Journal of Cardiovascular Disease Research
ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 6, 2024

Original Research Article

A Study of Histopathological Changes in Diabetic and Nondiabetic Cadaveric Pancreas with Respect to Diabetic Status

[1]Dr. Baneswar Baro, [2]Dr.Rupam Pegu,[3]Dr. Bornali Hazarika,[4]Dr. Usha Sarma,[5]Dr. Gunamani Rabha, [6]Simanta Kalita

[1]Associate Professor, Department of Anatomy, Diphu Medical College, Diphu, Assam, India.
[2]Assistant Professor, Department of Medicine, Tezpur Medical College, Tezpur, Assam, India.
[3]Associate Professor, Department of Anatomy, Gauhati Medical College, Guwahati, Assam, India.
[4]Professor, Department of Pathology, Gauhati Medical College, Guwahati, Assam, India.
[5]Assistant Professor, Department of Anatomy, Diphu Medical College, Diphu, Assam, India.
[6]Scientist B, Medical Research Unit, Diphu Medical College, Diphu, Assam, India.

Corresponding Author
Dr. Gunamani Rabha, Assistant Professor, Department of Anatomy, Diphu Medical College, Diphu, Assam, India.

Received: 23-03-2024 / Revised: 29-03-2024 / Accepted: 05-05-2024

ABSTRACT

Background
An islet of Langerhans is a mass of polyhedral cells, located in the vicinity of fenestrated capillaries and a rich autonomic innervation. Though the numbers of islets in human pancreas is about or more than 1-2 millions, its distribution within the different parts of pancreas varies with maximum numbers present within the tail area. The beta cells are the most common and account for 50-80% of the cells in the islets. Beta cells mainly secrete insulin and alpha cells secret glucagon. Alteration in functioning of insulin and glucagon hampers the glucose homeostasis which leads to development of diabetes mellitus (DM). Histopathological examination of the pancreas is an indispensable tool in the diagnosis and management of pancreatic diseases. IHC technique is applied to study beta cell mass in different parts of pancreas.

Methods
The study was conducted in the Department of Anatomy, Gauhati Medical College, Guwahati. A total of 103 specimens of human pancreas were collected after taking institutional ethical clearance from both male and female cadavers using simple random sampling method.

Results & Observation
Categorization of pathological changes is done on the basis of the histological feature changes such as fibrosis, fatty change, ductal hyperplasia & unremarkable. To study the histopathological changes of pancreas in relation to diabetes mellitus in terms of beta cell mass loss & try to grade accordingly. The researchers used Chi-Square test to analyze a significant association between the diabetic status and pathological variability.

Conclusion
Histopathological examination is crucial for diagnosing and understanding the underlying pathology of pancreatic diseases. Accurate diagnosis can guide appropriate therapeutic strategies and management. The data generated in our study with respect to beta cell mass provides the understanding the pathogenesis of diabetes mellitus. With the application of newer molecular technique, the detailed investigation of islets of Langerhans cells may be possible.
Key Words: Islets of Langerhans, Beta cells, Cadaveric pancreas, Pancreas.

INTRODUCTION

An islets of Langerhans is a mass of polyhedral cells, located in the vicinity of fenestrated capillaries and a rich autonomic innervation. Though the numbers of islets in human pancreas is about or more than 1-2 millions, its distribution within the different parts of pancreas varies with maximum numbers present within the tail area.[1] The endocrine pancreas occupies approximately1-2% of the entire parenchyma.[2]

The pathologic basis of development of insulin dependent diabetes mellitus (IDDM) development is based on the autoimmune damage to the β-cells of islets of Langerhans(IL) of endocrine pancreas.[3] The autoimmune destruction of beta cells leads to the development of gradual progressive endogenous insulin deficiency.[4] In Type 1 diabetes, autoimmune destruction of beta cells in the pancreas is predominant, whereas Type 2 diabetes features amyloid deposition. Beta cell destruction leads to reduction in the number of insulin-producing beta cells and in islet amyloidosis deposition of amyloid in the islets, mainly derived from islet amyloid polypeptide (IAPP).[5,6] Inflammation, beta cell destruction and alpha cell expansion are the key pathologic change noted in diabetes mellitus. Insulitis characterized by infiltration of inflammatory cellular infiltrate affecting the islets of Langerhans has been regarded as the characteristic lesion of recent onset Type I (IDDM) diabetes mellitus. Recent studies have stated that pathological changes in the pancreatic islets like hyaline degeneration[7,8], inflammation[9,10], beta cell loss[11,12] and alpha cell expansion[13] were associated with the DM. Hence localization of alpha & beta cell mass within the islets of Langerhans provided a detailed status of glucose homeostasis on this background, a cross sectional descriptive study has been undertaken with the aim & objective to study the expression of anti-insulin antibody in islets of Langerhans of pancreas with the help of immune histochemical staining also to look for age related change of endocrine pancreas. Specialized staining procedures or immune histochemical techniques are necessary to distinguish the three major types of cell, designated alpha, beta and delta.[14]

Histopathological changes in the pancreas can be complex and vary significantly depending on the underlying disease. Acute pancreatitis is characterized by sudden inflammation and damage to the pancreas. The pancreatic tissue undergone edema and congestion due to the interstitial spaces of the pancreas become swollen and congested with fluid. Chalky white areas of fat necrosis are due to the enzymatic destruction of fat.[15] Chronic pancreatitis involves long-term inflammation leading to irreversible changes characterized by fibrosis due to replacement of normal pancreatic tissue with fibrous tissue. Atrophy of acinar cells occurs due to loss of acinar cells leading to reduced enzyme production. Ductal changes occurs due to dilation and distortion of duct architecture often with protein plugs and calcifications. If chronic inflammation persists presence of lymphocytes and macrophages occurs and calcification occurs due to deposition of calcium salts within the pancreatic tissue.[16]

Pancreatic ductal adenocarcinoma is the most common form of pancreatic cancer. The glandular structures become poorly formed and irregular and desmoplastic

reaction, cellular atypia, perineural and lymphovascular invasion with cancer cells occurs.[17]Autoimmune pancreatitis is a type of chronic pancreatitis with distinct histopathological features which is characterized by lymphoplasmacytic infiltrate with dense infiltrate of lymphocytes and plasma cells, storiform fibrosis with whorled pattern of fibrosis and obliterative phlebitis leading to obliteration of veins.[18]

Literature on study of human pancreas are not available from Assam as well as other part of the North-Eastern states of India. The study was done considering the seriousness of pancreatic diseases and the utmost importance of its correct diagnosis and treatment. Histopathological examination of the pancreas is an indispensable tool in the diagnosis and management of pancreatic diseases. It provides essential insights that guide clinical decision-making and patient management. Continuous advancements in histopathological techniques and molecular pathology are enhancing our ability to diagnose and understand pancreatic disorders.[19,20,21,22] The results of the present study are expected to be helpful in correlating its functional capacity for further study in basic science and in decision making in clinical settings.

MATERIALS & METHODS

The present study was conducted in the Department of Anatomy, Gauhati Medical College, Guwahati from 16th May, 2016 to 15th May, 2022. A total of 103 specimens of human pancreas were collected from both male and female cadavers in the age group of 13 to 78 years. Simple random samplings method was used for sampling.

The study was conducted after obtaining ethical approval from the Institutional Ethical Committee of Gauhati Medical College, Guwahati. Written informed consent was sought from all guardians or attendants of the eligible individual after explaining the purpose and detailed procedures of the study before collecting the specimens. All the guardians or attendants of the cadavers were assured confidentiality of data obtained from the study.

Inclusion criteria:

1. Normal specimens of cadaveric and autopsy pancreas with intact viscera.

Exclusion criteria:

1. Any visible signs of pathological changes of the viscera
2. Any doubtful injury in pancreas
3. Death due to known poisoning
4. Pancreatic diseases
5. Specimens of medico legal cases.

Collection was done within 12 to 36 hours of death. During collection, approximate age, sex and cause of death were noted from record book. Then each specimen was marked with a code number for individual identification. The specimens were collected along with duodenum and spleen. After removal from the body, unwanted tissues were cleared and gently washed out in normal saline.

A midline incision was done to expose the abdominal contents. The coils of intestine were retracted and the pancreas was identified. Then the tail and body of the pancreas were turned to the right, stripping the splenic artery and vein from its posterior surface. After identifying the superior mesenteric vessels, portal vein and gastroduodenal artery they were detached from the pancreas.[23]

The pancreases were washed with tap water to clean the debris and the fatty tissue. All the blood and clots were removed from the surface of pancreas. The

specimens were again washed in normal saline. Then the pancreases were preserved in 10% formalin solution for microscopic study. Selection of the tissue was done according to Wolfe-Coote & duToit [24] as head, body and tail. Each part of the fixed tissue was again sectioned into 3 mm thickness. Sectioned tissues were cut into 3 mm × 3 mm size with scalpel. The sections were processed following the standard operating procedure. Mounting with DPX were done after both Hematoxylin and Eosin (H&E) and Immunohistochemistry (IHC) staining of the same tissue section.

Measurement of different regions of CP

The tissue sections were taken from head, body and tail regions (total 3 regions) from the CPs. Observations were done by using Nikon 80i Binocular microscope with image analyzing software which were recorded and entered in the MS excel sheet. The standard method of statistical analysis was performed by adopting the statistical software Graph Pad InStat Data.

RESULTS & OBSERVATION

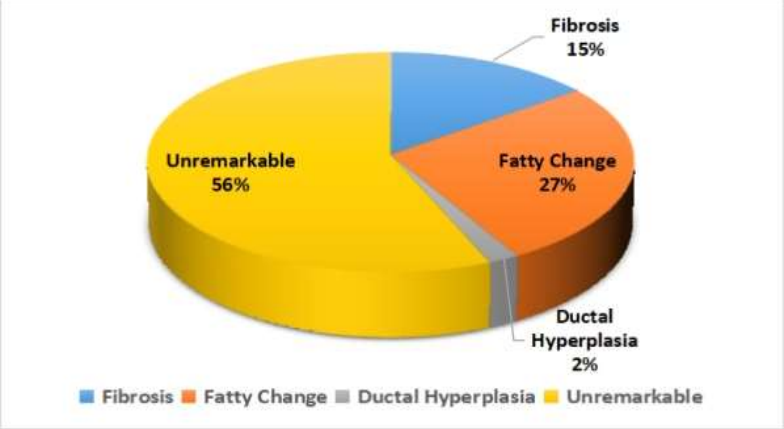
Categorization of pathological changes among entire 103 samples of CPs was done on the basis of the histological feature changes such as fibrosis, fatty change, ductal hyperplasia & unremarkable.

Table 1 & figur1 have shown that 56% of total CPs studied were histologically within normal limit whereas 27% of the total CP show fatty change and 15% show fibrosis, 2 cases show ductal hyperplasia.

Table 1: Distribution of entire 103 samples of CPs according to pathological variability.

Pathological Variable	Number	%
Fibrosis	15	15
Fatty change	28	27
Ductal hyperplasia	2	2
Unremarkable	58	56
Total	103	100.00%

Figure1: Pie diagram showing the % distribution of entire 103samples of CPs w.r.t. pathological variables.



To study the histopathological changes of pancreas in relation to diabetes mellitus in terms of beta cell mass loss & try to grade accordingly. Further Chi-Square test was

used to find whether there was a significant association between the diabetic status and pathological variability.

Table2: Association table between the diabetic status and pathological variability.

Pathological Variability DM Status	Fibrosis	Fatty change	Ductal Hyperplasia	Unremarkable	Total	df	Chi-squarevalue
DM	8	8	1	1	18	3	27.21**
ND	7	20	1	57	85		
Total	15	28	2	58	103		

**→Highly Significant

Figure 2: Bar diagram showing the number of 103 samples of CPs according to diabetic status & pathological variability.

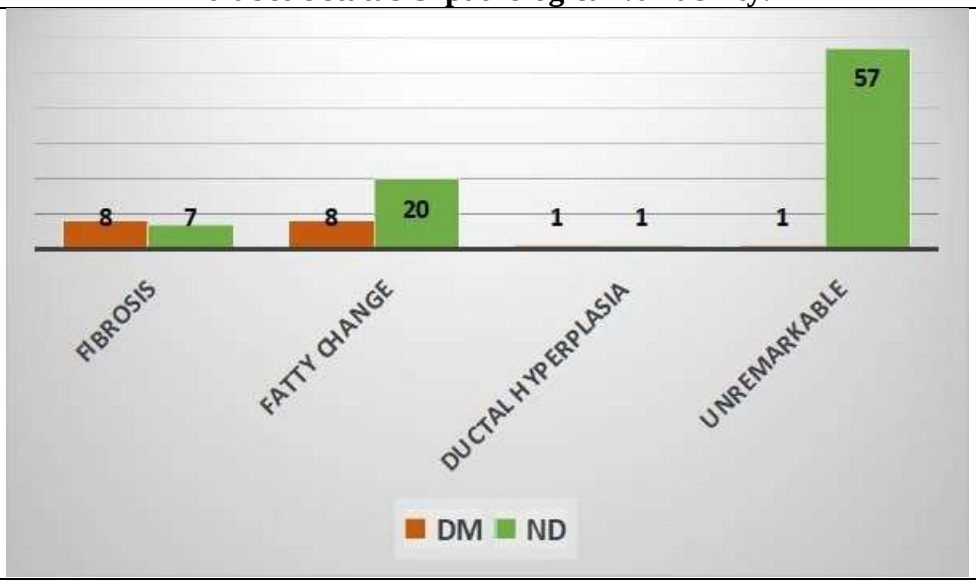
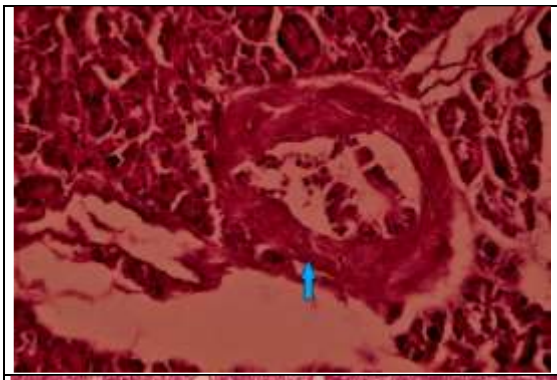
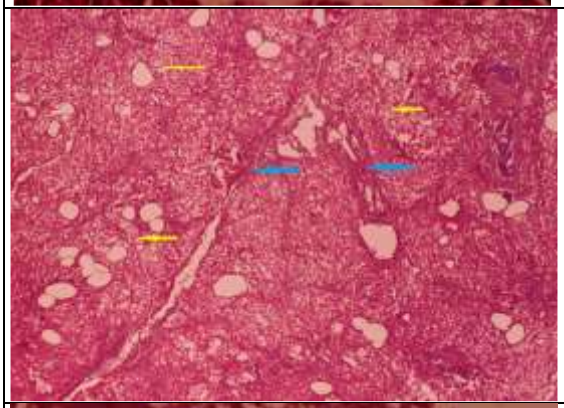
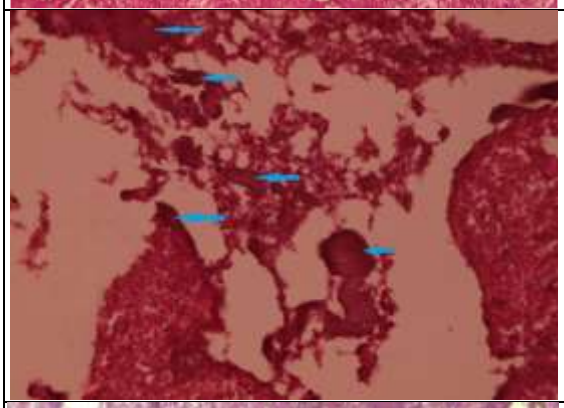
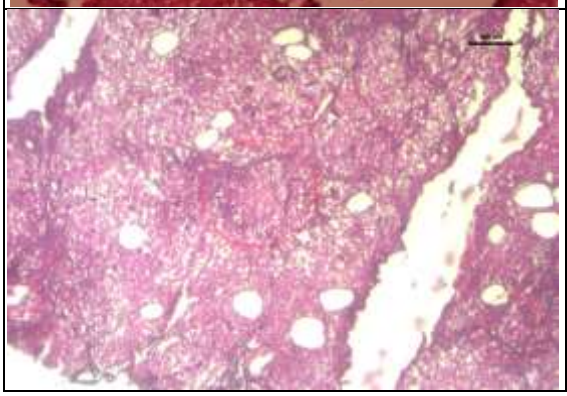


Table 2 and figure 2 have shown the number of 103 samples of CPs according to diabetic status & pathological variability. Out of total 18 diabetic CPs 8 have fibrosis, 8 have fatty change, only 1 have ductal hyperplasia and 1 is in the unremarkable category. Chi-square test is applied to test the significant association between diabetic status & pathological variability. It has been found that there is highly significant association between the two as $p>0.0001$.

	**Figure 3: Photomicrograph of the pancreas. This H&E – stained specimen shows periductal fibrosis (blue arrow). X400.**
	**Figure 4: Photomicrograph of pancreas showing fatty changes (yellow arrow) and fibrosis with fibrous bands (blue arrow) with complete replacement of beta cells (Negatively stained by anti-insulin antibody (IHC technique), X100.**
	**Figure 5: Photomicrograph of pancreas shows calcification with areas of focal calcified bodies (blue arrow) (H&E) X400.**
	**Figure 6: Photomicrograph of pancreatic lobule showing fatty change of pancreas after IHC stain. Pancreatic tissue inside the circle is fibrosed surrounding IL. Scale bar, 100 µm.**

DISCUSSION

Out of entire 103 sample CPs including both DM and NDM 56% of total CPs studied were histologically within normal limit whereas 27% of the total CPs shows fatty change, 15% showed fibrosis and 2% cases showed ductal hyperplasia. The present study is conducted to compare with the study done by Shimizu M et al.[25], Cloppel G et al.[26], Shahriah S et al.[27], Ghadially FN[28] and Cotran R Setal.[29] Shimizu et al.[25] which

mention that commonest changes due to increased age are in ducts as epithelial hyperplasia (88%) and periductal fibrosis (74%). They also mentioned that the ducts also showed cystic widening (62%) and intraluminal protein precipitates (40%) within the parenchyma which are main factors for intralobular fibrosis and total fibrosis lobules (88%). Cloppel G etal.[26] observed variations inducts which drained to fibrotic lobules. Shahriah S etal.[27] mentioned that the pancreas gradually started to grow to the adult size during the 2nd decade which was very less up to the 3rd decade, then dramatically it increased up to the 6th decade. Fibrosis was mainly associated with aging and increased fibrosis was noted in and around the islets of Langerhans. They also commented that epithelial hyperplasia, papillary projections and periductal fibrosis around small and medium sized duct started very early in Indian populations indicating the vulnerability to pancreatic diseases in the Indian population in early ages.

Ghadially FN[28] and Cotran R Setal.[29] mentioned fatty degeneration which occurs due to accumulation of lipid cells inside the epithelial parts of the larger ducts which was frequently observed in the aged pancreas. Accumulation of membrane bound lipid cells inside the other cell indicates fatty degeneration of these cells.

A significant association between the diabetic status and pathological variability are established among 103 CPs. Out of total 18 diabetic CPs, 8 shows fibrosis, 8 shows fatty change, 1 is ductal hyperplasia and 1 is in the unremarkable category. Chi-square test between diabetic status & pathological variability have been highly significant association between the two as $p>0.0001$.

A significant difference among the 3 variables (head, body & tail) among the DM status, 18 DM one way Analysis of Variance (ANOVA) i.e., F-test has been applied. The 'df' among 3 variables are 2 and within variables are 51. The 'F' value is 23.06 ($p<0.0001$), which is highly significant among the 3 variables. The present study has been compared with the study done by Rahier J et al.[30],Saito K et al.[31], Shahriah S et al.[27], Wang X et al.[32], Ravi PK et al.[33], Butler AE et al.[34],Yoon KH et al.[35].

Rahier J et al.[30] revealed that the average beta cell mass is about 39% lower in type 2 diabetic subjects compared with matched controls. They found that beta cell mass do not correlate with age but it decreases with duration of clinical diabetes. They also mentioned as 24 % lower than controls in subjects <5 years and 54% lower than controls in subjects>15 years of over diabetes respectively.

Saito K et al.[31] studied 28 samples of non-diabetic cases. The total beta cell volumes do not decrease with age. However, when the ratio between alpha and beta cells were examined, it tends to reduce with age, though it was not significant statistically.

Shahriah S et al.[27]reported that the number of beta cells gradually increased up to the 4th decade of life in head and body region and to the 6th decade in the tail region of the pancreas, then decreased.

In comparison to the American population as studied by Wang X et al.[32], Ravi PK et al.[33] showed among Indian population a 45% reduction of larger islet proportion in the head and body region with a 31.9% reduction in the tail region.

Butler AE et al.[34] have reported that beta cell mass as well as beta cell function is decreased in patients with T2DM. They have reported an approximately 65% beta cell mass decrease in people with T2DM compared with non-diabetic controls matched for age and BMI. Yoon KH et al.[35], Rahier J et al.[30] have also reported that beta cell mass in patients with T2DM is reduced by30-40%.

Saisho Y et al.[36] reported that in adults past 60 years of age, both total and parenchymal pancreas volumes gradually decline and atrophy and fat infiltration occured simultaneously. Noronha M et al.[37] and Stirling GA[38] reported that atrophy and

fat infiltration of the pancreas is seen with ageing in humans.

CONCLUSION

Histopathological examination is crucial for diagnosing and understanding the underlying pathology of pancreatic diseases. Accurate diagnosis can guide appropriate therapeutic strategies and management. The data generated in our study with respect to beta cell mass provides the understanding the pathogenesis of diabetes mellitus. Though the present study was done on 103 CPs, further studies including more number of samples and advanced stereological procedure will provide better information and knowledge. With the application of newer molecular technique, the detailed investigation of islets of Langerhans cells can be possible.

REFERENCES

1. Waugh A, Grant A. Pancreas, The Digestive System, Ross and Wilson Anatomy and Physiology in Health and Illness. 13th ed. London: Elsevier; 2018. p. 336
2. Longnecker D. Anatomy and Histology of the Pancreas, Pancreapedia: Exocrine Pancreas Knowledge Base, Version 1.0, March 21, 2014 http://dx.doi.org/10.3998/panc.2014.3
3. Burrack AL, Martinov T, Fife BT. T Cell-Mediated Beta Cell Destruction: Autoimmunity and Alloimmunity in the Context of Type 1 Diabetes, REVIEW article Front. *Endocrinol*. 2017 Dec 5. Available from URL: https://doi.org/10.3389/fendo.2017.00343.
4. Iki K, Pour PM. Distribution of Pancreatic Endocrine Cells, Including IAPP-expressing Cells in Non-diabetic and Type 2 Diabetic Cases. *J.Histochem. Cytochem*. 2007 Feb. [2006]. Available from: URL: https://doi.org/10.1369/jhc.6A7024.2006
5. Atkinson, M. A., & Eisenbarth, G. S. (2001). "Type 1 diabetes: new perspectives on disease pathogenesis and treatment." *The Lancet*, 358(9277), 221-229.
6. Clark, A., & Nilsson, M. R. (2004). "Islet amyloid: a complication of islet dysfunction or an endocrine biomarker of type 2 diabetes?" *Diabetes*, 53(Suppl 3), S164-S172.
7. Westermark P, Wernstedtt C, Wilander E, Hayden DW, O'brient TD, Johnsont KH. Amyloid fibrils in human insulinoma and islets of langerhans of the diabetic cat are derived from a neuropeptide-like protein also present in normal islet cells. *Proc Nati Acad Sci USA*.1987;84:3881-3885. https://doi.org/10.1073/pnas.84.11.3881
8. Kamata K, Mizukami H, Inaba W, Tsuboi K, Tateishi Y, Yoshida T et al. Islet amyloid with macrophage migration correlates with augmented βcell deficits in type 2 diabetic patients. *Amyloid*.2014;21:191-201. https://doi.org/10.3109/13506129.2014.937857
9. Yagihashi S, Inaba W, Mizukami H. Dynamic pathology of islet endocrine cells in type 2 diabetes: β-cell growth, death, regeneration and their clinical implications. *J Diabetes Investig*. 2016;7:155-165. https://doi.org/10.1111%2Fjdi.12424
10. Ehses JA, Perren A, Eppler E, Ribaux P, Pospisilik JA, Maor-Cahn R et al. Increased number of islet-associated macrophages in type 2 diabetes. *Diabetes*.2007;56:2356–2370. https://doi.org/10.2337/db06-1650
11. Saito K, Nobuhisa Y, Tohbu T. Differential volumetry of A, B and D cell in the pancreatic islets of diabetic and nondiabetic subjects. *Tohoku J Exp Med*. 1979;129:273–283. https://doi.org/10.1620/tjem.129.273

12. Gepts W. Pathologic anatomy of the islet cell system in juvenile diabetes mellitus. *Diabetes*. 1965;14:619–633. https://doi.org/10.2337/diab.14.10.619
13. Yoon KH, Ko SH, Cho JH, Lee JM, Ahn YB, Song KH et al. Selective beta-cell loss and alpha-cell expansion in patients with type 2 diabetes mellitus in Korea. Journal of Clinical Endocrinology & Metabolism. 2003;88(5):2300-2308. https://doi.org/10.1210/jc.2002-020735
14. Standring S. The Pancreas, Abdomen and Pelvis. In: Borley NR, Healy JC ed. *Gray's* Anatomy, The Anatomical Basis of Clinical Practice. 40th ed. London: Churchill Livingstone, Elsevier; 2008. p. 1183-90.
15. Lerch, M. M., & Saluja, A. K. (2006). "Runaway inflammation in pancreatitis: a key target in the treatment of acute pancreatitis." *Gastroenterology*, 130(4), 1304-1307.
16. Whitcomb, D. C. (2004). "Mechanisms of disease: Advances in understanding the mechanisms leading to chronic pancreatitis." *Nature Reviews Gastroenterology & Hepatology*, 1(1), 27-35.
17. Hruban, R. H., Pitman, M. B., & Klimstra, D. S. (2007). *AFIP Atlas of Tumor Pathology: Tumors of the Pancreas*. ARP Press.
18. Deshpande, V., & Chari, S. T. (2007). "Autoimmune pancreatitis: A systemic immune complex mediated disease." *American Journal of Surgical Pathology*, 31(11), 1537-1545.
19. Hruban, R. H., & Wilentz, R. E. (2009). Pancreas Pathology. *Encyclopedia of Life Sciences*. Wiley.
20. Deshpande, V., & Mino-Kenudson, M. (2015). Histopathology of the pancreas. *Current Opinion in Gastroenterology*, *31*(5), 433-439.
21. Klöppel, G. (2010). Chronic pancreatitis, pseudotumors and other tumor-like lesions. *Modern Pathology*, *23*(S1), S66-S79.
22. Adsay, N. V., & Basturk, O. (2013). Pathology of the pancreas: A practical approach. *Modern Pathology*, *26*(1), 78-91.
23. Villemin F. Sur la circulation arterielle du duodenum. *CR Ass Anat*. 1921; 16: 223-28.
24. Yule E. The arterial supply to the duodenum. *J Anat*. 1927; 61:344-45. https://pubmed.ncbi.nlm.nih.gov/17104148/
25. Shimizu M, Hayashi T, Suitor Y, Itch H. Interstitial fibrosis in the pancreas. *Am J Clin Pathol*. 1989;91:531-4. https://doi.org/10.1093/ajcp/91.5.531
26. Cloppel G, Malliet B. Pathology of acute and chronic pancreatitis. Pancreas 1993;8:659-70. https://pubmed.ncbi.nlm.nih.gov/1765357/
27. Shahriah S, Nurunnabi ASM, Begum GN, Rayhan KA, Perven HA. A postmortem histological study on the alpha and beta cells of the islets of Langerhans. *Bangladesh Med J*. 2014 Sep;43 (3). https://doi.org/10.3329/bmj.v43i3.26297
28. Ghadially FN. Ultrastructural pathology of the cell and matrix. 4th ed. Oxford: Butterworth–Heinemann, 1997:1014-37.
29. Cotran RS, Kumar V, Collins T. The pancreas, Robbins Pathologic Basis of Disease. 6th ed. Singapore: Harcourt Asia PTE Ltd; 1999. p. 839-40.
30. Rahier J, Guiot Y, Goebbels RM, Sempoux C, Henquin JC. Pancreatic beta-cell mass in European subjects with type 2 diabetes. *Diabetes, Obesity & Metabolism*. 2008;10(Suppl 4):32-42. https://doi.org/10.1111/j.1463-1326.2008.00969.x
31. Saito K, Yaginuma N, Takahashi T. Diffffferential volumetry of A, B and D cells in the pancreatic islets of diabetic and nondiabetic subjects. *Tohoku J Exp Med*. 1979; 129(3):273-83. https://doi.org/10.1620/tjem.129.273

32. Wang X, Misawa R, Zielinski MC, Cowen P, Jo J, Periwal V, Ricordi C et al. Regional differences in islet distribution in the human pancreas - preferential beta-cell loss in the head region in patients with type 2 diabetes. *PLoS One*. 2013;8:1-9. https://doi.org/10.1371/journal.pone.0067454
33. Ravi PK, Purkait S, Agrawal U, Patra S, Patnaik M, Singh SR et al. Regional variation of human pancreatic islets dimension and its impact on beta cells in Indian population. ISLETS. 2019;11(6):141-151. https://doi.org/10.1080/19382014.2019.1686323
34. Butler AE, Janson J, Bonner-Weir S, Ritzel R, Rizza RA, Butler, PC. Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. *Diabetes*. 2003;52(1):102-110. https://doi.org/10.2337/diabetes.52.1.102
35. Yoon KH, Ko SH, Cho JH, Lee JM, Ahn YB, Song KH et al. Selective beta-cell loss and alpha-cell expansion in patients with type 2 diabetes mellitus in Korea. *Journal of Clinical Endocrinology & Metabolism*. 2003;88(5):2300-2308. https://doi.org/10.1210/jc.2002-020735
36. Saisho Y, Butler AE, Meier JJ, Monchamp T, Allen-Auerbach M, Rizza RA et al. Pancreas Volumes in Humans from Birth to Age One Hundred Taking Into Account Sex, Obesity, and Presence of Type-2 Diabetes. Clinical Anatomy. 2007;20:933-942. https://doi.org/10.1002
37. Noronha M, Salgadinho A, Ferreira De Almeida MJ, Dreiling DA, Bor-dalo O. Alcohol and the pancreas. I. Clinical associations and histopathology of minimal pancreatic inflammation. *Am J Gastroenterol*.1981;76:114-119. https://pubmed.ncbi.nlm.nih.gov/7304546/ PMID: 7304546.
38. Stirling GA. The exocrine pancreas: Non-neoplasmic disorders. In: Wight DGD, editor. Liver, Biliary Tract and Exocrine Pancreas. 3rd Ed. New York, NY: Churchill Livingstone. 1994. p. 597-650.