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DEVELOPMENT OF PRE-CLINICAL DIABETIC MODEL USING PARTIAL PANCREATECTOMY IN SWISS ALBINO MICE- A BRIEF UPDATE

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Abstract

Pancreatectomy is the surgical removal of the pancreas. It may be total or partial. In case of total pancreatectomy whole pancreas is removed and partial mentioning is the elimination of part of the pancreas. For studies on diabetes, a large number of pharmacological agents, various surgical models and animals' models are used to understand the pathogenesis, complications, genetic and environmental influences. Pancreatectomy induced diabetic model being one of them. Work done so far deals with the restoration of euglycaemic status in 30% partial pancreatectomy-cyclosporine induced diabetic model. In this study, Pancreatectomised group of animals showed a rapid improvement of glycaemic status, starting from 15th post observational day, but the level of significance decreased gradually from 15th to 60th day. This was probable due to nesidioblastotic activity. Cyclosporine treated group of mice showed normal glucose level throughout the whole experimental period, but cholesterol level remained significant till the end of the experimental day. Gradually decrements in glycaemia of the diabetic pancreatectomised animals demonstrate islets neogenesis occurring after the operative activity, leading to normoglycaemic condition, probably attributed to β-cells proliferation.

Keywords: *Pancreatectomy, Pancreas, Diabetes, Cyclosporine, Glycaemic status, Nesidioblastotic activity, Islets neogenesis, Normoglycaemia.*

Introduction

Diabetes is a metabolic disorder, characterized by hyperglycaemia that has become a serious problem of modern society due to the severe long-term health complications associated with diabetes mellitus. It is an endocrinological disease originating from lack of insulin or due to effectiveness of insulin produced by the body. Around 200 million people of the world are presently suffering from diabetes and the figure is designed to increase to 300 million within 2025 as per the survey of world health organization. Diabetes is of two major types, namely type-1 or insulin dependent diabetes mellitus (IDDM) occur due to autoimmune destruction of pancreatic β-cells and type-2 or non- insulin dependent diabetes mellitus (NIDDM) occur due to β-cell of pancreas does not secrete sufficient insulin for proper function, or the cells within the body (insulin receptor) do not react to insulin (insulin resistance). In generally, type-2 diabetes mellitus (T2DM) is the most detected form of diabetes, accounting for more than 80% of the total case of diabetes. Defects in the glucose metabolism are major factors leading to diabetes. The insulin secreted by the pancreatic β-cells is the key hormone responsible for glucose homeostasis [1]. Insulin stimulates hepatocytes, myocytes, and adipocytes to uptake glucose from the circulatory system into fat and adipose tissues. Depending on need, glucose can either be used as a powerful source by glycolysis, or stored as glycogen inside muscle or liver cells. The improper utilization of insulin leads to insulin resistance, which is characterised by the ineffectiveness of cells to respond to normal levels of circulating insulin, thus leading to the occurrence of the diabetes [2]. Diabetes has an ancient origin. Susruta, father of Indian medicine, diagnosed diabetes mellitus as early as 1000 B.C. Ayurveda mentioned that insects were attracted to the urine of some people and the urine tasted sweet. Greek physicians enlightened the diagnosis of "dypsacus"(diabetes) associated with weakness of the kidneys and excess moisture from the body, leading to dehydration. In 1922 the discovery of insulin by Banting and Best formed the key milestone in the treatment of diabetes mellitus. Globally diabetes affects 246 million people and is expected to affects 346 million by 2030. At least 7 million new cases are reported annually. India accounts for largest diabetic population with 41 million patients, mounting to 6 percent of the adult population [3, 4]. A number of experimental diabetic models have been grown in last three decades such as type-1 diabetic model, type-2 diabetic model, type-3 diabetic model and type-4 diabetic model. In other hand, diabetic model classified as genetic or spontaneously induced models and non-genetic or experimentally induced models. Non-genetic models are more famous models than genetic models because lower cost, effortless to induce diabetes and easier to maintain. Various non-genetic models such as partial pancreatectomy, alloxan/streptozotocin (STZ) models, high fat-diet models, fructose fed models, nicotinamide-streptozotocin (STZ) models, monosodium-glutamate models and intrauterine growth retardation models [5]. Partial pancreatectomy is the very popular model for the development of diabetes. Pancreatectomy is the surgical removal of the pancreas may be total or partial. In case of total pancreatectomy whole pancreas is removed and partial mentioning is the elimination of part of the pancreas. There are certain types of pancreatectomy including pancreaticoduodenectomy (whipple procedure), distal pancreatectomy, segmental pancreatectomy and total pancreatectomy [6, 7]. We performed this study in an intention to understand the pancreatic regeneration process in the diabetic condition.

Literature review:

Literature review on experimental method of pancreatectomy:

- *Jayatunge et al.,* (2015) reviewed total pancreatectomy for lipomatosis (fatty restoration of the pancreas) and lipomatous pseudohypertrophy (benign state) of the pancreatic body and tail. It was informed that pathogenesis of pancreatic lipomatosis remains disputable, mostly due to blockage of pancreatic duct. The study assessed the radiological and histological diagnosis of pancreatic LipH and to focus on the essentiality of a total pancreatectomy for this combination [7].

- *Togashi et al.,* (2014) investigated the role of IRS-2 (insulin receptor substrate-2) in the

proliferation of β-cells after a 60% partial pancreatectomy. It was observed that IRS-2 $^{-/-}$ mice displayed beta cell enlargement and a significant inflation in β- cell proliferation after the pancreatectomy. It was assessed that expression levels of aurora kinase B, cyclin A and cyclin B1 in the pancreatectomized islets were also increase in the IRS-2 $^{-/-}$ mice. It was informed that, IRS-2 was not important for β-cell proliferation but as it may be required for functional β-cell mass after a pancreatectomy [8].

- *Ruffolo et al.,* (2012) reviewed on laparoscopic distal pancreatectomy. Literature review explains that LDP is a beneficial and protected method in patients with benign or low grade malignancies. It was observed that, laparoscopic distal pancreatectomy method does not need anastomosis or other reconstruction [9].

- Pandit *et al.,* (2010) investigated the progression of a hyperglycemic condition associated with consumption of a drug. The experiments proved that defective carbohydrate metabolism in the patient or genetic predisposition of diabetes markedly increases the chances for promoting drug induced diabetes [10].

- *Philip et al.,* (2008) investigated the pancreatic exocrine inadequacy is associated with diabetes or steatorrhea, as estimated by both direct and indirect function test. It was reported that pancreatic insufficiency not only influenced patients with type 1 diabetes, but also involved in type 2 diabetic patients [11].

- *Menge et al.*, (2008) investigated on metabolic consequences of a 50% partial pancreatectomy in humans. It was reported that effect of 50% partial pancreatectomy on glucose balance and insulin secretion [12].

- *Steven et al.,* (2006) reported that insulin resistance is a major factor which is responsible in the pathogenesis of type 2 diabetes. Certain problems in insulin signalling involving the IRS-1,GLUT4 cascade have been estimated in subjects with insulin resistance. Insulin signalling prohibited by inflammatory molecules and lipid metabolites through stimulation of various serine kinesis which play a major role in serine phosphorylation of IRS-1[13].

- *Efron et al.,*(2004) reviewed on central pancreatectomy with pancreaticogastrostomy (PG) method for cancerous (benign) pancreatic condition. It observed that, for the keeping of normal endocrine and exocrine function central pancreatectomy with pancreaticogastrostomy (PG) is an effective procedure [14].

- *Hardikar et al.,* (1999) investigated on effect of pancreatectomy on diabetes status and pancreatic proliferation after 50% pancreatectomy in BALB/c mice. They also reported that the restoration of normoglycaemic condition in streptozotocin (STZ)-induced diabetic BALB/c mice, after pancreatectomy method (50% pancreatectomy) [15].

- *Mohan et al.,* (1993) investigated on fibrocalculous pancreatic diabetes (FCPD) [16].

Literature review on cyclosporine:

- *Kockx et al.*, (2012) reported that cyclosporine induced hyperlipidaemia. It was observed that the cyclosporine induced hyperlipidaemia (hypercholesteremia or hypertriglyceridaemia) in transplants patients by increasing in plasma apolipoprotein-B levels [17].

- *Vaziri et al.*, (2000) investigated on effect of cyclosporine on HMG-CoA reductase, cholesterol 7α-hydroxylase, low density lipoprotein receptor, high density lipoprotein receptor, and very low density lipoprotein receptor and lipoprotein lipase. They also investigated that long-term cyclosporine treated animals showed significant elevation of plasma cholesterol and triglyceride concentrations. This

condition was associated due to down-regulation of cholesterol 7α-hydroxylase in the liver and reduction of lipoprotein lipase concentration [18].

- *Parving et al.,* (1999) reported nephrotoxic effect of cyclosporine in Type 1 diabetic patients [19].

- Jansson *et al*., (1988) investigated the effect of cyclosporine-A on the vascular permeability of the pancreatic islets and on diabetes status induced by multiple low doses of streptozotocin (STZ) in mouse. It was observed that i.p. injection of cyclosporine (10 to 50mg/kg body weight) did not protect against the low blood glucose level and at higher dose it potentiate diabetogenic effect [20].

- *Alejandro et al*, (1985) reported that successful long-term prolongation of pancreatic islet allografts in improvised or pancreatectomy induced diabetes in dogs and cyclosporine induced immune unresponsiveness. This study also reported that short-term cyclosporine therapy prolongs survival of islet allograft and induces immune unresponsiveness to islet alloantigens in dogs with experimental diabetes [21].

Conclusion:

Removal of partial pancreas (partial pancreatectomy) leads to diabetes mellitus or hyperglycaemic condition, and also influences various metabolic consequences. For studies on diabetes, various diabetic surgical models, chemicals and diabetogenic hormones are used at research level, pancreatectomy being one of them. The present study demonstrates that partial pancreatectomy is the new technique which leads to regeneration and proliferation of β-cells.

The Pancreatectomised and Pancreatectomised-Cyclosporine group of animals showed significant increase (247.66±19.23 and 283.42±3.71) in blood glucose level at the starting of the study with respect to normal control animals. At the end of 60 days of the experiment, glucose levels were found to be normal (147±13.22 and 151.33±8.4), probably due to nesidioblastosis. Cyclosporine treated group showed hyperlipidaemic condition throughout the whole experimental period as compared to normal control and Pancreatectomised group. The biochemical test for reduced glutathione showed significant reduction (25.65±2.35) in Pancreatectomised group of mice. The histopathological changes showed regeneration of β-cells in Pancreatectomised group.

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