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Chapter 4

Pancreas and Diabetes: From Redefining Pathways to Improving Care

Ambika G Unnikrishnan

INTRODUCTION

The increasing occurrence of diabetes worldwide is a matter of concern. Traditionally, diabetes is divided into several subtypes—type 1 diabetes, type 2 diabetes, and other specific subtypes of diabetes and gestational diabetes.[1] While this is important to facilitate the easy understanding of etiology and management, it has arguably led to narrow compartmentalization of different subtypes of diabetes.[1] However, researchers are now increasingly aware of the possibility of overlap between these subtypes. The pancreas gland, producer of insulin and glucagon, is now rightfully being assigned an important place in the understanding of diabetes. It is now well known that hybrid forms of diabetes may exist—a case in point being LADA or latent autoimmune diabetes of adults—which is now reported from India too.[2] In children, the distinction between type 1 and type 2 diabetes can be difficult, though being important. Diabetes in the young is more likely to be associated with future complications due to prolonged exposure to hyperglycemia over their lifetime. However, a particularly interesting disease has been fibrocalculous pancreatic diabetes (FCPD).[3,4] Unlike the classical varieties of pancreatitis worldwide, which are associated with alcohol intake, FCPD occurs in nonalcoholic individuals. The disease begins in young individuals with calculi formation in the pancreatic ducts, and is referred to as tropical chronic pancreatitis (TCP). Eventually, the pancreatic damage associated with TCP leads to FCPD. Subjects with FCPD are younger, have risk of developing microvascular complications, as well as exocrine deficiency. Macrovascular complications have not been reported commonly in these patients, but can occur.[5] The relative lack of macrovascular complications is probably due to their relative leanness, lower cholesterol levels, and youth. There is, however, a risk of pancreatic cancer in these patients.

CLARIFYING PANCREATIC DIABETES

A few years ago, a group of gastroenterologists, diabetologists, gastrointestinal surgeons, and endocrinologists got together to form the "Indian Pancreatitis Study Group." An online prospective registry was formed and the results of the prospective study were published.[3] The results were remarkable and surprising. TCP and FCPD are distinctly uncommon as causes of chronic pancreatitis and pancreatic diabetes in India. Idiopathic pancreatitis was common, as was alcoholic pancreatitis. This study clarified many clinical features of chronic pancreatitis and pancreatic diabetes in India. At the time, it was India's first collaborative academic study to have used an online portal for data collection.

CHRONIC PANCREATITIS AND PANCREATIC DIABETES IN INDIA

The aforementioned study was designed to answer the simple question—what is the pattern of chronic pancreatitis in India? Under the leadership of professor Balakrishnan, an internationally acclaimed pancreatologist, gastroenterologists, diabetologists, endocrinologists, and gastrointestinal surgery experts

assembled in a group (termed the Indian Pancreatitis Study Group) from across the country and decided on a data collection pro forma. This was then uploaded on a website and online data entry started. Thirty two centers participated and the results were published in 2008. The study team prospectively compiled data of 1,086 subjects.[3] Although idiopathic pancreatitis was the commonest subtype of chronic pancreatitis, alcoholic chronic pancreatitis accounted for nearly a third of the cases. Using well-defined criteria, only about 3.8% of cases could come under the definition of TCP. One hundred eighty nine subjects consumed cassava, thought to be a possible risk factor in TCP. About 40.5% of the subjects had diabetes and alcoholism was an independent risk factor for the development of diabetes in subjects with chronic pancreatitis. Data regarding diabetes therapy in subjects with chronic pancreatitis in India showed 16.8% were being treated with diet, 33.6% on oral hypoglycemic agents, and 49.6% on insulin. Despite certain limitations, the study clarified many aspects of chronic pancreatitis and pancreatic diabetes in India.

FIBROCALCULOUS PANCREATIC DIABETES: TYPE 1 OR TYPE 2

The occurrence of diabetes mellitus in India is increasing, and diabetes in India occurs earlier than in the West.[1,6] Consequently, a study was undertaken to understand the prevalence of type 1, type 2, and FCPD as causes of diabetes in the young. While an earlier study had suggested FCPD as a common cause of diabetes in the young, a latter multicenter study did not suggest this. Type 1 diabetes was overwhelmingly the commonest subtype of diabetes in the young, followed by type 2 diabetes and FCPD. This multicenter study also showed important differences between type 1 and 2 diabetes in the young as differentiation can be difficult, but is clinically important.[1,6] Other than type 1 and type 2 diabetes, latent autoimmune diabetes of adult has also been reported especially in subjects with a lean body mass index.

BEYOND THE PANCREAS AND DIABETES

In general, the treatment of diabetes in chronic pancreatitis would focus on insulin, as it has been suggested that insulin deficiency is an important cause of diabetes. Vascular complications of diabetes have been known to occur in patients with chronic pancreatitis and diabetes. It is well known that glucose control can prevent diabetic complications in general. Interestingly, metformin, it has been suggested, may even protect against pancreatic cancer, which is associated with longstanding chronic pancreatitis. A recent study which showed that metformin nanoparticles might be toxic to pancreatic cancer cell lines, might suggest that metformin could have cancer-prevention potential.[7] Metformin, it has been suggested, acts through several pathways including the mammalian target of rapamycin pathways in addition to the cyclic 5' adenosine monophosphate (AMP) kinase pathway and via them, it has been shown to reduce the risk of pancreatic cancer. The toxic effect of metformin on *in vitro* pancreatic cancer cell lines suggests that metformin may have a direct effect and that anti-pancreatic cancer effects of metformin may not exclusively be explained by a decrease in insulin levels owing to improvements in insulin resistance by metformin.[7] There are many intriguing aspects of insulin and its link to malignancy—some of this could be explained by different sensitivity of different tissues to the actions of insulin. For the present, does this impact clinical practice? Should all persons with type 2 diabetes receive metformin? Specifically, should subjects with pancreatic diabetes, given the excess risk of pancreatic malignancy in them, receive metformin? There are some risks to this strategy. Persons with chronic pancreatitis may already be thin due to exocrine insufficiency, would metformin further reduce weight in them? Would the vitamin B12 deficiency attributed to metformin therapy have any role when it is prescribed to patients with pancreatic diabetes? Clearly this is an area for more research. Interestingly, it is increasingly being suggested that metformin may have a role in prevention of aging.

INCRETINS AND PANCREATITIS: IS THERE A SERIOUS CONCERN?

The association between incretin therapy and pancreatitis, and even pancreatic neoplasia, has raised some concerns. Incretins are commonly prescribed diabetes-related therapies. Glucagon-like peptide-1 (GLP-1) and glucose dependent insulinotropic polypeptide (GIP) are both released from the gut in response to oral glucose intake. These incretins (GLP-1 and GIP) reduce glucose levels without producing hypoglycemia. GLP-1 is the main incretin and is rapidly degraded by an enzyme called dipeptidyl peptidase-4. Very recently, a controversial paper brought this association between gliptins and pancreatitis into focus.[8,9,10] However, even newer data from larger, longer term studies with gliptin,

have been recently published, which do not establish such an association.[11,12]

NEW APPROACHES

Clearly, the problem of diabetes in general is enormous, and while the study of the pancreas offers a solution, it is not the only approach.[13-15] It is well known that glycemic control—i.e., a reduction of glycosylated hemoglobin (HbA1c)—could beneficially reduce the onset and progression of diabetes-related vascular complication. However, can reducing the HbA1c completely eliminate the risk of complications? It is obvious that that this is not the case. This "residual" risk that remains despite reducing the HbA1c is not unlike the more conventional residual risk that occurs despite statin therapy. In the example of statin therapy, clinicians today question the utility of low density lipoprotein (LDL)-cholesterol alone as a target and talk about other markers like C-reactive protein, LDL-particle number, and others, including non-high density lipoprotein. The role of HbA1c as a marker of diabetes-related complications has been questioned. A recent paper questioned its role as a marker in Indians. Indeed changing albumin levels in diabetes seem to have an effect on HbA1c, in an inverse manner.[16] HbA1c is a marker of glycation and it is possible that in hyperglycemia, glycation of other proteins may impede the glycation of hemoglobin and vice versa. Thus, there is a requirement of other markers to supplement the use of HbA1c as a predictor of diabetes-related complications. Such markers might result in an improved care.

New research continues to offer hope, and the future looks promising for patients with diabetes. In recent years, the use of incretin axis and the sodium glucose cotransporters have both been harnessed to improve diabetes care. In addition, the metabolic benefits of bariatric surgery are also being researched to understand if pharmacotherapy could mimic these effects. Improvements in dietary research have led to fresh understanding about diabetes and cardiovascular health. Indeed unhealthy fats and carbohydrates have become more harmful than health fats. New approaches to insulin therapy and devices, as well as next-generation monitoring, are all promising to change diabetes care. Today, there is a greater understanding of the prevalence and management of gestational diabetes in India.[17] The increasing occurrence of diabetes and its complications underscores the need for more research.[18-21]

CONCLUSION

It is now clear that exocrine and endocrine aspects of pancreatic function are interdependent and not unrelated. Just like endocrine dysfunction occurs in chronic pancreatitis, exocrine dysfunction has been reported in type 1 and type 2 diabetes. This is an area that calls for multidisciplinary research in the years to come. The links between pancreatitis and diabetes is an exciting area for several reasons. First, the issue of TCP being a separate, distinct, and unknown form of disease, which is largely being clarified, is now thought to be part of the spectrum of chronic pancreatitis. Indeed, as the Indian Pancreatitis Study showed, alcoholic chronic pancreatitis seems to be increasing as the common cause of chronic pancreatitis in India. About 40% of patients with chronic pancreatitis have diabetes and patients with chronic pancreatitis also have an increased risk of pancreatic cancer. With regard to diabetes and pancreatitis, several drugs have been shown to increase the risk of acute pancreatitis and this also includes drugs used for diabetes. While incretin-based therapies have been linked to pancreatitis, conclusive proof is now lacking and doctors are advised to discuss benefits and risks with the patient, and not change incretin-based therapies unnecessarily. Thirdly, pancreatic cancer can be associated with diabetes; metformin can reduce the risk of pancreatic cancer. This leads to the somewhat "futuristic" question whether patients with chronic pancreatitis and diabetes need to be given metformin because chronic pancreatitis is associated with pancreatic cancer and metformin seems to mitigate that risk. Finally, it is increasingly been known that pancreatic cancer can manifest as new onset diabetes and clinicians need to be alert to this possibility. Further research in the coming decades will clarify further the exciting crosslinks between chronic pancreatitis and diabetes. Given the escalating problem of diabetes in the world, there has been a justifiable increase in research work on diabetes worldwide. New approaches are fast helping the understanding and management of diabetes and its complications worldwide. Recent research has suggested that the link between socioeconomic status and cardiovascular risk is complex and heterogeneous, and that it requires a focused approach. It is to be expected that the benefits of basic and clinical research will help reduce regional disparities in the availability of diabetes care and provide relief to millions suffering with diabetes and its complications.

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- RSSDI Update 2015 presents the depth and breadth of diabetes practice highlighting new advances and their potential to transform the established paradigms of prevention, diagnosis, and treatment
- Running in 31 sections and 107 chapters, the book makes for comprehensive reading
- Epidemiology, pathogenesis molecular mechanisms, the entire spectrum of clinical aspects, allied specialties (musculoskeletal, thyroid, liver disorders), tuberculosis, complications, and management of diabetes (treatment issues) are all extensively covered
- Novel insights with diabetes at the center-stage include artificial sweeteners, varying manifestations in the young and elderly, infertility, use of nutrients, sleep and stress, socioeconomic aspects, addiction, research, nondiabetic hypoglycemia, role of the government, private sector, industry, and using stem cells and system biology to tackle diabetes in the 21st century
- Written by national and international experts, the chapters provide for an elaborate understanding of our current knowledge of diabetes
- A clinic-friendly reference that provides to-the-point and crisp information and is geared toward the specific needs of the practicing clinicians and students of medicine at all levels of their careers.

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