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A Few Words about Pancreas

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1. Abstract

Diabetes is conditioned by genetic factors, often inherited, and is caused by decreased secretion or reduced biological action of the insulin hormone, or a combination of these two factors. This deficiency interferes with the exchange of carbohydrates, fats and proteins in the body, which causes recognizable symptoms, and after a long time affects the structure and function of blood vessels, nerves and other organs and organ systems. Diabetes is nowadays one of the most common endocrinological diseases with a tendency to increase steadily, especially in the developed countries of the world. Most often it is the consequence of modern lifestyles, among which the problem of obesity, which is a consequence of improper and unhealthy diet, and poor physical activity, should be emphasized. However, it should be noted that diabetes usually occurs in older life as a result of degenerative and sclerotic changes in the body, which also affect the pancreas, and can occur in young people due to genetic disorders or pancreatic damage in infectious diseases. This paper discusses the role of the pancreas in the human body.

2. Keywords: Pancreas; Diabetes; Pancreas; Health

3. Introduction

The gastrointestinal (GI) tract extends from the mouth to the anus and comprises several organs with distinct functions [1]. Separating the organs are specialized independently controlled thickened sphincters that assist in gut compartmentalization. The gut wall is organized into well-defined layers that contribute to the functional activities in each region. The mucosa serves as a barrier to luminal contents or as a site for transfer of fluids or nutrients. Gut smooth muscle mediates propulsion from one region to the next. Many GI organs possess a serosal layer that provides a supportive foundation but that also permits external input.

Interactions with other organ systems serve the needs both of the gut and the body. Pancreaticobiliary conduits deliver bile and enzymes into the duodenum. A rich vascular supply is modulated by GI tract activity. Lymphatic channels assist in gut immune activities. Intrinsic gut wall nerves provide the basic controls for propulsion and fluid regulation. Extrinsic neural input provides volitional or involuntary control to degrees that are specific for each gut region.

The primary functions of the gastrointestinal tract are the efficient processing of ingested nutrients and fluids and the elimination of undigested waste [2]. The disruption of this process leads to a number of complaints. The cardinal symptoms that suggest gastrointestinal pathology are heartburn, dyspepsia, problems of swallowing (odynophagia and dysphagia), chest pain, hiccups, nausea and vomiting, gas, diarrhea, constipation, abdominal pain, weight loss, and occult or overt gastrointestinal bleeding. These symptoms may be attributable to problems intrinsic to the gastrointestinal tract or may be a manifestation of a systemic disorder. The complaints may represent minor problems that are easily corrected by a change in diet or lifestyle, or may be indicative of serious pathology.

The pancreas functions both as an exocrine secretory and as an endocrine organ [3]. The cells that perform these distinct functions are derived from a common pancreas progenitor cell. Inductive and permissive signals specify the specific fate of these progenitors through mechanisms that are conserved in such disparate organisms as zebrafish and humans. The

development of the pancreas occurs in concert with the development of other endoderm-derived organs in the region of the foregut, and inappropriate temporal or spatial cues result in aberrant development. The functions of the pancreas, and their appropriate regulation, necessitate that the organ be highly innervated and vascularized. The development of these vascular and neural networks occurs simultaneously with development of the organ, with recruitment of neural crest cells and vascular endothelial cells into the developing organ.

4. Evidence-Based Medicine

Over the past four decades the emergence of evidence-based medicine (EBM) has had a substantial impact on clinical practice [4]. In the first half of the twentieth century, diagnostic tests or treatments, usually based on a strong scientific rationale and experimental work in animals, were routinely introduced into clinical care without good scientific proof of efficacy in people. Some of these interventions, such as gastric freezing for the treatment of ulcers and penicillamine therapy for primary biliary cirrhosis, were ultimately shown to be ineffective and harmful. There is little doubt that the widespread acceptance by physicians of unproved treatments has been detrimental to the well-being of many patients.

The popularity of EBM continues to grow. Although the explanations for this phenomenon are complex, one factor is that many practitioners recognize that ethical patient care should be based on the best possible evidence. For this, and other reasons, the fundamental concept behind EBM – the use of the scientific method in the practice of clinical medicine – has been widely endorsed by medical opinion leaders, patients and governments.

Evidence-based gastroenterology and hepatology is the application of the most valid scientific information to the care of patients with gastrointestinal and hepatic diseases. Physicians who treat patients with digestive diseases must provide their patients with the most appropriate diagnostic tests, the most accurate prognosis and the most effective and safe therapy. To meet this high standard individual clinicians must have access to and be able to evaluate scientific evidence. Although many practitioners argue that this has always been the standard of care in clinical medicine, a great deal of evidence exists to the contrary. Wide variations in practice patterns among physicians have been documented for many treatments, despite the presence of good data from widely publicized RCTs (randomized controlled trial) and the promotion of practice guidelines by content experts.

5. Criteria

In diagnostic practice, knowledge (of what diseases exist and what criteria define them) is more important than a visual memory for pictures [5]. The histopathology of any one disease entity is defined by the presence of a set of morphological (±clinical) criteria. Because any one or more of these criteria may dominate in a given instance of that disease, the overall histological picture may look dramatically different to a picture of the same disease occurring in another patient–the criteria for making that diagnosis, however, are the same.

6. Pancreas

The pancreas is a retroperitoneal organ lying posterior to the stomach and anterior to the first lumbar vertebrae [6]. It weighs roughly 100 g and is 14–20 cm in length, about the size of half of a hand. The pancreas is divided into four anatomical parts: the head, neck, body, and tail. The head sits to the right of midline positioned within the C loop of the duodenum, anterior to the vena cava. The uncinate process, a projection off the inferior aspect of the head of the pancreas, extends behind the superior mesenteric vein (SMV) and anterior to the inferior vena cava sitting adjacent to the superior mesenteric artery (SMA). The neck is a short segment that overlies the SMV and portal vein. The body and tail extend across the midline superior to the fourth portion of the duodenum forming the floor of the lesser sac.The tail extends into the hilum of the spleen. The intricate anatomic relationship between the pancreas and the main splanchnic blood vessels pose a challenge to the pancreatic surgeon. In the setting of pancreatic neoplasms, these vessels can be invaded, rendering surgery difficult at best or contraindicated at worst.

During the fourth week of gestation, two endodermal tissues, the dorsal and ventral pancreatic buds, come together to form the pancreas. They are derived from pancreatic epithelial stem cells and give rise to the exocrine and endocrine cell lines. The dorsal bud is larger and forms the superior head, neck, body, and tail of the gland. The ventral bud develops as part of the hepatic diverticulum in communication with the biliary tree and migrates dorsally as the foregut and duodenum rotate in a clockwise fashion between the fourth and eighth week of development. Both develop from the primitive duodenal endoderm. Normally, the ventral bud will form the uncinate process and the inferior portion of the head of the pancreas. The full development of acinar tissue extends into the postnatal period.

Abnormalities of fusion between the ventral and dorsal pancreatic ducts can result in pancreas divisum. Here, the dorsal duct drains the majority of pancreatic exocrine secretions into the duodenum via the minor duodenal papilla. The ventral pancreatic duct enters the duodenum via the major duodenal

papilla, yet drains only the minority of pancreatic exocrine secretions. This abnormal drainage can lead to obstructed or refluxed pancreatic secretions, which frequently leads to a clinical presentation of pancreatitis.

On a microscopic level, the exocrine secretions are formed in the acinar tissues of the pancreas. The enzymatic effluent drains from an acinus into intralobular duct, which will course through pancreatic lobules. These ducts then lead to interlobular ducts which course between lobules. Eventually, the extensive network of intralobular and interlobular ducts drain into the main or accessory ducts. The integrity of this ductal system is essential as leakage of enzymatic secretions can be damaging to surrounding tissue. Small perturbations in exocrine flow can lead to infiltration of effluent into the interstitial space of the pancreas. The local tissue damage manifests as pancreatitis, which can have varying phenotypic presentations from minor pain and inflammation to widespread pancreatic necrosis.

Historically, pancreatic surgery was generally avoided due to its technical difficulties and high mortality and morbidity rates [7]. However, in recent decades, mortality rates after pancreatectomy have decreased to less than 5%. This can be attributed to the development of high-volume, specialized pancreatic centers, as well as innovations in surgical techniques and perioperative management. Despite this progress, however, the incidence of postoperative morbidity remains high and can range from 30–60%. Delayed gastric emptying, post-pancreatectomy hemorrhage, and pancreatic fistula are the three major procedure-specific complications associated with pancreatic surgery. Postoperative pancreatic fistula (POPF) is considered the most common of these and the most significant determinant of postoperative morbidity and mortality associated with major pancreatic resections. POPF leads to increased length of hospital stay and resource utilization and thus has a significant economic impact on healthcare systems.

7. Diabetes

Diabetes mellitus refers to a group of metabolic disorders that result in increased blood glucose concentrations, either because the pancreas does not produce enough functional insulin (type 1 diabetes), or because cells do not respond to the insulin which is produced (type 2 diabetes) [8]. The causes of diabetes mellitus include the autoimmune destruction of pancreatic cells, viral infections, genetic and environmental factors, insulin or insulin receptor gene mutations, and altered pancreatic prostaglandin metabolism. Diabetes has significant health effects, impacting on the quality of life and life expectancy of those suffering with it.

Glycosylation of blood proteins including haemoglobin, albumin and lipoproteins is characteristic of diabetes mellitus. Under the hyperglycaemic conditions of diabetes mellitus, blood glucose interacts with specific amino acids on the surface of proteins, forming glycosylated protein products. These may undergo a series of further chemical modifications, resulting in the production of advanced glycation end products (AGE). The binding of AGEs to their receptors results in altered cell signalling which in turn results in free radical production. Indeed, diabetes mellitus has been shown experimentally to be associated with an increase in free radical formation and an associated decrease in antioxidant potential. Studies have directly linked oxidative stress with the impaired maintenance of glucose homeostasis and the enhanced lipid peroxidation seen in diabetes mellitus. Furthermore, increased total antioxidant levels have been measured in the blood and saliva of diabetic patients, further supporting the proposed role of oxidative stress in diabetes mellitus.

8. NETs

Neuroendocrine tumours (NETs) are neoplasia that can exhibit a range of features such as the production of neuropeptides, the presence of large dense-core secretory vesicles, and the lack of neural structures [9]. NETs can be found in many body regions including the head, neck, lungs, and abdomen. Gastroenteropancreatic (GEP) NETs can be functioning or nonfunctioning, depending on whether hormones are secreted. While the majority of NETs are sporadic, a smaller portion can be related to genetic syndromes such as multiple endocrine neoplasia (MEN), von Hippel-Lindau (VHL), and neurofibromatosis (NF). Compared with their epithelial counterparts, NETs have usually better outcomes. Surgical resections, ranging from enucleation to standard pancreatectomy and lymphadenectomy, play a key role in the management of these lesions, even in advanced disease. Long-term outcomes are correlated with the grading of the disease. Among GEP-NETs, small intestinal NETs (Si-NETs) have a higher incidence than pancreatic neuroendocrine tumours (PanNETs).

Neuroendocrine tumors (NETs) are considered rare malignancies, although their incidence and prevalence have significantly increased over the last two decades [10]. NETs arise from neuroendocrine cells, which are scattered throughout the digestive tract. Digestive NETs are classified on the basis of their site of primary origin, differentiation, and histologic grade, as well as their functional status which is based on the presence of a clinical hormonal syndrome caused by excessive hormone secretion by cancer cells (30–40% of digestive NETs). In specialized centers, 80–90 % of patients with midgut NETs and 60–70% of those with pancreatic NETs present with distant

metastases at initial diagnosis. Therapeutic approaches for metastatic disease include surgical, medical, radiologic, and nuclear medicine strategies.

Somatostatin (SST) analogs form the cornerstone of medical therapy of welldifferentiated NETs. Since the discovery of SST more than 40 years ago, analogs have been widely prescribed to relieve symptoms resulting from hormonal hypersecretion in functioning tumors, such as carcinoid syndrome. SST analogs have been further used for diagnosis and more recently for therapy with peptide-receptor-targeted radiotherapy (PRRT). In the last few years, two phase III studies have demonstrated that in addition to their antisecretory effect, SST analogs can also delay tumor progression in some NET patients. Moreover, underlying molecular mechanisms of action and resistance have been elucidated, giving a rationale for dose optimization and combination therapy with other targeted agents.

9. PETs

Pancreatic endocrine tumors (PETs) belong to the group gastroenteropancreatic endocrine tumors (GEPs) that originate from the diffuse neuroendocrine system of the gastrointestinal tract, which is comprised of various amine- and peptide-producing cells. GEP tumors were originally classified as APUDomas (amine precursor uptake and decarboxylation) as were carcinoids, PETs, pheochromocytomas, and melanomas because they share a number of features [11].

PETs can be classified into nine well-established functional syndromes, four possible functional syndromes, and nonfunctional tumors (NF-PETs). Each functional syndrome is characterized by specific symptoms due to the ectopically secreted hormone. NF-PETs secrete no products that cause a specific clinical syndrome. The symptoms caused by NF-PETs are entirely due to the tumor per se.

The prevalence of clinically significant PETs is approximately 10 cases per million, the most common being insulinomas, gastrinomas, and NF-PETs, with each having an incidence of 0.5–2 cases per million per year. VIPomas are two to eight times less common, glucagonomas are 17–30 times less common, and somatostatinomas are the least common. In autopsy studies, 0.5–1.5% of all individuals have a pancreatic PET, but in fewer than 1 in 1000 of the cases is a functional tumor thought to occur. PETs, except for insulinomas, commonly (>50%) show malignant behavior.

12. Stem Cell

Diabetes mellitus (DM) is one of the most pandemic chronic diseases that prevail worldwide, and the prevalence has continued to be growing in recent decades [12]. The patients with DM manifest a hyperglycemic state induced by impairments in insulin secretion (type 1 and at the late phase of type 2), insulin sensitivity (type 2), or both. Type 1 diabetes mellitus (T1DM), which accounts for less than 10% of patients with DM, occurs through mechanisms of an immune-mediated damage and destruction of pancreatic beta cells in the pancreatic islets of Langerhans, leading to absolute insulin deficiency (American Diabetes A 2011). Type 2 diabetes mellitus (T2DM), which accounts for more than 90% of patients with DM, is characterized by insulin resistance in peripheral tissues and relative insulin deficiency. Initially, patients with T2DM do not require insulin treatment; however as population and function of pancreatic beta cells declines over time, eventually exogenous insulin supplementation will be required at a late phase. DM is often complicated with major organ damage such as retinopathy, nephropathy, and neuropathy, as well as macrovascular diseases including coronary, cerebral, or peripheral vascular atherosclerosis.

Stem cells, characterized by the potential of multi-lineage differentiation and self-renewal, have demonstrated their unique roles in functional insulin-producing cell (IPC) regeneration, immune modulation, and other fields of regenerative studies. Compared to organ or tissue transplant, stem cell therapy has the following advantages in the treatment of DM. Autologous stem cells can accommodate a long-term stable source and are not limited by the source of donors. Stem cells are also able to secret numerous cytokines, modulate the local inflammation of pancreatic islets, and further improve the microenvironment and autoimmunity. Moreover, stem cell- derived IPCs can avoid graft rejection and eliminate the necessity of immunosuppressive therapy. Prospectively, novel attempts to replenish pancreatic beta cells in DM, with special regard to IPCs for transplant purposes, could be substituted beta cells by allo- or autografted stem cells. Hereby, we reviewed and discussed the recent advances in stem cell therapy for DM in attempt to clarify where we are and how we may go to reach the final goal of the cure of DM.

13. Elderly Patients

The use of a patient's biological age as an indicator of their health status is not accurate in predicting postoperative complications; thus, advanced age alone should not be considered contraindicative of major HPB surgeries [13]. However, elderly patients have been shown to have increased 30-day morbidity and mortality when undergoing pancreatic or hepatic resections. As a result, more detailed and accurate measurement tools are needed to assess elderly patient health status. This may be achieved by the utilization of a comprehensive geriatric assessment (CGA). A CGA is a

multidimensional diagnostic tool used to assess the medical, functional, and psychosocial status of elderly patients at risk for functional declines. Such assessments give clinicians a more detailed status of a patient's health and help identify vulnerable patients at risk for poor surgical outcomes. Overall elements should include, but are not limited to, assessment of a patient's physical health, mental health, nutritional status, functional status, socioeconomic status, and environmental factors.

While a CGA is meant to be an all-encompassing view of elderly patient health, performing a complete CGA preoperatively for all elderly patients would be an immense drain on both healthcare human and monetary resources. Depending on a CGA's components, a complete assessment can range anywhere from 30–40 min all while being performed by an experienced assessor, such as a geriatrician, physician assistant, or trained nurse. In recent decades, researchers have focused on developing screening tools to help identify at-risk patients who would benefit from undergoing a CGA while filtering patients who are deemed fit. As a result, clinicians and researchers across many disciplines have been looking at which CGA components are most indicative of patient fitness levels, with hopes of identifying specific tests or metrics that best identify vulnerable individuals who may require a complete CGA. This simplistic model can be utilized in practice in a manner that is both quick and efficient, while reducing cost and resource utilization that otherwise may be wasted on screening low-risk individuals.

14. Artificial Pancreas

Glucose–insulin dynamics in the human body has high levels of intra- and interperson variability [14]. The majority of the current AP (Artificial pancreas) systems rely on fixed physiological models. These models are developed based on measurements of complex physiological phenomena which requires detailed knowledge about the human body. However, due to variability of glucose–insulin dynamics of different people with T1D (Type 1 diabetes) and variations in glucose dynamics of the same person depending on various conditions, these models cannot be fitted to every person with T1D. They must be re-defined/tuned for different patients. Real-time modification may also be required due to different conditions such as MESS (Meals, exercise, sleep and stress) which are known to have significant effects on glucose– insulin dynamics. The computation cost of fixed physiological models is also high due to nonlinearities and large number of equations. Various automatic control strategies with fixed physiological modeling have been investigated during the last three decades. The parameters of the control strategies should also be retuned when a patient's metabolism, physical activities, or emotional state changes significantly. Adaptive control with frequently updated models provide an attractive solution for finding representative models for use in model-based controllers that respond better to the current state of the user.

An additional delay caused by mass transfer limitations from the blood vessels to subcutaneous tissue is added when CGM (Continuous glucose monitoring) measurements are used. An AP that is based only on CGM information cannot act fast enough to take action to minimize the possibility of exercise-induced hypoglycemia. By the time the effect is reported by CGM measurements, it might be too late for an AP system to manage glucose levels because the infused insulin may be delivered too late to balance the factors that caused the glucose increase. In addition to glucose measurement delays, insulin diffusion from the subcutaneous tissue to the blood stream has significant delay as well. For example, exercise at moderate levels increases insulin sensitivity which causes more glucose to be absorbed from the blood stream with the same amount of insulin. An AP system that is not aware of exercise may cause hypoglycemia due to lack of information about insulin sensitivity change. Additional data from wearable devices can be collected in real time to capture exercise information before BGC (Blood glucose concentration) is affected and initiate actions to mitigate the effects of physical activity.

People with T1D may experience hypoglycemia episodes during their daily lives. The brain uses exclusively glucose for energy and when BGC drops, its functions are impaired. Their brain is not able to make rational decisions during severe hypoglycemia and implement measures to increase the BGC to safe levels. Many people with T1D state that they had very severe hypoglycemia (20–30mg/dl) at least once in their life, such that, even when they knew that they must consume some carbohydrates they were not able to take action. Factors ranging from excessive overdosing of insulin to insufficient carbohydrate consumption, exercise, illness, and emotional stress may cause hypoglycemia. If hypoglycemia occurs during sleep, patients may not be aware of low glucose levels and may not wake up even when hypoglycemia alarms are issued. Fear of hypoglycemia is an important concern for people with T1D. Survey sindicate people with T1D have reduced fear of hypoglycemia if they use an AP system. Hence, AP system must have reliable algorithms for predicting hypoglycemia and regulating BGC by control action, rescue carbohydrates, and/or dual-hormone use.

The development of a fully automated AP that can function without any manual information and accommodate MESS will necessitate additional research to develop multivariable and adaptive AP systems that use information from wearable

devices such as wristbands and modify their models used in model-predictive alarm and control systems to adapt to the changes in the metabolic state of the user.

15. Conclusion

The pancreas secretes the juice rich in gastric enzymes essential for digestion of nutrients, but also the vital hormones insulin, glucagon, somatostatin and pancreatic polypeptide. Like any other organ, the pancreas play a significant role in maintaining the health of the body. Like other organs, it is susceptible to certain diseases, some of which lead to a fatal outcome. The pancreas belongs to the vital organs without human body cannot function. It is located in the upper part of the abdomen behind the abdominal handkerchief and rests on the spinal column at the level of the first lumbar vertebra. It is divided into three parts - head, body and tail. In the region of the pancreatic head is the main bile duct, which removes bile from the liver and connects with the main pancreatic duct in the wall of the duodenum.

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