FIBROCALCULOUS PANCREATIC DIABETES

Dr. V. Mohan., MD., Ph.D., D.Sc., D.Sc (Hon. Causa), FRCP (London, Edinburgh, Glasgow & Ireland), FNASC., FASC., FNA, FACP, FACE, FTWAS

CHAIRMAN
DR. MOHAN’S DIABETES SPECIALITIES CENTRE,
GOPALAPURAM, CHENNAI

PRESIDENT & DIRECTOR
MADRAS DIABETES RESEARCH FOUNDATION,
SIRUSERI, CHENNAI

WHO COLLABORATING CENTRE FOR NONCOMMUNICABLE DISEASES

IDF CENTRE OF EDUCATION

ATDC Keystone Symposium, Practical Ways to Achieve Targets in Diabetes Care, July 17-20, 2014, Denver
Declaration of potential conflict of interest

I have no conflict of interest to declare
Etiologic classification of diabetes mellitus

(ADA Expert Committee (1997))

首位

Type 1 diabetes  (β cell destruction, usually leading to absolute insulin deficiency)

a. Immune mediated
b. Idiopathic

Type 2 diabetes  (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)
Other specific types

Genetic defects of β cell function
Genetic defects in insulin action
Diseases of the exocrine pancreas e.g. FCPD
Endocrinopathies
Drug - or chemical induced
Infections
Uncommon forms of immune-mediated diabetes
Other genetic syndromes sometimes associated with diabetes

Gestational diabetes mellitus (GDM)
HISTORICAL BACKGROUND OF FCPD

1959
Zudeima’s first description from Indonesia

1960
Shaper’s report from Uganda

1962
Geevarghese’s first study from Kerala, world’s largest series around 1700 patients cases - considered to be the Father of TCP

1962 - 1981
Existence of FCPD confirmed in Brazil, Kenya, Nigeria and several countries in Asia eg. Thailand, Bangladesh, Sri Lanka
<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Till 1985</td>
<td>This entity was not given due recognition</td>
</tr>
<tr>
<td>1985</td>
<td>WHO study group report introduced the term Malnutrition Related Diabetes Mellitus (MRDM) where the term Fibrocalculous Pancreatic Diabetes (FCPD) was introduced</td>
</tr>
<tr>
<td>1997</td>
<td>ADA expert committee deleted MRDM. FCPD now classified as a subtype under other specific types as diseases of the Exocrine Pancreas</td>
</tr>
<tr>
<td>1998</td>
<td>Provisional report of WHO consulting group ratified ADA recommendation</td>
</tr>
</tbody>
</table>
FCPD DEFINITION (Mohan et al, 1985)

Diabetes secondary to non-alcoholic chronic pancreatitis of uncertain etiology predominantly seen in tropical developing countries
FCPD DEFINITION

- Severe diabetes
- Associated with undernutrition
- Usually non ketotic
- Presence of pancreatic calculi on X-ray abdomen or evidence of chronic pancreatitis on ultrasound or CT
- Usually requires insulin for control
- Usually seen in poor people
WORLDWIDE DISTRIBUTION OF MRDM (FCPD) AND PDDM

Reproduced from WHO study Group on Diabetes Mellitus (1985) with permission
DISTRIBUTION OF FCPD IN INDIA
DIAGNOSTIC CRITERIA FOR FCPD
(MOHAN et al, 1985)

- Occurrence in tropical country
- Diabetes (WHO criteria)
- Evidence of chronic pancreatitis
  - Pancreatic calculi
  - OR
  - ERCP evidence of CP
  - OR
  - Ultrasound/CT features
  - Plus h/o abd. Pain / steatorrhoea
  - Plus abnormal pancreatic function
- Absence of other causes of CP (eg. alcoholism)

Classical triad of FCPD

- Abdominal pain
- Pancreatic calculi
- Diabetes
PLAIN ABDOMINAL RADIOGRAPH SHOWING MULTIPLE PANCREATIC CALCULI
ULTRASOUND IMAGE OF PANCREAS IN A FCPD PATIENT
ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAM (ERCP) OF FCPD PATIENT
Macroscopic appearance of pancreas in FCPD
Histopathology of pancreas in FCPD

Dense fibrosis entirely replacing exocrine tissue
CLINICAL SPECTRUM OF FCPD

WHAT IS THE EXPLANATION FOR KETOSIS RESISTANCE?

C-PEPTIDE LEVELS IN DIFFERENT GROUPS OF DIABETES

FCPD AND KETOSIS RESISTANCE

- Partial presentation of beta cell function (insulin reserve)
- Pancreatic alpha cell (glucagon) deficiency
- Low adipose mass/decreased supply of non-esterified fatty acids
- Carnitine deficiency

PROTECTION FROM KETOSIS
DO MICROVASCULAR COMPLICATIONS OCCUR?

MICROVASCULAR COMPLICATIONS DO NOT OCCUR IN SECONDARY FORMS OF DIABETES

Harrison’s Textbook of Diabetes (1981)
Prevalences of Microvascular and Macrovascular diabetic complications in subjects with FCPD compared with NIDDM patients

<table>
<thead>
<tr>
<th>Percentage of subjects with complications</th>
<th>Type 2 Diabetes (n = 277)</th>
<th>FCPD (n = 277)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinopathy</td>
<td>37.2</td>
<td>36.1</td>
</tr>
<tr>
<td>Non-proliferative</td>
<td>31.4</td>
<td>32.9</td>
</tr>
<tr>
<td>Proliferative</td>
<td>5.8</td>
<td>3.6</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>15.0</td>
<td>10.1</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>25.3</td>
<td>20.9</td>
</tr>
<tr>
<td>Macrovascular disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infarction</td>
<td>5.4</td>
<td>2.2</td>
</tr>
<tr>
<td>Ischaemia</td>
<td>6.5</td>
<td>2.5*</td>
</tr>
</tbody>
</table>

*p = 0.04 compared to Type 2 diabetes

NATURAL HISTORY OF FCPD

TCP (PRE-FCPD)  TCP-IGT  FCPD WITHOUT COMPLICATIONS  FCPD WITH COMPLICATIONS
NORMAL GTT  IGT  CLINICAL DIABETES

Fibrocalculous Pancreatic Diabetes

Long-term survival analysis

VISWANATHAN MOHAN, MD, MNAMS, PHD
GOPAL PREMALATHA, MBBS
AUDINARAYANAN PADMA, BSC, MA
SURESH T. CHARI, MD, DM
CAPECOMORIN S. PITCHUMONI, MD, FRCP

OBJECTIVE — To determine the long-term survival and causes of death in fibrocalculous pancreatic diabetes, a form of diabetes secondary to tropical chronic pancreatitis.

RESEARCH DESIGN AND METHODS — A cohort of 370 patients with fibrocalculous pancreatic diabetes were analyzed with respect to survival time from the date of occurrence of the first symptom of the disease as well as after the onset of diabetes. The cause of death was analyzed in the patients who died. Cumulative survival rates were calculated by the actuarial method, and life table graphs were plotted by mathematical calculations.

RESULTS — Long-term survival of patients with fibrocalculous pancreatic diabetes is much better today than that described 30 years ago. About 80% of patients were alive 35 years after the first episode of abdominal pain. The median survival time after the diagnosis of diabetes was 25 years. These figures, however, are still considerably lower than the life expectancy of the age- and sex-matched general population. Diabetic nephropathy was the main cause of death. Pancreatic cancer and other chronic pancreatitis-related causes as well as malnutrition and infections were also important contributors to mortality.

CONCLUSIONS — The overall prognosis for patients with fibrocalculous pancreatic diabetes appears to have improved possibly because of earlier diagnosis, better management of diabetes, and improved nutrition.

Fibrocalculous pancreatic diabetes is a unique form of diabetes secondary to tropical nonalcoholic chronic pancreatitis (1-3). Tropical chronic pancreatitis invariably sets in soon thereafter (2,3,8-11). The prevalence of diabetes in tropical chronic pancreatitis is considerably higher (>90%) than in temperate-
<table>
<thead>
<tr>
<th>Cause</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes Related (Nephropathy etc)</td>
<td>10</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>8</td>
</tr>
<tr>
<td>Infection / Emaciation</td>
<td>4</td>
</tr>
<tr>
<td>Chronic Pancreatitis Related</td>
<td>5</td>
</tr>
<tr>
<td>Surgical Complications</td>
<td>1</td>
</tr>
<tr>
<td>Keto Acidosis</td>
<td>1</td>
</tr>
</tbody>
</table>

ORIGINAL ARTICLE

Secular Trends of Fibrocalculous Pancreatic Diabetes and Diabetes Secondary to Alcoholic Chronic Pancreatitis at a Tertiary Care Diabetes Centre in South India

Rozario Papita1, Adamsha Nazir1, Viknesh Prabu Anbalagan1, Ranjit Mohan Anjana1, Capecomorin Pitchumoni2, Suresh Chari3, Viswanathan Mohan1

1Dr. Mohan’s Diabetes Specialities Centre and Madras Diabetes Research Foundation. Chennai, India. 2Saint Peter’s University Hospital. New Brunswick, NJ, USA. 3Mayo Clinic. Rochester, MN, USA

ABSTRACT

Context Data on prevalence and trends in diabetes secondary to chronic pancreatitis in developing countries is scarce. Objective To compare the secular trends in the prevalence of fibrocalculous pancreatic diabetes (FCPD) and diabetes secondary to alcoholic chronic pancreatitis (ACP) at a diabetes centre in south India. Design A retrospective analysis was done of all patients registered at Dr. Mohan’s Diabetes Specialties Centre, Chennai, India between January 1991 and December 2010. Patients A total of 1,079 subjects with diabetes secondary to chronic pancreatitis were identified, of whom 47 were excluded because of difficulty in classification. Main outcome measure The number of patients with FCPD and diabetes secondary to ACP were calculated as a function of the total number of patients registered at the centre each year.

### Prevalence of FCPD and diabetes secondary to ACP at our centre from 1991-2010

<table>
<thead>
<tr>
<th>Period of study</th>
<th>Total diabetes patients registered at the centre</th>
<th>No. Prevalence of FCPD*</th>
<th>No./ Prevalence of diabetes secondary to ACP**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991-1995</td>
<td>23,788</td>
<td>371 (1.6%)</td>
<td>12 (0.1%)</td>
</tr>
<tr>
<td>1996-2000</td>
<td>35,368</td>
<td>226 (0.6%)</td>
<td>25 (0.1%)</td>
</tr>
<tr>
<td>2001-2005</td>
<td>48,192</td>
<td>179 (0.4%)</td>
<td>40 (0.1%)</td>
</tr>
<tr>
<td>2006-2010</td>
<td>70,394</td>
<td>122 (0.2%)</td>
<td>57 (0.1%)</td>
</tr>
<tr>
<td>Total cases</td>
<td>177,742</td>
<td>898 (0.5%)</td>
<td>134 (0.1%)</td>
</tr>
</tbody>
</table>

*P for trend* < 0.001; **P for trend = 0.155

Change in mean age at diagnosis of patients with FCPD and diabetes secondary to ACP during the years 1991 to 2010

ETIOPATHOGENESIS

- Malnutrition - ? Overt
  - ? Micronutrient
- Cassava (Tapioca)

- LIMITED EXPERIMENTAL EVIDENCE
- NO DIRECT PROOF FOR CASSAVA AS A PANCREATIC TOXIN
- MOST OF THE STUDIES ARE SHORT-TERM
Genetic studies on FCPD

<table>
<thead>
<tr>
<th>TYPE 2 DM</th>
<th>FCPD</th>
<th>TYPE 1 DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>INSULIN GENE</td>
<td>HLA-DQβ</td>
<td>HLA-DQα</td>
</tr>
<tr>
<td>Trypsinogen gene</td>
<td>-</td>
<td>No association</td>
</tr>
<tr>
<td>REG gene</td>
<td>-</td>
<td>No association</td>
</tr>
</tbody>
</table>

Mohan V and Hitman GA, Diabetes / Metabolism Research and Reviews. 2000;16:454-457
GENE MUTATIONS ASSOCIATED WITH FCPD

Genetic alterations in the trypsinogen pathway

- Serum protease inhibitor Kazal type 1 (SPINK1)
- Cationic trypsinogen (PRSS1)
- Anionic trypsinogen (PRSS2)
- Chymotrypsinogen C (CTRC)

Alteration in other genes

- Cystic fibrosis transmembrane conductance regulator (CFTR)
- Regenerating islet-derived genes 1α (REG1A & REG1B)
- Cathepsin B (CTSB)
- Angiotensin converting enzyme (ACE)
- Calcium-sensing receptor (CASR)
ASSOCIATION OF SPINK GENE WITH FCPD


- Schneider A, et al. SPINK1/PSTI mutations are associated with tropical pancreatitis and type II diabetes mellitus in Bangladesh Gastroenterology. 2002.


Current Theories About The Aetiopathogenesis of FCPD

Genetic Factors
Association SPINK gene and other genes

Defective B cell growth and repair
Calcite stone formation
Duct obstruction

Acinar and B cell damage

Pancreatic exocrine deficiency
Impaired Glucose Tolerance
Steatorrhea
FCPD

Environmental Factors
Malnutrition
Excessive dietary oxidants and / or antioxidants
Dietary toxins
MANAGEMENT OF FCPD – PRINCIPLES

- Treatment of abdominal pain
- Use of pancreatic enzymes
- Management of diabetes
Management of Diabetes

★ **Diet**
- Principles similar to that of other types of diabetes
- More liberal calorie intake
- High protein intake

★ **Oral Hypoglycaemic drugs**
- Sulphonyureas can be used if β cell function is good
- Biguanides usually not used as the FCPD patients are lean

★ **Insulin**
- Would be needed in majority of the cases to achieve blood sugar control in FCPD patients
# Heterogeneity in FCPD

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
</table>
| **1. Symptoms** | - Asymptomatic  
- Marked symptoms |
| **2. Carbohydrate intolerance** | - Normal glucose tolerance  
- IGT  
- Overt diabetes |
| **3. B - cell reserve** | - Good  
- Poor  
- Negligible |
| **4. Response to therapy** | - Diet alone  
- Oral agents  
- Insulin |
| **5. Proneness to ketosis** | - Ketosis - resistant  
- Ketosis – prone |
| **6. Exocrine dysfunction** | - Only after provocative tests  
- Clinical steatorrhoea |
| **7. ERCP** | - Absent to mild ductal changes  
- Marked ductal changes |
| **8. Histopathology** | - Mild changes : calculi  
- absent or small  
- Marked changes : extensive  
- fibrosis, ductal dilatation,  
- multiple calculi |