International Journal of Pharmacognosy and Pharmaceutical Sciences

ISSN Print: 2706-7009
ISSN Online: 2706-7017
IJPPS 2023; 5(1): 13-15
www.pharmacognosyjournal.net
Received: 09-10-2022
Accepted: 13-12-2022

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Fibrocalculous pancreatic diabetes

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DOI: https://dx.doi.org/10.33545/27067009.2023.v5.i1a.100

Abstract
Chronic Pancreatitis and the type of diabetes associated with it have been named as "Fibrocalcific Pancreatic Diabetes" (FCPD). Initially categorized by WHO in 1985 as a subtype of Malnutrition Related Diabetes Mellitus (MRDM), FCPD has subsequently been included as a disease of the exocrine pancreas under other specific forms of diabetes. Despite many years since its first description, the etiopathogenesis of FCPD remains obscure. While insulin secretion defects are definitely the crux of the problem, there is growing body of evidence to suggest that insulin resistance may play a key role in glucose metabolism in these individuals. Moreover, the role of free fatty acids, counter-regulatory hormones like glucagon and impact of hepatic and peripheral lipid distribution on the dynamics of insulin secretion remains to be explored. Other factors related to alterations in energy expenditure may compound the pathogenetic picture. In fact, not all people with Fibro calculous Pancreatitis will develop diabetes and a search for the exact triggers for hyperglycemia might provide the clue to this enigmatic disease pathophysiology.

Keywords: Chronic pancreatitis, fibrocalcific pancreatic diabetes, insulin resistance pathogenetic

Introduction
Type 2 and Type 1 are the most common forms of Diabetes worldwide. However, about 1 to 5 percent of patients who present with diabetes that may be secondary to other disorders. Of these, the disorders of the pancreas are the most common. [1] Various Pancreatic disorder can cause diabetes including pancreatic infections, inflammation, neoplasms, post pancreatic surgery, cystic fibrosis and hemochromatosis. However chronic pancreatitis is the commonest pancreatic disorder associated with diabetes. [2] Chronic Pancreatitis is a heterogeneous disease. From a worldwide perspective, alcoholism is the most common cause of chronic pancreatitis [3] However, in many tropical countries akin to India, the etiology frequently includes so-called 'Tropical Chronic Pancreatitis [4, 5] and the type of diabetes associated with it has been named as "Fibrocalcific Pancreatic Diabetes" (FCPD). Initially categorized by WHO in 1985 as a subtype of Malnutrition Related Diabetes Mellitus (MRDM) [6], FCPD has subsequently been included as a disease of the exocrine pancreas under other specific forms of diabetes, as suggested by a workshop held at Cuttack (Orissa), India in 1995 [7].

Epidemiology of the disease
Over the past six decades there have been several publications where pancreatic calcification in nonalcoholic young individuals from various tropical countries and a majority of cases reported from Southern parts of India. It was Zuidema (1959) who originally reported a series of 45 patients of pancreatic calcification with diabetes mellitus from Indonesia.8 Following this report there were a series of publications of a similar type of patients from various part of Asia (India, Bangladesh and Sri Lanka) [9-10], Africa (Uganda, Nigeria, Zambia, Madagascar) [11- 13] and even in Brazil [14] The majority of publications arise from India. [15-22] More recently, a study by Balaji et al. (1994) [33] in 28,567 inhabitants from Quilon district of Kerala detected a prevalence of 0.09% [23] A study from Chennai showed a similar trend and a reduction in the incidence of FCPD. Initial studies during 1991-1995 showed a prevalence of 1.6%. However subsequent studies have shown a prevalence of 0.36% during 2001-2003 & 0.2% during 2006-2010, respectively [24-25] conducted a nationwide prospective study on chronic pancreatitis based on clinical and radiological

criteria and reported a prevalence of FCPD of 3.2%, Idiopathic Pancreatitis (60.2%), while Alcoholic Pancreatitis comprised 38.7%. This study has demonstrated the presence of a changing profile of chronic pancreatitis in India. [26] Studies from different part of India showed variable prevalence and changing hues of FCPD patients with changing times [27-28]

An etiopathogenesis: The etiopathogenesis of FCPD is still poorly understood. Several hypotheses have been proposed based on epidemiological data. Preliminary studies have described malnutrition as the main underlying osteopathological factor of FCPD [29-32] however recent studies on FCPD described malnutrition as the effect rather than the cause of disease. [33, 34]. The McMillan and Gee Varghese hypothesis linked FCPD to the consumption of cassava. [35,36] Cassava contains two important cyanogenic glycosides linamarin and lovastatin, which in the setting of malnutrition, do not get detoxified leading to pancreatic damage and thus diabetes sets in. [37] However, recent epidemiologic and experimental studies have questioned the cassava hypothesis. Heightened oxidant stress along with relative deficiency of antioxidants has also been proposed to be a possible pathogenic mechanism for FCPD. Braganza *et al*. had shown that patients with chronic pancreatitis including FCPD as associated with a heightened oxidative detoxification reaction mediated by cytochrome P450-1. [38] while preliminary study on FCPD patients have shown a high level of malondialdehyde and a decreased antioxidant level.41 Familial clustering of FCPD has been described by several authors and the role of genetic predisposition has been actively pursued. Pitchman has reported that the familial aggregation of FCPD in 17 families with two or more members had evidence of pancreatitis. A study from Chennai has shown that 8% of patients with FCPD have evidence of familial aggregation. Initial genetic studies on FCPD were conducted to detect an association with the HLA complex. Recent studies have shown alterations in Serum protease inhibitor Kazal type 1 (SPINK1), Cationic trypsinogen (PRSS1), Anionic trypsinogen (PRSS2), and Chymotrypsin C to be associated with FCPD.

Clinical features

The typical clinical presentation and natural history of FCPD includes abdominal pain, pancreatic calcification, pancreatic exocrine deficiency (steatorrhea) and Diabetes Mellitus. The onset of diabetes is usually between ages 20-30 years. Large ductal calcifications, ductal dilatation usually involving the main pancreatic duct and marked increase in risk of pancreatic malignancy are the key distinguishing features of FCPD.

Insulin secretion and insulin resistance in FCPD

The unique natures of clinical presentation of the disease and the intriguing pathogenetic mechanisms governing it have been areas of research for decades. While widespread destruction of the pancreatic β-cells would obviously lead to an impaired insulin secretion, the wide fluctuations in blood glucose levels and lack of ketosis point to a pathogenesis significantly different from the insulin deficient type 1 Diabetes Mellitus. Whether like Type 2 Diabetes Meliitus, there is a role of insulin resistance at the level of the liver and peripheral tissues, remains to be fully elucidated. Moreover, the contribution of body fat distribution and energy expenditure might also be significant in explaining the onset of diabetes in FCPD. We therefore propose a comprehensive study of metabolic and body composition parameters in individuals with Fibro calculous Pancreatic Diabetes. The novelty of our study lies in utilizing pancreatic clamps, which is the gold standard, to study the physiological variations in insulin sensitivity. This will be further Introduction 5 supplemented by the use of advanced MRI and DEXA techniques to estimate the body fat and body composition. The characterization of insulin mediated glucose fluxes and the possible relationship with body composition indices might have significant therapeutic ramifications. Diabetes management in these patients remains cumbersome, and often the widespread use of insulin leads to fatal hypoglycemia. Especially in countries like India, where discrepancies between insulin injection and adequate food intake are a major concern, this assumes even greater significance.

Conclusion

Despite many years since its first description, the etiopathogenesis of FCPD remains obscure. While insulin secretion defects are definitely the crux of the problem, there is growing body of evidence to suggest that insulin resistance may play a key role in glucose metabolism in these individuals. Moreover, the role of free fatty acids, counter-regulatory hormones like glucagon and impact of hepatic and peripheral lipid distribution on the dynamics of insulin secretion remains to be explored. Other factors related to alterations in energy expenditure may compound the pathogenetic picture. In fact, not all people with Fibro calculous Pancreatitis will develop diabetes and a search for the exact triggers for hyperglycemia might provide the clue to this enigmatic disease pathophysiology.

References

1. American Diabetes Association. Diagnosis and Classification of Diabetes. Diabetes Care. 2010;33(suppl 1):S62-9.
2. Chen N, Unnikrishnan IR, Anjana RM, Mohan V, Pitchumoni CS. The complex exocrine-endocrine relationship and secondary diabetes in exocrine pancreatic diabetes. J Clin Gastroenterol. 2011;45:850-61.
3. Gullo L. Alcohol and chronic pancreatitis: Leading or secondary enteropathogenic role? Journal of Pancreas. 2005;6(suppl 1):68-72.
4. Geeverghese PJ. In Calcific Pancreatitis. Varghese Publishing House, Bombay, c1985.
5. Mohan V, Premalatha G, Pitchumoni CS. Tropical chronic pancreatitis: an update. J Clin Gastroenterol. 2003;36:337-46.
6. WHO Study Group Report on diabetes mellitus. WHO Technical Report Series No.727. Geneva: WHO, c1985.
7. Report of the Expert Committee on the diagnosis of classification of diabetes mellitus. Diabetes Care. 1997;20:1183-97.
8. Assan R, Assan D, Thiebaut MF, Laloux S, Clauser E, Boukersi A. Diabetogenic Tropical Pancreatitis. Diabetes Metab. 1988;14:299-312.
9. Mohan V, Premalatha G. Fibro calculous pancreatic diabetes. Int J Diabetes. 1995;3:71-82.
10. Mohan V, Alberti KGMM. Diabetes in the tropics. In: Alberti KGMM, DeFranzo RA, Keen H, Zimmet P

(Eds): International Textbook of Diabetes Mellitus. John Wiley and Sons Ltd, Chichester. 1999;177-96.
11. Anand BS. Clinical profile of chronic pancreatitis in Delhi. In: Balakrishnan V (Eds): Chronic Pancreatitis in India. Trivandrum: Indian Society of Pancreatotomy, 1987; pp. 15-22.
12. Chari ST, Mohan V, Jayanthi V, *et al*. Comparative study of the clinical profile of alcoholic pancreatitis and tropical chronic pancreatitis in Tamil Nādu, South India. Pancreas. 1991;7:2-58.
13. Chari S, Jayanthi V, Mohan V, Malathi S, Madan Gopalan N, Viswanathan M. Radiological appearances of pancreatic calculi in tropical and alcoholic chronic pancreatitis. J Gastroenterology Hepatology. 1992;7:42-4.
14. Zuidema PJ. Cirrhosis and disseminated calcification of the pancreas in patients with malnutrition. Trop Georg Med. 1959;11:70-74.
15. Azad Khan AK, Banik NG, Mahtab H, Malnutrition Related Diabetes Mellitus in Bangladesh. In: Rifkin Holwell JA, Taylor SI(Eds). Proceedings of 14th IDF Congress. Amsterdam: Elsevier Sciences Publishers. 1991; pp. 944-9.
16. IIIangovekara V. Malnutrition related diabetes in Sri Lanka: fact or fiction? J Ceylon College of Physicians. 1995;28:16-25.
17. Shaper AG. Chronic pancreatic disease and protein malnutrition. Lancet. 1960;1:1223-4.
18. Kinnear TWA. Patterns of diabetes in a Nigerian teaching hospital. W Far Med J Niger PR act. 1963;40:228-33.
19. Castle WM, Wicks ACB. A follow-up of 93 newly diagnosed African diabetics for 6 years. Diabetology. 1980;18:121-3.
20. Dani R, Penna FJ, Nogueira CE. Etiology of chronic calcifying pancreatitis in Brazil: a report of 329 consecutive cases. Int J Pancreatic. 1986;1:399-406.
21. Viswanathan M. Pancreatic diabetes in India: an overview. In: Podolsky S, Viswanathan M (Eds). Secondary Diabetes: The spectrum of the diabetic syndromes. Raven Press, New York. 1980;105-116.
22. Moses SGP, Kanan V. The clinical profile of undernourished diabetes aged 30 or less with associated complications in Madras, India. In: Babam S, Goto Y, Fukui I (Eds). Diabetes Mellitus in Asia. Excerpta Medica, Amsterdam. 1976; pp. 259-262.
23. Tripathy BB, Kar BC: Observations on clinical patterns of diabetes mellitus in India. Diabetes. 1965;14:404-12.
24. Hedge JS, Kituri KH, Channappa NK. Pancreatic diabetes in Hubli area, North Karnataka. J Assoc Phys Ind. 1976;24:305-7.
25. Ahuja MMS. Talwar GP, Varma VM, Kumar A. Diabetes mellitus in Young Indians: Indian J Med Res. 1965;53:1138-47.
26. Balakrishnan V. Tropical pancreatitis (pancreatic tropicale). In: Bernades P, Hugier M (Eds): Maladies du Pancreas Exocrine. Doin, Pairs. 1987;207-27.
27. Rao SV, Chowdhutani CPD, Satyanarayana S. Pancreatic calculi and diabetes. In: Patel JC, Talwalkar NG (Eds). Diabetes in the Tropics. Diabetic Association of India, Bombay. 1966;224-238.
28. Yajnik CS. Diabetes secondary to tropical calcific pancreatitis. Baillieres Clin Endocrinol and Meta. 1992;6:777-96.
29. Kini MG. Multiple pancreatic calculi with chronic pancreatitis. Br J Surg. 1937;25:705-6.
30. Elizabeth T, Stephen PM. Pancreatic calculi. J Indian Med Assoc. 1954;24:126-8.
31. Pitchumoni CS. Special problems of tropical pancreatitis. Clin Gastroenterol. 1984;13:941-59.
32. Geevarghese PJ. Pancreatic Diabetes: A clinico pathological study of growth onset diabetes with pancreatic calculi. Popular Prakash an, Bombay; c1968. p. 110-15.
33. Balaji LN, Tandon RK, Tandon BN, Banks PA. Prevalence and clinical features of chronic pancreatitis in southern India. Int J of Pancreatic. 1994;15:29-34.
34. Mohan V, Farooq S, Deepa M. Prevalence of fibrocalculous pancreatic diabetes in Chennai in South India. Journal of the Pancreas. 2008;9:489-492.
35. Papita R, Nazir A, Anbalagan VP, *et al*. Secular trends of fibro calculous pancreatic diabetes and diabetes secondary to alcoholic chronic pancreatitis at a tertiary care diabetes center in South India. Journal of the Pancreas. 2012;13:205-9.
36. Balakrishna V, Unnikrishnan AG, Thomas V, *et al*. Chronic pancreatitis. A prospective nationwide study of 1,086 subjects from India. Journal of the Pancreas. 2008;9:593-600.
37. Mittal N, Mehrotra R, Agarwal G, *et al*. The clinical spectrum of fibro calculous pancreatic diabetes in north India. Natl Med J India. 2002;15:327-31.
38. Garg PK, Tandon RK. Survey on chronic pancreatitis in the Asia-Pacific region. J Gastroenterol Hepatol. 2004;19:998-1004.
39. Mohan V, Mohan R, Susheela L, *et al*. Tropical pancreatic diabetes in South India: heterogeneity in clinical and biochemical profile. Diabetology. 1985;28:229-32.