A LINKING BRIDGE TO DIABETES MELLITUS

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ABSTRACT

BACKGROUND

The bile is emulsifying and corrosive agent. The secretion of bile and pancreatic digestive enzymes are carried into duodenum through common opening by major duodenal papilla. When the bile and pancreatic enzymes are trapped by chance, inside the duct system of the pancreas they behave like two biotoxic agents to the insulin molecules and cells of the islets of Langerhans and initiate the process for diabetes. The major and minor duodenal papilla are the openings present at posteromedial aspect of the second part of the duodenum. In the supine position these openings become dependent part for the flowing acidic chyme. If these openings are weak and defective or the microparticle of the chyme may regurgitate inside the pancreas and induce immunological reaction with the islets of Langerhans. In long run, these events initiate the process for diabetes. The congenital anomalies of the pancreas, the biliary apparatus, the duodenum and heavy pressure on the pancreas by abdominal obesity may provoke an obstruction to the normal flow of the bile, the chyme, the enzyme and may get its infiltration inside the pancreas. These events may initiate the process for diabetes.

METHODS

The experimental animals are dogs and human. It should carried out on a trial and error basis by the team of scientists with the ethical rules. Here, the experiment is done to search an innovative aetiological factor for the diabetes, inject few millilitres of chyme or bovine milk inside the defective, weak sphincter of Oddi through the endoscopic retrograde approach or by the higher artificial intra-abdominal pressure; created on second part of duodenum and its immunological reaction on islets of Langerhans for the injected material are studied.

RESULT

The microinfiltration of these biotoxic elements inside the pancreas creates antigenic reaction and stimulates type 1 and type 2 diabetes.

CONCLUSION

The defective, weak sphincter of Oddi in supine position becomes one of the aetiological factor. After long time, the weak sphincter allows the microinfiltration of chyme in reverse direction inside the pancreas and initiates a process for idiopathic diabetes.

INNOVATIVE TREATMENTS: Like,

1. Shunt surgery. 2. Bypass duct surgery. 3. Implantation of islets of Langerhans. 4. Repair of congenital anomalies of duodenum, biliary duct system, pancreas will prevent and mitigate the prevalence of diabetes.

KEYWORDS

Bile, Pancreatic Enzymes, Chyme, Microregurgitation, Weak Sphincter of Oddi, Biotoxic Elements.

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INTRODUCTION: As per the WHO, Diabetes mellitus is a heterogeneous metabolic disorder characterised by common feature of hyperglycaemia with disturbance of carbohydrate, fat and protein metabolism. It is classified as,[1]

1. Insulin dependent diabetes mellitus (Type 1) with absolute deficiency of insulin.
2. Immune mediated or idiopathic.
3. Non-insulin-dependent diabetes mellitus (Type 2) with decrease deficiency of insulin.
4. Secondary diabetes mellitus associated with some pathological conditions.

AIM AND OBJECTIVES OF THE STUDY:

The Study Objectives are to Search Answer to the Following Questions:

1. The islets of Langerhans are usually most numerous in the tail region.[2] of the pancreas.
2. Why the islets of Langerhans are less or absent at head region of the pancreas?
3. The foetus for its nutrition depends entirely from the placenta side. Why it is not taking any food including fatty food.

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The amniotic fluid consists of water fluid with 2% solids which consist inorganic salts, urea, proteins and sugar. From the beginning of the fifth month, the foetus swallows its own amniotic fluid about 400 mL a day.[3] The bile secretion usually starts from third month.[4] to fifth month.[5] of intrauterine period. When there is no intake of food in the intrauterine period, why bile has to secrete early? What is its function? Is it an advantage or disadvantage?

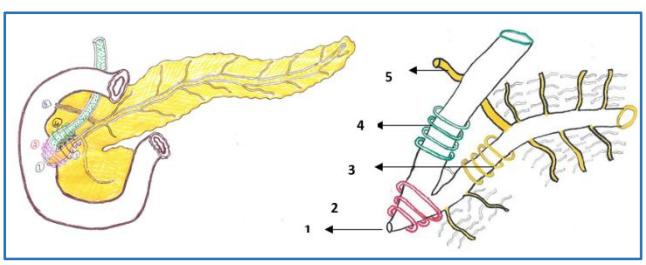
4. The adenohypophysis develops from the ectodermal Rathke's diverticulum that grows upwards from the roof of the stomatodaeum during third week of intrauterine life. Second month, the diverticular connection becomes cut off from the stomodaeum.[6] why?
5. The thyroid gland develops by endodermal diverticula from the foramen caecum of the tongue during the seventh week of intrauterine life, soon after that the thyroglossal duct, a connection between developing mouth cavity and the gland disappears.[7] why?
6. The foetal lung is not functioning. The surfactants are secreted in the lung during seventh month and contributes for viability of the foetus.[8] Imagine why they are not secreted just like bile during the third month of foetal life? What happens?
7. The angle between the openings of the common bile duct with the duct of Wirsung at hepatopancreatic ampulla is acute. Why?
8. The connecting angle between the duct of Santorini and duct of Wirsung is acute or may be obtuse, if it is so, what are the disadvantages? Why?
9. The opening of the duct of Santorini at minor duodenal papilla is independent without the connection of bile duct in 15% of the individuals.,[9] it is functioning. What will be the advantage?
10. Sphincter ampulla (Oddi) and the sphincter pancreaticus are weak and sometime are missing.[10] is it advantage or disadvantage?
11. Filling of the gallbladder by the bile and its entrance into the duodenum is regulated by pressure gradient. In the biliary apparatus during the interdigestive period, the sphincter of Oddi remains closed and when the pressure of the bile (Nearly about 7 cm of water) in common bile duct rises, the bile forces its way through cystic duct in to the gall bladder.[11] If the sphincter pancreaticus is weak or absent, the same bile, will it enter the duct of Wirsung or not? What are the disadvantages?
12. The Anatomical variations of the duodenum, the pancreas, the common hepatic duct and the sphincters around the ampullary part are many.[12] What are the impacts of these variations on the function of the islets of Langerhans?
13. The answers for these questions probably may stimulate the future of the study research to explore the hidden truth behind the diabetes mellitus.

Diabetes Mellitus has Many Aetiological Factors

(1) Genetic susceptibility. (2) Autoimmune disorder to β cells. (3) Target cells are resistant to insulin. (4) Insulin receptors are less. (5) Antibodies to insulin receptor. (6) Antibodies to insulin molecule. (7) Pancreatitis. (8) Diseases of the other endocrine glands and organs. (9) Environmental factors and risk factors, e.g. Obesity, Hypertension, Family History, Ageing, Food habits, etc.

Early exposure to bovine milk proteins induces autoimmune process to beta cells and stimulates diabetes. Pancreas is an exocrine and also an endocrine gland. It is situated retroperitoneally over the posterior abdominal wall, at the level of L1 and L2 vertebrae. The pancreas does not lie in one plane. It is draped over the structures in the retroperitoneum and the vertebral column and forms distinct shallow curve.[13] The main pancreatic duct of Wirsung joins with the common bile duct in an obliquely angle and forms hepatopancreatic ampulla of Vater which opens on the summit of major duodenal papilla, an elevation present posteromedially, aspect of the second part of the duodenum, 8 to 10 cm distal to the pylorus. The accessory pancreatic duct of Santorini opens at the minor duodenal papilla which is present 2 to 4 cm above the level of opening of major duodenal papilla.

The terminal part of the bile duct is surrounded by sphincter choledochus. It is always present. Another less developed sphincter pancreaticus is usually (but not always) present around the terminal part of the pancreatic duct. A third sphincter surrounds the hepatopancreatic ampulla (Oddi) and encloses the lower parts of the bile duct and pancreatic duct. Sometimes all these three sphincters are called as sphincter of Oddi.[14]



Diagrammatic view of Duodenum, Pancreas and its Duct, Bile Duct and Sphincters

1. Opening of the major duodenal papilla.
2. Hepatopancreatic ampulla with sphincter of Oddi.
3. Main pancreatic duct (Wirsung) with sphincter pancreaticus.
4. Common bile duct with sphincter choledochus.
5. Accessory pancreatic duct (Santorini) opening at minor duodenal papilla.

The axis of the duct of Wirsung and the axis of the common bile duct towards the ampulla is directed downwards and medially may probably help in the easy flow of its contents towards the gravity side without much effort. The presence of a common drainage for the common bile duct and the pancreatic duct may allow reflux of bile or pancreatic enzymes in to the pancreatic duct during the

passage of a gallstone through the ampulla. Reflux may also occur if the wall of the common bile duct becomes oedematous even though the gallstones have not entered the common ampulla. Blockage of Hepatopancreatic ampulla leads to pancreatitis.[15]

In such cases, the reflux of the bile in the pancreatic tissue may stimulate the emulsification of cell membrane of the serous acini and endocrine cells and begins a process for diabetes mellitus. The islets of Langerhans are more situated towards the tail region and less or absent towards the head region. In this research, we are searching an answer for the question why the endocrine cells are less or absent towards the head region. Insulin hormone is a two chain polypeptide with 51 amino acid joined by two disulfide bridge. It is synthesised in the β cell in the same manner as other proteins and are secreted into the blood by exocytosis of vesicles. The secretary vesicular membrane undergoes docking priming and fusion with plasma membrane to release their contents into extracellular domain.

Daily 1 mg of international standard insulin is secreted by the β cells. Nearly half of the insulin entering portal vein from pancreas is inactivated in first passage though liver. Other half of insulin is degraded after receptor mediated internalisation, in the target cell[16]. In this research, we are searching an answer for the question can we bypass the damage of some part of the active insulin hormone which is draining inside the portal vein through the shunt Surgery to the retroperitoneal vein.

SUGGESTED MATERIAL AND METHODS:

a. Use a separate dog for a separate experiment. Inject few millilitre of Chyme or Bovine milk or Bile salts or Pancreatic enzymes inside the pancreatic duct through the endoscopic retrograde approach.
b. Tie temporarily two elastic ligatures, one at superior another at inferior duodenal flexure of second part to the duodenum of a child or aged person or an animal. So that it should not lead to strangulation of the organ. Then, inject some bovine milk mixed with radio-opaque liquid material into the second part of the duodenum through the endoscopic instrument. Ask the person to sleep in supine and left lateral position for few hours. Press or do slight massage on the duodenal region of the abdomen for few hours. Then take radiographs and look for whether the particles of bovine milk and radio-opaque material has regurgitated inside the duct of Wirsung and other parts of the pancreas or not. With this we can prove some of the new idiopathic aetiological factors which initiate the process for diabetes.

Hypothetical Observation: Take postoperative care of the animal. Then, look for all the parameters for diabetes mellitus including immunological reaction, serum amylase, serum with peptide levels, blood and urine examination and pancreatitis.

Probably, all the animals will suffer from type 1 or may be type 2 diabetes. If necessary study the post-mortem histopathological reports of the pancreas.

DISCUSSION: The bile secretion starts form the third to fifth month of the intrauterine life. In adults, nearly about 500 to 1000 mL of alkaline bile and nearly about 1200 to 1500 mL of pancreatic juice is secreted per day. Bile salts are emulsifying and corrosive chemical. It reduces the surface tension and increases the surface area of the lipid droplets. It breaks the lipid in the smaller droplets and creates an environment for pancreatic enzymes to act on lipid droplets for digestive and absorption.[17] The cell covering consists phospholipid, glycolipid, cholesterol, trilaminar lipid membrane permeable to lipid soluble chemicals.[18] Prolonged exposure of bile endogenously causes chronic inflammation and tissue death. The regurgitation of bile in stomach is one of the aetiological factors for peptic ulcer.[19]

The regurgitated bile may stimulate the emulsification of phospholipid cell membranes of β cells and acinar cells. Any damage to the pancreatic acinar cells release pancreatic enzymes into the local tissues and leads to pancreatitis.[20] This event auto-digests the cells of islets of Langerhans and stimulates diabetes. The following anomalies may obstruct the normal easy flow of bile salts and pancreatic enzymes and stagnates it in the duct system and stimulate the process for diabetes.

It has to be evaluated in this research project.

a. Anomalies of the Duodenum:

1. Duodenal atresia, stenosis of the part of duodenum.
2. Non-development of nerve plexuses inside duodenum.
3. External pressure by abnormal peritoneal bands in relation to duodenum.

b. Anomalies of the Pancreas:

1. Annular pancreas.
2. Divided pancreas.
3. Bifid tail pancreas.

c. Anomalies of the Duct System:

1. Atresia of hepatopancreatic ampulla.
2. Duct of Santorini may become major opening.
3. Inversion of pancreatic duct system.
4. Termination of duct system is abnormal.

d. Anomalies of the Sphincters:

1. Spasm of the hepatopancreatic sphincters.
2. Sphincter pancreaticus is missing or less developed or weak.
3. Sphincter of Oddi is missing or weak.
4. Sometimes sphincter of pancreaticus and Oddi are missing or weak.

e. Increased Intra-Abdominal Pressure on Pancreas and Duodenum May Also Stimulate the Process for Diabetes:

1. The abdominal obesity, pregnancy like other factors will increase the intra-abdominal pressure and press the flow of bile and enzymes. These factors may become one of the aetiology for infiltration of bile and enzymes at microlevel inside the pancreatic tissue and trigger of the diabetes.
2. The sphincters of hepatopancreatic ampulla and minor duodenal papilla opens on the posterior medial aspect of the second part of the duodenum.

The sphincter openings in the supine position becomes dependent part for the flowing acidic chyme. The heavy intra-abdominal pressure on the duodenum and pancreas the antispasmodic drugs and alcohol which are present inside the blood ripens and weakens the sphincteric opening of hepatopancreatic ampulla and minor duodenal papilla. These events may stimulate the engulfment of the chyme in microlevel in reverse direction into the duct of Wirsung. Here, the molecules of the chyme and bovine milk behave like antigen and produces immunological reaction with the islets of Langerhans, and degrades the insulin molecules inside the pancreas only. The degraded insulin molecules which are drained through the portal vein becomes unidentified, and behaves separately and are rejected towards the level of hormone-receptor complex of the target cells.

The venous drainage of the pancreas is primarily into the portal system. Sometimes, small venous channels exist between all parts of the gland and are drained through retroperitoneal veins in to lumbar veins. The healthy insulin molecules which are drained through retroperitoneal veins at tail side of the pancreas will escape from its degradation inside the pancreas by the stagnated bile, chyme and enzymes are healthy and active. These active insulin molecules are useful to the target cells. If it becomes true, we can prevent some percentage of diabetes in susceptible individuals by doing shunting operation connecting one of the vein at tail end of the pancreas to one of the retroperitoneal veins or lumbar veins.

The diverticula of the Rathke's pouch disappears soon after the time of the development of hypothesis cerebri in the intrauterine life. Otherwise the saliva would have infiltrated through the diverticula and destroyed the functions of the endocrine cells and created new syndromes. We are lucky here. The thyroglossal ducts also disappear at the time of the development of thyroid gland in the intrauterine life. Otherwise the saliva would have infiltrated through the diverticula and destroyed the functions of the endocrine cells and created new syndromes.

Suppose in the development of lung, if the surfactants are secreted by the alveolar type II cells at glandular and canalicular phase of the foetal life, it would have destroyed the development of the pneumocytes. We are lucky here.
Only the endocrine cells of the pancreases has kept the relation with the bile and digestive enzymes. This is a disadvantage, because of this relation only some individuals are suffering and some are not from diabetes mellitus. Now we have to do the research towards this angle to disconnect the relation of the common bile duct with pancreatic duct to prevent some percentage of diabetes.

CONCLUSION: The bile, chyme, and bovine milk, inside the pancreatic tissue acts like a biotoxic elements and are waiting for an opportunity to infiltrate inside the pancreas to destruct the insulin molecules and islets of Langerhans cells. The inflammation, or weakness or anomalies of the sphincter of Oddi invites the regurgitation of these biotoxic elements in microlevel inside the pancreatic tissue and initiates a process for diabetes. The head area of the pancreas is more prone for the leakage and stagnation of these biotoxic elements and destruction of the islets of Langerhans cells. Hence the islets of Langerhans, during the evolution process might have migrated more towards the body and tail regions and are absent at head region. The adenohypophysis closes its connection with the mouth cavity soon after its development. It is an advantage to us. It prevents the regularisation of the saliva and food particles from the mouth to pituitary gland. Otherwise we would have got extra type I and II pituitary diseases.

The thyroglossal duct closes its connection with the mouth cavity soon after the development of the thyroid gland. It is an advantage to us. It prevents the regurgitation of the saliva and food particle from the mouth cavity in to the thyroid gland. Otherwise we would have got extra type I and II thyroid diseases. But in the case of pancreas it is different. Pancreas has kept the connection with the bile and chyme through the ducts controlled by sphincter mechanism. Any defects in the sphincteric mechanism leads to diabetes mellitus. The opening of the major and minor duodenal papillae are present on the posterior medial aspect of the second part of the duodenum. This is also disadvantage to us. These openings when they are defective, become depended part in the supine position of the body for the engulfment of the chyme and bovine milk inside the pancreas. Even a very little volume of chyme and bovine milk inside the pancreas provokes an autoimmune reaction and stimulates the process for diabetes mellitus.

Suggested Treatment for Diabetes Mellitus: For obesity a permanent bariatric bypass surgery to the gut is done. For myocardial infarction, vascular bypass surgery to coronary vessels is done. Here, we can prevent the diabetes disease by suggesting following surgery methods:

1. **The Venous Vascular Shunt Operation:** Connect one of the tributaries of the veins of the pancreas which is present at lateral part of the pancreas to one of the retroperitoneal or lumbar vein. Here, the drainage of insulin molecules are diverted from its first passage through liver and made to drain through the retroperitoneal vein. These insulin molecules reach the target cell directly for its degradation after receptor mediated internalisation.

2. **The Duct Bypass Surgery Named Choledochoduodenostomy:** Disconnect connection between the common bile duct with the duct of Wirsung and reconnect the common bile duct to a new opening created on the superior aspect of the first part of the duodenum.

   This operation will prevent regurgitation of bile inside the duct of Wirsung and save the existing group of islets of Langerhans by its corrosive effect and prevent the diabetes for some extent.

3. **The Implantation (Seeding) Of Healthy Cells of the Islets of Langerhans and its Stem Cells** in the other organs which are devoid of bile and digestive enzymes are healthy. This implantation surgery will prevent the deficiency of the insulin and its other hormones.

4. **Repair of the Congenital Anomalies** of the duodenum, Pancreas and common bile duct that are creating pressure and obstruction to the normal easy flow of chyme inside the duodenum, flow of bile and pancreatic enzymes inside the sphincter of Oddi. These obstructed biotoxic elements inside the pancreas stimulate the inflammatory reaction and also degrade the excytosed insulin molecules. Hence, surgical repair of congenital anomalies will prevent the stagnation of these elements and prevent the diabetes. These new hypothesis will provoke the few teams of the scientists to do the research on different animal models and opens new chapter in the area of diabetic science. This hypothesis needs encouragement and support for its evaluation and research.

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