is a clinical syndrome characterized by albuminuria, hypertension, and progressive renal insufficiency⁴. It is characterized by nephrotic syndrome and diffuse glomerulosclerosis⁵.

The main signs and symptoms of diabetes nephropathy are;

- Albumin or protein in the urine
- High blood pressure
- Ankle and leg swelling, leg cramps
- Morning sickness, nausea, and vomiting

CASE REPORT;

A 44 yrs old man was admitted to Malla Reddy-Narayana medical college hospital and research center, Suraram with chief complaints of high blood pressure, ankle and leg swelling. This patient was a known diabetes mellitus which was previously diagnosed and undergoing treatment for past 11 years. He is an employee in manufacturing industry for past 7 years. He is on following treatment with Humalin-30/70 and in social history he is alcoholic and non-smoker.

LAB INVESTIGATIONS:

Complete Blood Picture	Liver Function Test
Hb(g/dl) (M-11-16 F-11-14) : 10.5--- decreased RBC(millcells/cumm)(4-6.5) : 3.5--- decreased WBC(cells/cumm)(4000-11000) : 7,500 Differential Leukocyte Count Neutrophils(40-75%) : 65% Lymphocytes(20-45%) : 30% Eosinophils(01-06) : 5% Monocytes(02-10%) :2% Basophils(upto 1) : Platelet Count(1.5-4.5lakhs/cumm) : Adequate Peripheral Smear RBCs : WBCs :	Serum Bilirubin Total(upto 1mg/dl) : 0.7 Direct (upto 0.25mg/dl) : N Indirect : SGPT (upto 65 IU/L) : 44 SGOT (upto 37 IU/L) :33 Alkaline Phosphatase(15-116 IU/L) : 110 Total Proteins (6-8gm/dl) : 7 Albumin (3.2-5.8gm/dl) : N Globulin (2.2-4.8gm/dl) : N
ESR (M-0-10mm/hr F-0-20mm/hr) :	Lipid Profile (mg/dl)
Urine Analysis	Total Cholesterol (140-250) : 220 HDL Cholesterol (30-65) : 45 LDL Cholesterol (80-180) : 90 VLDL Cholesterol (5-45) : 35 Triglycerides (25-160) : 140 TC/HDL Ratio (upto 4.5) : N
Color : pale yellow Appearance : Pus Cells : no Albumin : 295 mg/day ----- INCREASED Epithelial Cells : no Glucose : RBC :	Biochemical Investigations (mg/dl)
Thyroid Functions Test	Serum Creatinine (0.6-1.4) : 2.2 mg/dl--- INCREASED Blood Urea nitrogen (14-45) : 48----- INCREASED
T ₃ (60-181 ng/dl) : N T ₄ (7.3-15µg/dl) : N TSH (0.55-4.78µIU/L) ;N	

DISCUSSION;

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. In this present case, the patient had a past history of Diabetes mellitus, which was previously diagnosed and undergone treatment for past 11 years. He is on following treatment with Humalin-30/70.

Currently, the patient was admitted in the hospital with chief complaints of high blood pressure, ankle and leg swelling. When the patient blood parameters were investigated, it was founded that there was a increase in albumin in urine (albuminuria), serum creatinine and blood urea nitrogen. With the subjective (symptoms) and objective (lab investigation) data, the patient was diagnose with Diabetic nephropathy. Although patient's blood glucose levels were controlled to some extent by using humalin and other medications, there was a difficulty in controlling complication of diabetes mellitus.

The pathogenesis of diabetic complications (diabetic nephropathy) are;

1. Non-enzymatic protein glycosylation (Vascular)
2. Polyol pathway mechanism. (metabolic)

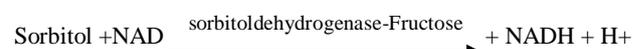
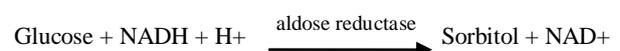
Non-enzymatic protein glycosylation;

The free amino group of various body proteins binds by non-enzymatic mechanism to glucose; this process is

called glycosylation and is directly proportionate to the severity of hyperglycaemia. Various body proteins undergoing chemical alterations in this way include haemoglobin, lens crystalline protein, and basement membrane of body cells. There is accumulation of labile and reversible glycosylation products on collagen and other tissues of the blood vessel wall which subsequently become stable and irreversible by chemical changes and form advanced glycosylation end-products (AGE). The AGEs bind to receptors on different cells and produce a variety of biologic and chemical changes e.g. thickening of vascular basement membrane in diabetes, which gradually leads to microangiopathy and decreases the blood flow and oxygen supply to renal cells and final leads to nephropathy⁶.

Polyol pathway mechanism;

This mechanism is responsible for producing lesions in the aorta, lens of the eye, kidney and peripheral nerves. These tissues have an enzyme, aldose reductase, which reacts with glucose to form sorbitol and fructose in the cells of the hyperglycaemic patient as under:



Intracellular accumulation of sorbitol and fructose is produced results in entry of water inside the cell and consequent cellular swelling and cell damage. Also,

intra-cellular accumulation of sorbitol causes intracellular deficiency of myoinositol which promotes injury to Schwann cells and retinal pericytes. These polyols result in disturbed processing of normal intermediary metabolites leading to complications of diabetes⁷.

With the above mechanisms diabetes mellitus (high blood sugar) mainly induces or exacerbate the diabetic nephropathy.

It just came to know regarding the revolutionary artificial pancreatic system. The artificial pancreas is a technology developed to help the people with diabetes to automatically control their blood glucose level by providing the substitute endocrine functionality of a healthy pancreas.

The goals of the artificial pancreas are:

1. To improve insulin replacement therapy until glycemic control is practically normal as evident by the avoidance of the complications of hyperglycemia, and
2. To ease the burden of therapy for the insulin-dependent.

The patient was recommended to undergo artificial pancreatic system treatment, it was observed that there was a significant improvement in patients serum glucose levels, creatinine, albumin levels and restored kidney function to some extent during undergoing artificial pancreatic treatment(2nd sitting, 1 week gap will be given for each sitting).

The main mechanism that was underlying in effective treatment of diabetic nephropathy by artificial pancreatic system compared to insulin pump is;

Generally, when a person eats carbohydrates (e.g. sugar), the pancreas sends oscillating pulses of insulin to the liver. For induction and maintenance of insulin-dependent enzymes essential for glucose metabolism in the liver (e.g. hepatic glucokinase, phosphofructokinase, and pyruvate kinase), the hepatocytes require a defined insulin level (200-500 $\mu\text{U}/\text{ml}$ in the portal vein) concomitant with high glucose levels (which acts as a bimolecular signal). The liver responds to this unique pulse pattern (insulin) by making activation of some 33 different enzymes needed by the cells of the body to metabolize carbohydrates. Carbohydrate metabolism creates adenosine triphosphate - the chemical energy all cells require to accomplish their functions in the body⁸.

But, for patients with diabetes mellitus (type 1 & type 2) their liver will not receive correct oscillations and concentrations of insulin from the pancreas. Therefore, the liver does not produce and/or secrete the enzymes required for proper metabolism. Improper metabolism mainly leads to high blood sugar and causes diabetic

microangiopathy. Microangiopathy causes the walls of very small blood vessels (capillaries) to become so thick and weak that they bleed, leak protein, and slow the flow of blood⁹. Diabetics may develop microangiopathy with thickening of capillaries in many areas including the eyes, feet, legs, and kidneys¹⁰.

Artificial pancreas system mainly sends oscillating pulses of insulin to the liver and activates the insulin-dependent enzymes essential for glucose metabolism in the liver (e.g. hepatic glucokinase, phosphofructokinase, and pyruvate kinase). The liver responds to this unique pulse pattern by making some 33 different enzymes needed by the cells of the body to metabolize carbohydrates. Carbohydrate metabolism creates adenosine triphosphate - the chemical energy all cells require to accomplish their functions in the body.

Artificial pancreas system mainly restores the proper carbohydrate metabolism through secretion of insulin via portal veins in to liver and activates the insulin dependent enzymes for carbohydrate metabolism, which is difficult to achieve with the insulin replacement pumps. Due to proper carbohydrate metabolism through artificial pancreatic system there will be decrease in glucose mediated non enzymatic protein glycosylation and polyol pathway and finally inhibits the renal damage or diabetic nephropathy.

In this present case, after the artificial pancreatic system treatment it was observed that there was a significant improvement in patients serum glucose levels, creatinine, albumin levels and restored kidney function to some extent during undergoing artificial pancreatic treatment(2nd sitting, 1 week gap will be given for each sitting).

CONCLUSION;

According to our study we conclude that the insulin replacement (through insulin pumps) mainly helpful in maintaining blood sugar levels in a safe range, but it does not show any effect on the carbohydrate metabolism. Normal insulin pumps which is delivered other than intravenous route cannot achieve normal momentary concentration in hepatic portal veins due to which the insulin mediated enzymes are not activated and mainly results in improper carbohydrate metabolism and finally results in diabetic complications. But whereas artificial pancreas mainly simulated insulin pulses are delivered intravenously. Within 4 seconds, the defined insulin level (200-500 $\mu\text{U}/\text{ml}$ in the portal vein) concomitant with high glucose levels (which acts as a bimolecular signal) enters in to the liver through hepatic portal vein and activates the insulin-dependent enzymes which are essential for glucose metabolism in the liver (e.g. hepatic glucokinase, phosphofructokinase, and pyruvate kinase). These activated enzymes mainly help full in maintaining proper carbohydrate metabolism and generation of ATP, require accomplishing the cellular functions in the body.

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