AETIOPATHOLOGY OF MALNUTRITION RELATED DIABETES MELLITUS (MRDM) PATIENTS IN BANGLADESH

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DEDICATED TO

MY DEAR WIFE: PROF. DR. HOSNE ARA TAHMIN

AND MY DARLING DAUGHTERS

DR. TABASSUM TAHMIN SAJANI

TANJILA TAHMIN SARNALI

TILOTTAMA TAHMIN SHARUPA

AND MY INLAW ENGR.YASIR MURSALIN

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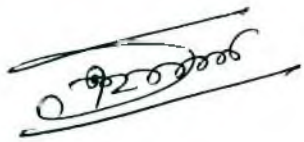

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CONTENTS

List of Abbreviations Used

BC		Before Chriest
BIRDEM		Bangladesh Institute of Research & Rehabilitation in Diabetes, Endocrine & Metabolic Disorders
BMI		Body Mass Index
BUN		Blood Urea Nitrogen
CT scan		Computerized Tomography Scanning
DM		Diabetes Mellitus
ERCP		Endoscopic Retrograde Cholangiopancreatography
ESRD		End Stage Renal Disease
FCPD		Fibrocalculus Pancreatic Diabetes
FF		Filtration Fraction
FFA		Free Fatty Acid
GFR		Glomerular Filtration Rate
GH		Growth Hormone
GMD		Gestational Diabetes Mellitus
HbA_1c		Glycosylated Haemoglobin
HLA		Human Leukocytic Antigen
IDDM		Insulin Dependent Diabetes Mellitus
Ig		Immunoglobulin
IGT		Impaired Glucose Tolerance
IMC		Ibrahim Medical College
ISE		Ion Selective Electrode
MHC		Major Histocompatibility Complex
MRDM		Malnutrition Related Diabetes Mellitus
NIDDM		Non Insulin Dependent Diabetes Mellitus
PDPD		Protein Deficient Pancreatic Diabetes
PSP		Pancreatic Stone Protein
NIH		National Institute of Health
NDDG		National Diabetic Data Group
ADA		American Diabetic Association
RID		Radial Immunodiffusion
RPF		Renal Plasma Flow
AIHA		Auto Immune Haemolytic Anaemia
SLE		Systemic Lupus Erythomatosus
H&E		Hematoxylin and Eosin
FBS		Fasting Blood Sugar
RTI		Respiratory Tract Infection
STP		Serum Total Protein
T_1D		Type 1 Diabetes
T_2D		Type 2 Diabetes
WHO		World Health Organization

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Photograph (MRDM patients, Control, Radiology & ERCP plates)

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Illustrations

IHC for T cell (CD3), B cell (CD20), p53, & bcl 2

Summary

1.0 SUMMARY

Malnutrition Related Diabetes Mellitus (MRDM) is a new entity of insulin requiring diabetes mentioned in the classification of diabetes by WHO expert committee on diabetes in 1985. The patients are undernourished, usually under 30 years of age, body mass index (BMI) <17, who requires large doses of insulin for their glycemic control, but due to some insulin reserve do not develop residual ketoacidosis. Although in recent WHO classification (1993) this type of diabetes have been merged in the category of pancreatic diabetesw,this type of diabetes is very common in the developing countries of the tropics and Asia, Africa, Pacific regions of the World, including Bangladesh where the incidence of IDDM is rare or much less than the developed countries. In Bangladesh, under 30 diabetics(MRDM) accounts for about 30% of the total registered patients at Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM). Many epidemiological factors like malnutrition, infection, immunological destruction of pancreatic beta cells, consumption of cyanogenic food like cassava etc. are implicated in its etiopathology, but their precise role is uncertain. More over these studies were carried out in other countries. To help understanding the etiopathology of under 30 diabetics(MRDM) in the context of Bangladesh. I have studied 45 MRDM patients and 20 age and sex matched control, (BMI <17, under 30). Their detail history, food habits, socioeconomic condition, height, weight, family history of diabetes, education status, smoking habit, history of taking insulin or any other drug, present or past stigmata of malnutrition, clinical complains were recorded in a prescribed Proforma. Biochemical tests like FBS, RBS, HbA_{1c}, Lipid profile, STP, Urea, Creatinine, Amylase, Electrolytes, HLA typing for ABC loici, C3 and C4, immunoglobulins like IgA, IgM, IgG, blood grouping and Rh were done and the results were recorded. The data were analyzed statistically using two way multi variance test and Chi square test and the results are plotted in tables, graphs and placed in the thesis.

Anthropometric measurements and BMI showed significant difference between MRDM and controls. Height (mean ±SD) of MRDM patients were 153.27±10.53 cm and those of control were 160.25±07.07 cm, p<0.003; while weight (mean ± SD) of MRDM patients were 35.42±10.05 kg and for control it was 40.35±10.20 kg, p<0.079; the BMI (mean ± SD) of MRDM patients were 14.98±2.72 and for control this 17.27±1.79, p<0.00 respectively.

Glycaemic status (FBS, PPS, HbA1c) showed statistical significanct difference between MRDM patients and control subjects (Mean±SD of FBS, PPS, HbA1 were 21.24±6.20mmol/l, 30.28±7.65mmol/l, 13.46±2.56% vs 4.70±0.49mmol, 5.76±0.43mmol/l, 5.12±0.30%, p<0.000). indicating the role of hyperglycemia producing oxidative stress and increased apoptosis in pancreatic beta cells, uncontrolled diabetes, non enzymatic glycosylation in the etiopathology of this type of diabetes.

Dyslipidemia was associated with MRDM. This was evidenced by higher TG level in patients (mean±SE) 178.58±77.21 mg% than controls (mean±SE) 145.89±55.83 mg%. Also there were significant lowered value of HDL and total cholesterol in MRDM than the control subjects. Mean±SE of HDL and total cholesterol in MRDM patients were 33.07+4.60 mg% and 141.21±23.28 mg% while that of control subjects were 50.85+6.08 mg% and 159.42±37.63 mg% (p<0.000 and p<0.05).

Renal function tests were within normal limit in both MRDM and control patients but, some significant difference was observed among MRDM and control group between the observed value. BUN level was higher in MRDM patients (mean ±SE 27.22±14.09 mg%) than control (mean±SE 24.73±2.85 mg%, serum creatinine was significantly higher (mean±SE 0.92±0.21 mg% in MRDM, 0.75±0.21 in controls, p<0.001) and serum total protein was significantly lowered (mean±SE 7.39±0.12 vs 7.82 ±0.64 g/l) in MRDM than the controls (p<0.01). This reflects increased catabolism, lower protein intake in MRDM than the controls.

Exocrine pancreatic function was abnormal in MRDM patients. This was reflected by significant lower serum amylase level in MRDM patients (mean ± SE 150±0455.48 mg%) than the control (mean±SE 171.60+19.26 mg%, p<0.02).

Electrolyte imbalance was also a common feature of MRDM patients. Serum potassium was higher (mean ± SE 4.61±0.73 meqv/1) in MRDM than controls (mean±SE 4.34±0.29 meqv/l). Serum sodium (mean±SE 135.71±3.86 meqv/l, 137.26±3.57 meqv/l), CO_2 were lower in MRDM (mean±SE 24.59±3.78 mequ/l 25.62±1.47) than controls where as serum chloride level was significantly lower (p<0.001) in MRDM (mean±SE 95.63±5.21 meqv/l) than the control (mean±SE 111.73±18.26 meqv/l).

Immunological abnormalities could be an important factor in the development of MRDM. The concentration of IgG, IgM were statistically same in both MRDM and the control, but IgA concentration in MRDM patients was statistically higher (p<0.004) (mean+SE 313.39+22.25) than controls (mean±SE 206.89±42.66). Serum complement level also showed abnormality in MRDM patients, C3 level was similar in MRDM (mean±SE 134.29±46.76) and the control (mean±SE 137.32±30.78), but C4 level was significantly higher (p<0.05) in MRDM (mean±SE 41±23.21) than the control (mean+SE 28.16±10.70). So complement mediated immuno-destruction of pancreatic beta cell may be an associated factor in MRDM.

Poverty seems to be an important contributory factor in the development of MRDM. Patients with low income are statistically more prone to develop MRDM (p<0.05) than the controls. Similarly illiteracy is also another associated factor in the development of MRDM. Significant association with illiteracy is seen in MRDM patients (p<0.005) when compared to control group.

Genetic association to some extent have been found to be associated in MRDM patients. Significant association was found in MRDM patients having blood group "O", "A" when compared to control ($p<0.02$). HLA typing with A,B,C antisera showed higher A2 (40%), CW5 and CW6 (20%) positive in MRDM patients whereas, A9 and All (40%) and CW4 (20%) were found to be common in control subjects.

Histopathological examination of the pancreatic tissue from 20 FCPD patients showed marked fibrosis, glandular atrophy, dense chronic inflammatory infiltrate pointing towards immunological medicated injury of pancreas. The findings are more marked in MRDM patients when compared with patients of chronic pancreatitis. It is evident from the IHC that there is T and B cell activation leading to both humoral and cell mediated immunity in the etiopathogenesis of MRDM particularly the FCPD variant.Also there is indirect evidence of increased apoptosis as evidenced by complete negative bcl-2 staining and p53 staining. This corroborates that immunological destruction and increased apoptosis of pancreatic beta cells are responsible for the etiopathogenesis of MRDM.

Diets containing cyanides like Khesari Dal (*Lathyrus Sativum Linn*), Mug dal, cucumber(*Cucumis sativus*), papaya (*Carica papaya*), used commonly by poor people and other toxic substances like arsenic contained in water commonly used by poor people particularly in rural areas of Bangladesh may be implicated in the development of MRDM as evident from their dietary history. However, these factors need to be substantiated from more elaborative studies in future.

Introduction

2. INTRODUCTION

Diabetes mellitus (DM) is a world wide chronic disease with the prevalence rate varying from 0.24 to 5.5% (Thandanand et al. 1984). Three small surveys in Bangladesh showed the prevalence rate of IGT and DM to be 1.5 to 3.3% respectively (Ali SKM et al, 1985, Mahtab H et al. 1976, Sayeed M et al. 1985, Sayeed et al. 1992). Diabetes afflicts large numbers of people of all social conditions throughout the world. There are many factors which play a role in the development of the disease including genetic predisposition environment, nutrition, infection, hormones, drugs etc.

Diabetes and its complications are major health problems for the patients. Acute complications including diabetic ketoacidosis, hyperosmolar non-ketotic coma and hypolycaemia are almost always treatable and reversible. But the chronic complications like retinopathy, nephropathy, neuropathy, cardiovascular complications and diabetic foot care are persistent problems not always reversible and may lead to organ loss or even death.

Apart from the two primary forms of diabetes, insulin dependent diabetes mellitus (IDDM) and non-insulin dependent diabetes mellitus (NIDDM), malnutrition related diabetes mellitus (MRDM) has been recently recognized as a separate entity (WHO Study Group on diabetes mellitus, 1985). Incidence of IDM is rare or even absent in the developing and under developed countries, and therefore, MRDM accounts for 30-70% of all cases of youth onset diabetes in general in these countries. This new category of diabetes includes the variety of types known in the past as tropical diabetes, pancreatic diabetes, pancreatogenetic diabetes, endocrine pancreatic syndrome and ketosis resistant diabetes of the young. Extensive review of epidemiological, clinical and biochemical studies on MRDM have suggested the existence of two subclasses of MRDEM, viz (a) fibrocalculous pancreatic diabetes (FCPD) and (b) protein deficient pancreatic diabetes (PDPD).

Although WHO study group in 1999 changed this classification and now it is recommended that the class MRDM be deleted, The form subtype of MRDM, PDPD (PDPD or PDDM)

may be counted as a malnutrition modulated or modified form of diabetes mellitus for which were studies are needed. The other form subtype of MRDM, FCPD is now classified as a disease of the exocrine pancreas, fibrocalculos pancreatic which may lead to DM.

2.1 Fibrocalculous pancreatic diabetes:

The characteristic features of FCPD is the stone formation in the main pancreatic duct and its branches, together with extensive fibrosis of pancreas. Cases of FCPD have been reported in several countries of the world including Bangladesh, Brazil, India, Indonesia, Jamaica, Madagascar, Nigeria, Sri Lanka, Thailand, Uganda, Zaire and Zambia. The several of these countries an estimated 20-70% of the diabetics, first present below the age of 30 years and many during childhood (King H et al. 1983, West KM et al. 1980, Tjkroprawiro A et al. 1990, Bajaj JS et al. 1988, Ekoe JM et al. 1985, Tripathy BB et al. 1984, Ratnam VJ et al. 1984, Gupta OP et al. 1984, Tandhanand S et al. 1987). Also these patients complain of recurrent attacks of abdominal pain. Male female ratio among these diabetic is 3:1 patients are grossly underweight and other stigmata of past or present malnutrition may be seen. The key metabolic features are moderate to severe hyperglycaemia that requires insulin for control, sometimes in high does and the absence of ketosis. There is extensive damage of pancreatic islets of these patients with greatly diminished residual insulin production and associated concomitant glucagon deficiency. This probably explains the characteristics though not invariable absence of ketosis in this particular type of diabetes.

There is no association between FCPD and gall bladder disease, or, in most cases, excessive alcohol intake, and no indication that the characteristic fibrosis is post inflammatory in nature.

Epidemiological observations strongly suggest an association between the global distribution of FCPD and the consumption of Cassava Root (tapioca, manico). Cassava is

the main source of cattle feed in several regions. Cassava root contains several cyanogenic glucosides, namely linemarin and lotaustralin, which liberates hydrocyanic acid on hydrolysis, is the most import. Cyanide is detoxified by several pathways, mainly those involving sulfur containing amino acids. The main end product is thiocynate which is excreted in the urine. High Cassava intake combined with inadequate intake of protein, particularly if deficient in sulfur containing amino acids, creates conditions for the accumulation of cyanide in the body (Tripathy BB et al. 1984, Oil NJ et al. 1980, Samal KK et al. 1992, Patney NL et al. 1984, Venkataraman S et al. 1990, Bajaj Js et al. 1984).

Studies indicate that protein intake is low in Cassava consuming populations and this has been suggested as an explanation for the high prevalence of FCPD in parts of Indonesia and Kerala state in India. The hypothesis that Cassava intake and protein malnutrition are casually related to FCPD requires further detailed nutritional and epidemiological studies in the developing countries where this form of diabetes is found.

Other foods, such as Sorghum Yam Millet and some variants of beans may also be sources of dietary cyanide. Amygdalin, a cyanogen, occurs in fruits, such as, almond, apricot, peas and quince. High intake of other toxic food factors, such as, nitrosamine, may act similarly when combined with malnutrition. Malnutrition may also enhance susceptibility to certain infective agents.

The mechanism of stone formation in FCPD and the relation between cyanide, food and stone formation are not very clear. However, recent experimental evidence has shown that in the rats fed on a high Cassava diet for a period upto 18 months, morphological changes in the pancreas such as dilatation of ductules, papillary infoldings, cellular disquamation and presence of eosinophilic material in ductular system can well be demonstrated. These changes resemble those which have been observed in early stages of FCPD. It has,

therefore, been suggested that the following constitute the two essential process underlying

the causation of stone formation in FCPD.

1. Desquamation of ductular epithelium, dilatation of ductules and presence of proteinacious eosinophilic material in ductular system.
2. High calcium content in the pancreatic juice with crystallisation of calcium carbonate leading to the presence of crystalline aggregate which get enmeshed and embedded in gelatinous material in the pancreatic duct and its branches. In addition, presence of high calcium in pancreatic juice in subjects with FCPD leads to crystallisation of calcium carbonate. It has been suggested that the calculogenesis may be aggrevated by a decrease in the amount of pancreatic stone protein (PSP). Although no quantitative measurement of PSP in stones obtained from subjects with FCPD are yet available, it is of interest to note that the PSP from such calculi is immunologically identical to that present in calculi in patients with alcoholic pancreatitis. This may indicate that while the initiating mechanism and early pathogenic pathways may be different, there may yet be a common final pathway contributing to stone formation (Bajaj JS et al. 1985). Recently gene markers SPINK1 gene N34S mutation is found to be strongly associated with pancreatitis of FCPD in Bangladesh (Md. Zahid Hassan, 2006)

From the above review, it may be summarized that stone formation is possibly facilitated by desquamated epithelial cells and proteinous secretion inside the dilated ducts. It is possible that these two elements form a Indus which when calcified gives rise to stone. It is conceivable that elevated level of calcium in the pancreatic juice furthers the development of stone.

Diagnosis of FCPD is based upon the characteristic is clinical features and supported by radiographic demonstration of calculi in the pancreatic ducts. Pancreatic calcification can be

detected in 75% of patients with FCPD. In the remainder ultrasonography may indicate obstruction, dilatation and calcification of the pancreatic ducts. Other supportive investigations included computerized tomographic imaging and endoscopic retrograte cholangiopancreatography. Abnormalities of exocrine pancreatic function are also present.

Microscopically the most typical features are diffuse interlobular and periductular pancreatic fibrosis with progressive acinar and islet replacement by fibropathy tissue. There is little or no evidence of inflammation. Although the viscid material in the main pancreatic duct and its branches is almost always bacteriologically sterile but it does not exclude the possibility of FCPD being initiated by a non-bacterial infective process.

2.2 PDPD

The important feature of this type of MRDM is resistance to the development of ketosis, partial resistance to the action of insulin, extreme degree of wasting and emaciation and an onset of symptoms before the age of 35 years, commonly between 15 and 25 years of age. Pancreatic calcification and fibrosis are absent. Male preporderance were found in Asian subjects and equal sex distribution in some areas of India and Africa (Gupta et al. 1984, Ahuja MMS et a. 1983, Samal KC et al. 1990).

The disease is commonly seen and reported from Bangladesh, Brunei Darussalam, Fiji, Ghana, India, Indonesia, Jamaica, Kenya, Malawi, Malaysia, Nigeria, Papua New Guinea, South Africa, Uganda, United Republic of Tanzania and Zaire. It has been described previously as J-type diabetes, M-type diabetes, malnutrition diabetes and ketosis resistance youth onset diabetes.

The sex incidence varies considerably in different parts of the world. In Asia, men are predominently affected (2-3:1), whereas in African countries, such as Nigeria, the sexes are equally affected, a female preponderence from the West Indies.

Patients with both types of MRDM are characteristically underweight and have clinical stigmata of present or past malnutrition and of other deficiency states, but three features appear to distinguish the protein deficiency type-(i) absence of a history of recurrent bouts of abdominal pain, (ii) absence of radiographic or other evidence of interductal pancreatic calcification or dilatation of the ducts, and (iii) absence of demonstrable malabsorption of nutrients caused by exocrine pancreatic insufficiency.

Measurement of insulin secretion in patients with protein deficient pancreatic diabetes (PDPD) demonstrated a decreased but non-delayed response to an oral glucose load, whereas in carefully matched IDDM patients, the insulin response was virtually absent. It is the residual insulin secretion, which probably explains the absence of ketosis in PDPD patients.

The decreased insulin response after oral glucose loading is similar to that observed in kwashiorkor and contrasts with the nearly normal response in marasmus (kwashiorkor and marasmus are both syndromes of infantile and early childhood malnutrition). Damage to the B-cells in kwashiorkor may well explain the associated impaired carbohydrate tolerance. The experimental induction of protein malnutrition in the rhesus monkey (Macaca mulatta) produce a pattern of endocrine and metabolic features thatresemble those of kwashiorkor and protein deficient pancreatic diabetes (Bajaj JS et al. 1985).

As MRDM is a new entity of diabetes recognized recently, there are major lacunae in our knowledge regarding its aetiopathology including genetic predisposition, immunological status, prevalence complications etc. Therefore, these factors need to be studied more closely, particularly in the context of Bangladesh.

With the above background, the present study has been, designed with the following objectives:

Objectives

3.1 . General objective:

The general objective of this research to study the etiological heterogeneity of MRDM patients as a part of an attempt to explore the etiopathogenesis of diabetes mellitus in the young Bangladeshi population.

3.2 . Specific objective:

(1) To identify etiological factor/factors responsible for MRDM in Bangladesh.

(2) To see whether there is any genetic predisposition for development of MRDM.

(3) To find out impaired immunological status (cellular and humoral antibody status) in MRDM patients, if any.

(4) To see the histopathological changes in the pancreas in Fibrocalculus Pancreatic Diabetes(FCPD) patients.

This work may throw light on identification of some possible markers of MRDM and will subsequently lead to evolve better strategies for its early management in Bangladesh.

Review of Literature

4.1. Background of Diabetes Mellitus

Diabetes mellitus (DM) has been known to affect human individuals for thousands of years. The oldest documentation of diabetes was traced back to Egyptian Papyrus around 1550 years BC (Major 1939). DM was also known to the ancient Indian genius Sushruta and Acharya Charak. Graphic pictures, presumably depicting diabetes like symptoms, had been mentioned in the compiled teachings of Acharya Charak in "The Charak Samihta' around 600 BC (Tripathy et al., 2002). Sushruta, an astute physician, around 400 BC described a comprehensive account of diabetes mellitus in his famous writing 'The Sushruta Samihta' (Tripathy et al., 2002, Frank 1957). Sushruta termed the disease as Madhumeha 'rain of honey' obesrving the feature of ants attracted to the urine, a suggestion of sweetness of urine. He clearly mentioned two distinct froms of diabetes-one associated with emaciation, dehydration, polyuria an lassitude, a hint of present day type 1 DM and the 'other group' associated with stout built, gluttony, obesity and sleeplessness, which refers to present day type 2 NIDDM).

The Greek word Diabetes, 'means flow trhrough siphon', was coined by 'Aretaeus' of Cappedocia in Asia Minor in the second century AD because of profuse amount of urine passed by a diabetic patient (Papaspyros 1964) and the adjectives 'Mellitus' (both in Latin and Greek it means honey) used by Thomas Wills in 1675 after rediscovering the sweetness of urine and blood of patients 'first noticed by the ancient Indians. It was only in 1776 that Dobson firstly confirmed the presence of excess sugar in urine and blood as a cause of their sweetness (Dobson 1776). The role of the pancreas in pathogenesis of diabetes was discovered by von Mering and Minkowski (von Mering and Minkowski 1889). However, this finding was preceded by discovery of small islands 'heaps' of cells within the pancreas by Paul Langerhans in 1869, later termed as Islets of Langerhans (Langerhans 1869).

The important features of this type of diabetes mellitus as first described by Hugh Jones in 1955 of cases of insulin resistant, ketosis, youth onset diabetes that the entity was dedicated as J-type diabetes from Jamaica (hence J-type diabetes) include resistant to the development of ketosis, partial resistance to the action of insulin, extreme degree of asting and emaciation and onset of symptoms before the age of 35 years, commonly between 15 to 25 years of age. The disease has since been reported from several countries in Asia and Africa. The previous name for this disease, such as J-type diabetes, M-type diabetes, ketosis resistant , youth-onset diabetes etc. have been discarded by the WHO Study Group on diabetes mellitus 1985.

Since then a large number of such case have been reported from several tropical and some non-tropical developing countries, including, Bangladesh, Brunel, Barussalam, Cameroon, Ethiopia, Fiji, Ghana, India, Indonesia, Ivory Coast, Kanya, Malawi, Nlgeria, Papua New Guinea, South Africa, South Korea, Sri Lanka, Togo, Tanzania, Thailand, Uganda and Zaire.

Since its early description in Indonesia an Z-type diabetes mellitus FCPD has been recognized and reported in several countries including Bangladesh, Benin, Brazil, Cameroon, Ghana, India, Ivory Coast, Jamaica, Kenya, Madagaskar, Nigeria, South Africa, Sri Lanka, Thailand, Togo, Uganda, Zaire and Zimbabwe.

Criteria for diagnosis of MRDM

At present there are three available methods for diagnosing MRDM.

Table 1.A (Ahuja,1972)

1. The criteria for the diagnosis of MRDM as given by Ahuja.

   (a) A blood glucose greater than 200 mg% at anytime

   (b) Onset of diabetes before the age of 30 years

   (c) Body Mass Index less than 18 kg/m^2

   (d) Absence of ketosis

   (e) Poor socioeconomic status or history of childhood malnutrition

   (f) Insulin requirement, end more than 60 units/24 hours or more than 1.5 units/kg/24 hours.

Table 1.B (Bajaj,1988)

2. Bajaj's criteria for diagnosis of MRDM

Clinical profile	Point score
Age of onset between 10-30 years	1
Leanness with body mass index below 19	2
Frequency history of malnutrition in childhood	1
Stigmata of present or past malnutrition and deficiency status	2
Moderate to severe hyperglycemia	2
Non-proneness to ketosis in the absence of stressful situation	2
Metabolic control; but no insulin dependent for prevention of ketosis	2
Pancreatic calcification	2
	14

An aggregate of 10 points or more is considered diagnostic and score between 7 to 9 are suggestive of MRDM.

3. Diagnostic criteria as suggested by the Kobe Indonesia Research Committee in 1989 are:

A. Suggestive MRDM

Diabetes Mellitus Criteria (WHO 1989)

Malnutrition : Random Body Weight(RBW) <80%

Age : 15-40 years

Insulin resistance

Ketosis resistance

Pancreatic calcification may or may not be present.

B. Definite MRDM

All the above, plus

BT-PABA excretion test in urine <60%.

4.3. Classification of Diabetes Mellitus

Diabetes mellitus is a heterogeneous group of disorders characterized by abnormally his level of blood glucose, due to either insulin deficiency or impaired effectiveness of insulin. Diabetes afflicts in large numbers of all social conditions throughout the world globally, there are at least 30 million diabetics, the greater of whom lack over the benefit of care, depending on the clinical distinctiveness, severity, prevalence epidemiological study the WHO export committee on diabetes mellitus charted out the following classification of DM which has been generally accepted allover the would.

Diabetes mellitus has long been classified based on its clinical presentation, age of onset and special features, and need for insulin of the individuals to control blood glucose. Lawrence (1951) was first to introduce the nomenclature Type 1 and Type 2 to describe two

distinct forms of DM. It was in late seventies National Institute of Health (NIH), United States of American (USA), took the first collective efforts on formulation and diagnostic criteria of diabetes by setting up the National Diabetes Data Group (NDDG), who introduced the term insulin dependent diabetes mellitus (IDDM, Type 1) and non-insulin dependent diabetes mellitus (NIDDM, Type 2) to describe two main classes of diabetes (NDDG 1979). In the following year a WHO Expert Committee on Diabetes endorsed the ADA classification with some modifications especially regarding diagnostic criteria (WHO 1980). Subsequently another WHO Study Group on Diabetes Mellitus brought out a revised classification in 1985, which introduced MRDM as the third major type of diabetes mellitus (WHO 1985). MRDM comprised of two subclasses (i) fibrocalculus pancreatic diabetes (FCPD) and (ii) protein deficient pancreatic diabetes (PDPD) (WHO 1985). Although the WHO (1985) Study Group Classification of DM was widely accepted internationally many issues remained to be addressed.

Table 2.A
Classification of Diabetes Mellitus (WHO Expert Committee, 1985)

A. Clinical classes

Diabetes Mellitus (DM)

Insulin dependent diabetes mellitus (IDDM)

Non-insulin-dependent diabetes mellitus (NIDDM)

(a) Obese

(b) Non-obese

Malnutrition related diabetes mellitus (MRDM)

Other types of diabetes associated with certain conditions and **syndromes.**

1. pancreatic disease;
2. disease of hormone etiology;
3. drug-induced or chemical induced conditions;
4. abnormalities of insulin or its receptors;
5. certain genetic syndromes; and
6. miscellaneous.

Impaired glucose tolerance (IGT)

(a) Obese

(b) Non-obese

(c) associated with certain conditions and syndromes gestational diabetes mellitus (GDM).

B. Statistical risk classes (subjects with normal glucose tolerance but substantially increased risk of developing diabetes).

Previous abnormality of glucose tolerance

Potential abnormality of glucose tolerance.

All the classifications mentioned above, including the one by WHO Study Group in 1985, were based on a combination of clinical and etiological backgrounds designed to be useful for the purpose of management and disease epidemiology. With FCP the expansion of knowledge the need for a revised and more useful classification of DM was keenly felt. Therefore, the ADA set up a Committee, which, in 1997 suggested major changes in the classification. In this approach etiological factors were used as the basis for the formulation of the classification and this was subsequently endorsed by the WHO Consultation Group on Diabetes (WHO 1994). In the latest classification the two major classes have been renamed as type 1 and type 2 instead of IDDM and NIDDM respectively. MRDM has been removed and FCPD, one of the two subsclasses of MRDM, was assigned under diabetes of exocrine pancreas 'under major head of 'Other Specific Types'.

A shortened version of the current WHO classification is as follows:

Table 2.B

Etiological classification of diabetes mellitus (WHO 1999)

A. **Type I (beta-cell destruction, usually leading to absolute insulin deficiency)**

(i) Type 1A – Autoimmune mediated type

(ii) Type 1B – Non-immune medicated idiopathic type.

B. Type 2 (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with or without insulin resistance).

C. **Other specific types**

(i) Genetic defects of beta-cell function

(ii) Genetic defects in insulin action

(iii) Diseases of the exocrine pancreas

(iv) Endocrinopathies

(v) Drug or chemical-induced

(vi) Infections

(vii) Uncommon forms of immune-mediated diabetes

(viii) Other genetic syndromes sometimes associated with diabetes.

D. **Gestational diabetes.**

MRDM IN OTHER COUNTRIES:

A search for patients fitting the published criteria for malnutrition diabetes was made among 773 patients of a diabetic clinic in Addis Abada, Ethiopia, a country where poverty and malnutrition are common. Only four cases who fit the criteria were found, none were convincing cases. It is concluded that although many patients were thin and undernourished, the Ethiopian diabetes can generally be classified into IDDM (type I) and MRDM (type II), the latter usually non-obese with no need to evoke a third syndrome.

Both the association of malnutrition diabetes with food cyanogens and our laboratory observation support a role for cyanide in its pathogenesis. In recent years evidence has

been marshalled to suggest that diabetes is divided into two basic patterns in the temperate zone, individuals who develop diabetes rather suddenly and who are predisposed to ketone formation regularly require insulin. They are usually young, but not always. An islet autoimmune response is often detectable early in the disorder. In the second form are elevated post absorptive blood sugar is found in nature individuals, who are often without symptoms; ketone bodies are not found and insulin is not required usually. A familial pattern is commonly seen and overweight appears to be predisposing.

A form of diabetes that does not fit into either temperate zone category has been recognized in tropical countries for more than two decades. Affected individuals are usually adolescents or young adults, characteristically undernourished, who require considerable amounts of insulin to maintain or increase body weight, but who do not develop ketoacidosis. This condition without other findings are often referred to as type J diabetes, because of its initial description in Jamaica.

The association between the geographical distribution of malnutrition diabetes and cassava consumption supports a hypothesis that the combination of cyanide exposure and low protein intake may play an aetiologic role in malnutrition diabetes.

A link between cyanide ingestion, protein calorie malnutrition and diabetes is supported by both geographic distribution analysis and animal studies. Firm support for the concept that cyanide ingestion, combined with malnutrition, causes youth onset insulin dependent diabetes produced by analysis on identical twins.

Cases of MRDM conforming to the description of protein pancreatic diabetes type in Ethiopian patients were compared with type I (insulin dependent) and type II (non-insulin dependent) diabetic. Fourteen out of 39 MRDM patients fat malabsorption compared with only two out of ten type I diabetic patients and one of the nine control subjects. Xylose

absorption was normal favouring a pancreatic cause for the malabsorption. Plasma C peptide during oral glucose test was significantly lower than that in type II diabetic patients and normal control subjects and was also consistently but not significantly higher than in type I diabetic patients. Glucagon secretion partners were similar in malnutrition related and type I diabetic patients. Out of 23 newly diagnosed MRDM patients 14 remain ketosis free for over eight days while another six developed ketoacidosis or significant ketonuria within two to six days during the trial.

The similarity of the malnutrition related and type I diabetes mellitus in age of onset, insulin requirement for diabetic control and appearance of ketosis proneness in some cases, together with similarity of C peptide and glucagon secretion pattern suggest that the protein deficient pancreatic diabetes variant of MRDM may be type I diabetes mellitus modified by the background of malnutrition rather than an aetiological separated entity.

Cyanoglucosides are important chemical constituents of cassava. And it seems that excessive cassava intake combined with allow intake of protein, deficient in certain aminoacids, provides an essential milieu for the accumulation of cyanide in the body with resultant toxicological effects. Alternative sources of dietary cyanide include Sorghum, Yam, Millet, maize, lima beans and linseed. Gold there possibly be other toxic factors, especially food toxins, which may interact with malnutrition to produce similar clinical and morphological changes? We need much more information about other factors which either singly or in consent with protein energy malnutrition, may lad to FCPD syndrome. Cyanoglucoside in cassava have also been implicated in the etiology of tropical ataxic neuropathy and of endemic goiter in several regions of Africa.

Protein deficient diabetes mellitus (PDDM) described as J-type, K-type or M-type of diabetes. There is now considerable evidence that protein malnutrition in early childhood, results in partial failure of β-cell function. A continuing low level of protein intake may make

this process progressive and irreversible, resulting in the clinical onset of diabetes mellitus at a young age.

Records of 849 consecutive diabetes ethiopians revealed that 171 had type I diabetes, 462 type II non obese, 210 type II obese and four drug induced. Under nutrition (BMI <18 kg/m^2) was present in 12.9% of patients. Abdominal radiography have been done for 189 patients mainly in the young, thin and insulin requiring pancreatic calcification has been found in two cases, both middle aged men with a history of alcohol intake. Only one patient with parotid enlargement was seen. Cassava was not eaten in Ethiopia. Diabetes mellitus was induced in one patient by steroid, in three by pentamidine therapy for leishmaniasis a known cause of diabetes. Diabetes mellitus followed viral hepatitis in four cases.

It has long been recognized that both hypoglycemia and impaired glucose tolerance can be associated with chronic malnutrition. More recently, the possibility was raised that protein calorie malnutrition may induce permanent damage to pancreatic β-cells that leads to progressive deterioration of their function. In this perspective, malnutrition is viewed as a risk factor that predisposes populations of developing countries to diabetes. The characteristics, progressivity and reversibility of the changes in glucose homeostatic brought about by chronic protein calorie malnutrition were studied in rat. Four weeks old male rats received a control diet (15% protein) or a low protein diet (5% protein) until the age of 28 weeks, and then the control diet. In malnourished rats, fasting plasma glucose levels and both fasting and fed plasma levels were lower than in control rats. Though the hepatic glucogen stores were increased in malnourished rats. Four glucagen or arginine caused a smaller rise in plasma glucose levels than in control rats. The insulin response was also impaired and unlike the glucose response was not restored by six weeks on a control diet. The hypoglycemia induced by intravenous insulin was more sustained in malnourished that in control rats, but this abnormality was corrected by refeeding a control died or six weeks. The results thus show that chronic protein calorie malnutrition in the rat

severity impairs insulin secretion but only mildly alters glucose tolerance, likely because of an associated with high seventing to insulin.

In conclusion, chronic protein calorie malnutrition affects several aspects of glucose homeostasis in the rats. It mainly causes a severe and poorly reversible impairment or insulin release, which does not lead to progressive deterioration of GT, because of a high sensitivity of the tissues to the hormone. It remains possible, however, that long-lasting malnutrition also increase vulnerability of β-cells and thereby facilitates development of diabetes on particular genetic backgrounds, in the presence of insulin resistance bearing increased damage or after toxic or viral aggression

Tripathy(1984) has postulated that calorie malnutrition might act as on important form of stress in the malnutrition of clinical diabetes, particularly in case of young lean, ketosis resistant diabetes, the so called J-type diabetes. The explanation is based on hormonal pattern in these individuals. The interval between two meals in these individuals often runs to 18 to 24 hours. During the prolonged remote post prandial period growth hormone level may remain high. Subsequent taking of large carbohydrate meal may impose excessive strain on the rather unhealthy pancreas. One of the following factors may be operation in these individuals. The insulin sensitivity may be low after a period of starvation. Alternately there is an increase in plasma levels of free fatty acid which creates a state of relative insulin resistance thereby large amounts of insulin are needed for the same quantum of metabolic work. These factors can bring about an earlier exhaustion of β-cells leading to glucose, intolerance in susceptible subjects an may account for the earlier onset of diabetes, underweight and relative resistance to insulin.

Viswanathan(1985) believes that gross under nutrition makes the susceptible person more prone to infective, degenerative or toxic effect lading to destruction of islets of Langerhans, thus resulting in diabetes.

Pancreatic β-cells function depends on (1) Circulating insulin (2) C peptide suspected malnutrition group is characterized by the presence of residual β-cell function as distant from the classic IDDM i.e. JOD or type I cases in whom no trace of β-cell function can be detected. This was evidence from the elevation, though small in magnitude, of circulating insulin and C peptide concentrations.

Table: 3

Insulin conc.	C peptide	
147%	93%	MRDM
610%	489%	Normal
556%	470%	Connbial
435%	425%	NIDDM
2μU/ml(Less than, hardly detectable)	01.to 0.14 pmol/ml/	IDDM

Does malnutrition lead to diabetes ?

Carbohydrate, fat and protein metabolisms are mainly regulated by insulin. Under conditions of absolute or relative insulin deficiency a diabetic situation develops. On the other hand, under the condition of inadequate nutrition intake i.e. under the condition of malnutrition would absolute or relative insulin deficiency develop leading to the diabetic condition.

Malnutrition which mainly is due to poor socioeconomic factors, includes low calorie intake, low protein, low fat, low carbohydrate consumption and vitamin deficiencies. The meal size is small and the time interval between each meal is longer due to the absence of between meal snacks. Above all the there is constant stress on the person due to hunger and many other socioeconomic problems. Such miserable conditions could be faced from very early childhood or even from infancy.

Small meal size: Firstly due to unfavourable socioeconomic factors, eating habits have to be adjusted to small meal size with a longer interval between meals. Thus the hypothala has to adapt to the particular eating and satiety behavior. As the eating and satiety behavior is family adjusted by the enterophypothalamo insular axis any change in the meal dependent glucostatic and lipostatic mechanism would affect the entire entero hypothalame insular axis. A downward shift i.e. decrease in the sensitivity of hunger to meet satisfaction with the small meal size would result in suppression of insulin secretion and enhancement of glucagon secretion in order to prevent occurrence of hypoglycemia. It has also been suggested that glucagon also plays a major role as a satiety factor in rats. Such a condition in the longer night probably lead to the diabetic condition. Small meal size, long intervals between meals and inadequate calorie supply could lead to a fasting condition shortly after meal, probably in less than four hours. During a brief fast the limited stores of liver glycogen are rapidly exhausted within a few hours. Hepatic glycoeogenesis, primarily from aminoacids, then be comes the main source of blood glucose, glycerol released from adipose tissue severs as a subsidy some of glucose. With more prolonged fasting a drop in circulating blood glucose and insulin concentration and an increase is FFA takes place, accompanied by hepatic ketoacid production. It this stage the tissues, especially the brain begin to use betahydroxybutyrate and aceto acetate as 60-80% of their fuel in lien of glucose, gluconeogenesis and lipolysis are accompanied by a rise in glucagon. A high insulin concentration suppresses muscle proteolysis, while a low insulin concentration would not be capable of suppressing it. Some of the protein and fat intake which is small in quantity, might well be diverted towards energy production through gluconeogenesis. This condition could lead to an increase in growth hormone (GH) concentration in an attempt to presence cellular proteins and to entrance incorporation of the limited quantity of available aminoacid into proteins. Agair high GH levels will also enhance lipolysis. The result would be high FFA levels. Thus in an attempt to meet the needs of calorie deficiency and to presence tissue integrity, insulin could be confronted with two strong hormonal antagonist

namely glucagon and growth hormone. Under such conditions insulin may not be effective

to facilitate the utilization of either blood glucose of FFA, resulting in high concentration of these substances in the present malnutrition suspect, insulin dependent cases. High glucagon levels might result in hypercalcemia facilitating the calcification the calcification of a pancreas which has been reported to be of a high incidence in young African diabetics and uncommon in Bangladesh.

In cases of DM secondary to pancreatic disease, the incidence of metabolic diabetic complications are considerably lower than in patients with genetically determined diabetes. By far the least commonly encountered vascular lesion in diabetes following chronic pancreatitis is intercapillary glomerulosclerosis, while some patients with chronic pancreatitis have been diagnosed as showing diabetic nephropathy on the basis of clinical findings alone, a review of literature revealed that only three histologically proved examples of nodular (specific) intercapillary glomenlosclerosis (Kimmelstiel Wilson) have thus far been recorded in such patients. Five more instances have been described in an abstract published in 1969 by Ennis et al, but histologic documentation of these cases has not appeared in print.

The question why vascular complication, including in particular, nodular intercapillary glomerumblosclerosis the chorological factors involved. The development of vascular complications in diabetes in clearly related to time, the necessary mean interval between the onset of pancreatogenic diabetes and the appearance, of vascular lesions was variously estimated or calculated to be seven, 13,10 to 15 years. On the other hand, patients with diabetes secondary to chronic pancreatitis have a significantly reduced life expectancy in Deitsyler and Martins series, death occurred after a mean interval of seen and a half following the onset of diabetes, so that many if not most, of the these patients never reach the age at which diabetic vascular complications ordinarily manifest themselves, other factors implicated in the reduced incidence of such complications in

these patients included the deficient growth hormone levels recorded by Vinik et al and especially the low blood lipid concentration observed in many of then, they may record the development of vasculopathy low calorie intake because of diarrhoea and steatorrhoca secondary to exocrine pancreatic insufficiency has also been thought important. (Nodular Intercapillary glumerulosclearosis in diabetes secondary to chronic calcific pancreatitis, Wellmann KF, Wolkk BW,1976).

Synonyms for PDDM include J-type diabetes, ketosis resistant diabetes in the young, ketosis resistant youth onset diabetes, malnutrition diabetes, M-type diabetes, K-type diabetes, protein malnutrition related pancreatic diabetes and protein deficient pancreatic diabetes.

In contrast to FCPD where an interaction of malnutrition and dietary toxin constitutes possible etiological basis, there is now considerable evicdence that in PDDM protein energy malnutrition in early childhood with or without a deficiency of other micronutrients, initiates a functional impairment of pancreatic β-cell.

Pancreatic disease might be related to malnutrition. Not because these patients were emaciated but because some showed characteristics signs of severe protein malnutrition changes of hair (fall out of hair by combing, brownish black reddish colour), hypertrophy of parotid glands. Now a days this relation is generally accepted. Post mortem studies of children with acute PEM and of patients with chronic malnutrition have demonstrated serious pancreatic changes, atrophy of acinar and islet cells followed by proliferation of fibrous tissue. Many authors doubt that protein malnutrition is the sole factor in the genesis of this pancreatic disease. They point out that the disease frequently occurs in areas where cassava is an important constituent of the diet. Cassava contain cyanogenic glycosides which may be a source of toxic cyanidew in the diet. Protein malnutrition may render the pancreas more susceptible to these agents.

On may 31, 1939 a 39 years old Indonesian male weight 30 kg was admitted in the hospital treatment 1500-2000 cal, 100-150 g carbohydrate and two daily injection of 20 IU insulin. He was apathetic, listless, without any obvious reason his condition deteriorated and died on June 10 (first case of reported MRDM by Zuidema PJ).

Adrenocortical activity was investigated in experimentally induced protein malnutrition in Rhesus monkeys. Control studies were carried out in the same animals before inducing protein malnutrition. Plasma cortisol levels were elevated in the protein malnourished state. There was a total abolition of the diurnalrythm of cortisol secretion. Fasting hypoglycemia was also observed in the protein malnourished state. It is concluded that increased adrenocortical activity and sustained steroidogenasis result from protein deficiency. Hypoglycemia may be an important stimulus in addition to the metabolic stress imposed by protein deprivation. The recognition of increased adrenocorticoid activity is important in a protein host, since the defense against infection might be impaired in such a situation.

A complex interplay exists between magnesium and glucose metabolism. Hypomagnesemia has been reported in both IDDM and NIDDM patients. It has been shown that the diabetes mellitus is the chronic disease most frequently associated with hypomagnesemia. The importance of hypomagesemia is inversely related to the quality of blood glucose control, largely results from hypermagnesemia, and may reflect a substantial depletion of body stores of magnesium. On the other hand magnesium may also influence glucose homeostasis. Circumstantial evidence has been presented that hypomagnesemia could cause insulin resistance during treatment of diabetic ketoacidosis. This suggestion is in keeping with invitro studies,which ascribe to magnesium may also involved the regulation of the β-cell function . In vitro variation of extracellular concentration modulate glucose induced insulin release and insulin biosynthesis. Moreover, several insulin secretagogues markedly affect magnesium fluxes in islet cells.

In recent years evidence has been accumulated to prove that genetic factors play a crucial role in the etiology of both insulin dependent and non insulin dependent diabetes mellitus. However, environmental factors are still considered to be essential in precipitating clinical diabetes in individuals who have inherited a genetic susceptibility to the disease.

Among the environmental factors life style and in particular, nutrition are certainly of great importance especially in the etiology of NIDDM. The emergence of diabetes as a major health problem in population that have undergone recent and rapid changes in life style indicates that modern life style and diet may be etiologically linked to diabetes.

A diet apt to control body weight rich in fibre and low in fat seems at present to be the best approach for preventing diabetes. Epitorial can DM be prevented by diet (Riocardi G and Rivellese AA.

Diabetes in Tropical Africa: a prospective study, 1981-81, ABM Swai, J Lutale, G McLarty 272(22.8%) patients had diabetes requiring insulin, 825(66.0%) had diabetes not requiring insulin and 153(12.2%) had diabetes of uncertain type.

Twenty seven percent of patients were underweight (body mass index 20 kg/m^2) and 14.6% were obese (body mass index 30 kg/m^2). Hypoperation was diagnosed in 211(26.7%) of 791 patients not requiring insulin. Nine (3.3%) of these requiring insulin may have had the protein deficient type of diabetes related to malnutrition. The fibrocalculous variety of diabetes related to malnutrition was not observed.

Eighty one percent of 254 requiring insulin had a firs degree relative with diabetes, compared with 11(14.4%) and 10(7.5%) of 771 not requiring insulin and 133 with uncertain type diabetes respectively.

The peak month of presentation were August to November.

Alcohol significantly more diabetic men drank alcohol than men in the community population 378(48%) vs 208(33%), p<0.001. No difference was observed among women 84(25%) vs 194(23%), p<0.15.

Pancreatic calcification was found in three patients in a consecutive series of plain abdominal x-ray films in 106 patients. As all three patients aged over 30 and had a history of heavy alcohol intake, no patient in this limited series was found to have the fibrocalculous type of diabetes related to malnutrition. In addition, among the 272 patients with diabetes requiring insulin, there were four patients who had all the criteria for diagnosis of the protein type of diabetes related to malnutrition apart from age that is all four patients were over 30 years.

Diabetes related to malnutrition has been the subject of recent extensive review. The fibrocalculous variety, as described in Uganda and Ibaqdan (Nigeria), does not seem to occur in Tanzania. In patients with a calcified pancreas alcohol seems to be the main associated factors as in the case in Zimbabwe. The existence of the protein deficient type of malnutrition related diabetes without pancreatic calcification in controversial, but in our study, nine of the 272 patients with diabetes requiring insulin met the criteria of Ahuja for the diagnosis of protein deficient diabetes, although this is not proof of its occurrence.

Insulin resistance in fibrocalculous (tropical) pancreatic diabetes Mohan V, Ramachandran A, Vijay G, Kumar C, Snehalatha M and Viswanathan,1988.

Insulin resistance assessed by insulin tolerance test (ITT) in 12 patients with FCPD, 10 with NIDDM and 12 age and sex matched control subjects. The mean BMI of the FCP was lower than the NIDDM and control groups (p<0.001).

The data suggests that patients with FCPD have evidence on insulin resistance and this is similar to that seen in NIDDM patients.

FCPD is a form of diabetes secondary to chronic, non-alcoholic, calcific pancreatitis seen in the tropical countries (Geevarghese 1968). This from of diabetes has recently been included as a separate entity by the WHO Study Group Report on DM under the board category of MRDM (WHO Study Group Report 1985). FCPD is characterized by severe, insulin requiring diabetes which, however, is resistant to ketosis on withdrawal of insulin. Pancreatic beta cell function studies have shown that these patients have residual β-cell secretion which probably protects them against ketoacidosis.

This paper reports on insulin resistance in FCPD and to our knowledge, this is the first report on this subject. Two forms of MRDM have been recognized, namely PDPD and FCPD. PDPD is believes to be characterized by extreme insulin resistance with requirement of large doses of insulin. In FCPD, however, there is little data on whether insulin resistance is seen. This report shows that these patients have evidence on insulin resistance. The ITT was used to assess insulin resistance in this study for several reasons. Methods, such as glycemic clamp technique require 300-400 ml of blood. Many patients with FCPD in this study were underweight, anaemic and had signs of protein chronic malnutrition. Hence, it was not considered ethical to do tests which need large quantities of blood. For the ITT less than 50 ml of blood is required. Secondly, it has been shown that the results of the ITT obtained with the insulin tolerance test collected well with the M valve obtained by the englycemic clamp technique (r=0.902) Proto, Ferrannini and DeFronzo, 1985).

In summary, patients with FCPD have evidence of insulin resistance and in this report they are similar to patients with NIDDM.

Songer TJ, Laporte RE, Dormen JS, Orchard TJ, Cruickshanks KJ, Becker DJ, Drash AL, 1992 investigated Motor Vehicle accidents and IDDM.They found that female diabetic drivers, however, showed a marked increased risk for motor vehicle accidents. The accident risk among female cases was five times higher than among the female control subjects ($p<.05$). Age and marital status were also significantly associated with accident probability in the multivariate model. The results suggest that IDDM have an effect on the accident rate of diabetic drivers, particularly women. However, the traditional risk factors for automobile accidents, i.e. data with respect to a composite index of maternal deprivation that has been shown to very significantly with an index of health state in the northern region.

Historical background:

Knowledge regarding diabetes dates back to centuries before Christ. An Egyptian Papyrus Ebers (Ca 1500 Bc) described an illness associated with the passage of much urine. Celsus (30 BC to 50 AD) recognized the disease but it was not until two centuries later that another Greek physician Aretaeus of Cappadocia, gave the name diabetes (Siphon). He also made the first complete clinical description, describing it as "a melting down of flesh and limbs to urine".(Ajgaonkar,1984)

During third to six centuries AD scholars in China, Japan, India wrote a condition with polyuria, in which the urine was sweet and sticky. However, although it had been known for centuries that diabetic urine tasted sweet, it remained for Wilils in 16% to add the observation "as if imbued with honey and sugar". The name diabetes mellitus (mellitus = honey) was thus established. A century after Willis, Dobson demonstrated that the sweetness was, indeed due to sugar.

From the time of the earliest recorded history of diabetes progress in the understanding of the disorder came slowly until the middle of the 19th century. However over these centuries gradually the course and complications of the disease were recognized. Gangrene had been described (passed with seed) as well as two general verities, one with the classic acute symptoms noted above (type I or IDDM in todays terminology) and the other with "torpor" indolence and corpulence" (type II or NIDDM).

Autoimmune destruction of β –cells in BB rats in invariably proceeded by insulitis. This study suggests that once insulitis has been established the fate of the β –cell is determined by the events involving immunocytes rather than by intrinsic properties of the β-cell themselves. The authors gagged the number of monounclean cells in BB/W rats by measuring in pancreatic sections (lymphocytes and monocyte) per unit surface of islet tissue as well as the volume of the islet cells.

4.4. Genetic and MRDM

Genetic factors account for about one-third of the susceptibility to type 1 diabetes, the inheritance of which is polygenic. Over 20 different regions of the human genome show some linkage with type 1 diabetes but most interest has focused on the human leucocyte antigen (HLA) region within the major histocompatibility complex on the short arm of chromosome 6: this locus is designated IDDM 1. The HLA haplotypes DR3 and/or DR4 are associated with increased susceptibility to type 1 diabetes in Caucasians. These DR3 and DR4 alleles are in linkage disequilibrium i.e., they tend to be transmitted together with the neighbouring alleles of the HLA-DQA1 and DQB1 genes and the latter may be the main determinants of the genetic susceptibility.

HLA class II antigens (which are coded by the HLA class II genes) on the surface of cells present foreign self-antigens to T lymphocystes and play a key role in initiating the autoimmune response. Some polymorphisms of the HLA-DQB1 gene that result in specific amino acid substitutions ion the beta cell chains of class II antigens may affect the ability of the class II molecule to accept and present autoantigens derived from pancreatic islet beta cells, and will so etermine whether or nto autoimmune damage will take place. Variants of the DQ beta cell chain which carry an uncharged anino acid residue (e.g. alanine, serine or valine) at position 57 appear to be diabetogenic, whereas the presence of aspartate is protective against type I diabetes, at least in Caucasian populations.

The region of the insulin gene on chromosome 11p (designated IDDM 2) is also linked with type 1 diabetes. Insulin or its precursors may act as a beta cell autoantigen: altematively, the level of insulin production can determine the activity of the beta cell and its expression of other autoantigens. Other weaker diabetes susceptibility loic include IDDM 3,IDDM 4 and IDDM 5, which lie on chromosomes 15q, 11q and 6q respectively, but their gene products and modes of action are unknown.

Genetics:

Genetic factors are more important in the etiology of type 2 than I diabetes, as shown by studies in monozygotic twins where concordance rates for type 2 diabetes approach 100%. The majority of cases of type 2 diabetes are multifactorial in nature, with interaction of environmental and genetic factors. The nature of the genetic contribution is largely unknown, but it is evident that several genes are involved. In this polygenic model, inheritance of variation in individual genes would not be sufficient to cause type 2 diabetes directly, but would confer an increased (or decreased) susceptibility . Over 200 candidate susceptibility genes have been investigated, such as insulin, the insulin receptor, glucose transports and glycogen synthase, but there has not been consistent association of variants in candidate genes with type 2 diabetes. Genome-wide searches have identified

susceptibility genes on chromosome 1q, 12q and 20q, but the underlying genes have not been identified.

Molecular genetics has allowed the identification of certain specific and clinically identifiable forms of diabetes, which are caused by single gene defects. However, these subtypes, such as maturity onset diabetes of the young (MODY), are uncommon and constitute less than 5% of all cases of diabetes. Determining the molecular genetic etiology can help to define the prognosis, optimum treatment, and risk of diabetes in relatives.

Genetic Susceptibility:

Type 1 diabetes has a complex pattern of genetic associations, and putative susceptibility genes have been mapped to at least 20 loci. Many of these associations are with chromosomal regions, and the particular genes involved are not known yet. Of the multiple loci that are associated with the disease, by far the most important is the class II MHC (HLA) locus, according to some estimates, the MHC contributes about half genetic susceptibility, and all the other genes combined make up the other half.

4.5. HLA Genes in T1D

HLA molecules associated with diabetes susceptibility:

The best evidence for a genetic component in the susceptibility to T1D come from studies of HLA genes (IDDM1, MIM 222100) in both populations and families as well as in animal models. It has been estimated that HLA provies up to 40-50% of familial clustering of T1D (Noble et al., 1996). The HLA region is a cluster of genes located within major histocompatibility complex (MHC) on chromosome 6p21.The HLA complex is classically divided into four regions, known as class I, class II, class III and class IV (Gruen and Weissman 2001). The class II MHC region encode the class II HLA molecules which are involved immune process and turn out to be important candidate in the pathogenesis of T1D.

Several studies have confirmed the earlier findings and concluded that rather than individual genes, HLA-DRB and DQB haplotypes confer disease associated risk and protection in individuals. This DRB1 and DQB1 gene association with T1D was later confirmed as the major contribution to the T1D by chromosomal peak (Herr et al., 2000).

HLA has also been found to confer protection from diabetes. The best known protective allele is DQB1*0602, usually found on DR2 (DRB1*150-DQA-DQA1*0102-DQB1*0602) haplotypes. Approximately 20% of American and European children without diabetes have DRB1*1501-DQA1*0102-DQB1*0602 where as less than 1% of children with diabetes carry (DRB1*1501-DQA1*0102-DQB1*0602). Protection conferred by DRB1*1501-DQA1*0102-DQB1*0602 haplotypes have been found to be dominant.

Mechanisms of diabetogenicity of HLA molecules:

Class II molecules are critical to present antigens to CD4+ T cell. Thus different disease associations of class II molecules suggest that particular HLA molecules may be more effective either in binding antigen, or in inactivating T cell receptor and thus influencing disease susceptibility. It has been postulated that the predisposing effect of DR3 and/or DR4 associated alleles arises as a result of more efficient binding of a particular 'diabetogenic peptide'.

The model presented by Nepom (1990) describes that peptide with HLA molecule present with the highest affinity. Diabetes susceptibility or protection associated with HLA molecules may be related to their ability to present peptides of relevance to diabetogenic T cells.

Diabetes susceptibility or protection associated with HLA molecules may be related to their ability to present peptides of relevance to diabetogenic T cells. Individuals with HLA

molecules that are not able to effectively present specific peptide to naive T cells in thymus might fail to engender tolerance. Alternatively, specific HLA alleles may selectively present an islet peptide to mature T lymphocytes that have escaped negative selection. These proposed mechanisms 'lack of central tolerance affecting the T cell receptor in the thymus or abnormal tolerance in the periphery' – are not mutually exclusive and could coexist. The ability to present antigens may depend on conformational properties of the HLA molecule with some alleles binding to peptides in such a fashion that antigens would never be effectively presented to T cells.

T2D patients from families in which T1D is also found as more frequently GADab (18%) vs 8% and DQB1*0302/X genotype (25% vs 12%) positive than patients from families with only T2D ; however, they have a lower frequency of DQB1*02/0302 genotype compared with adult onset type I (LADA) patients (4% vs 27%). In the mixed families, the insulin response to oral glucose load was impaired in patients who had HLA class II risk haplotypes, either DR3-DQA1*0501-DQB1*02 or DR4*0401/4-DQA1*0301-DQB1*0302, compared with patients without such haplotypes independent of the presence of GAD ab (Li et al., 2001). This led to a conclusion that T1D and T2D cluster in families and share a common genetic background defined by HLA irrespective of autoantibody positively and thus in turn leads to impaired insulin secretion.

4.6. HLA AND MRDM

Studies of the relationship between diabetes and the HLA system have shown definite association between IDDM and certain HLA antigens. High frequencies of HLA B8, B15, CW3, DW3, DW4 and DRW4 have been found in white Caucasians with this disease (Ryder LP et al. 1979); HLA and disease registry third reprint Munksgaard, (Copenhagen). Studies in American blacks established a clear association between IDDM and HLA DR3 and DR4 but no such relationship at the A,B,C loci (Duquesony RJ et al. 1979) Tissue

Antigan 13, 369; (Radey GE et al. 1979); In the Japanese the disease has been associated with HLA BW54 but not with B8 or B15 (Kawa A, Nakazawa M, Sakaguchi S 1977); HLA system in Japanese patients with diabetes mellitus 26, 591: (Nakoo V et al. 1979); HLA system in Japanese patients with diabetes mellitus.

Omar, Hammond and Asmal studied the HLA system and diabetes in young Africans and Indians (70 African and 56 Indians with IDDM, 61 Indians with NIDDM). Their HLA were typed A,B,C specificities by mean of a 2 stage micro lymphocytotoxicity test. Forty seven patients of IDDM were typed for HLA DR antigen using β-cell enriched lymphocytes. The antigen frequency was compared to those found in healthy African and Indian control. African patients with IDDM compared to controls showed a significant increase in the frequency of either B8 or B14 (37.1% vs 19.7%) and also DR4 (36.7% vs 9.3%), whilst B12 was low (8.6% vs 25.5%). The Indians with IDDM showed a significant increase in the frequency of B8 (18.4% vs 6.1%), of DR4 (43.8% vs 10.8%) and these under 20 years AW24 (51.3% vs 27.6%). NIDDM in Indians was associated with an increase in the frequency of BW61 (41% vs 16.8%), This study was has shown a clear relation between the HLA system and diabetes in Indians and Africans. HLA DR4 was associated with IDDM in both groups. Indians HLA D8 was strongly associated with IDDM and BW61 with NIDDM. There was a negative correlation between IDDM in Africans and BW42. (Omar MAK, Hammand MC and Asmal AC). The HLA system and diabetes in going Africans and Indians in DM in developing countries, Chapter 11, p. 71). Thus it can seen that there are differences in the specific allelic associations among various either groups.

Susceptibility IDDM is conferred by genes in the HLA-D region of the major histocompatibility complex (MHC) on chromosome 6 gene in this complex. Control immunse responses. HLA region comprises three loci DP, DQ, DR. The HLA DR allele, HLA DR4 is strongly associated with IDDM in al ethnic group, whereas HLA DR3 allele shows IDDM association only in coucasian an some black population. (Kobberling J and

Tattersall R: ed. The genetics of DM. London, Academic Press, 1982. The highest risk of IDDM is carried by individuals with both HLA DR3 and HLA DR4 alleles, i.e. HLA-DR3/4 heterozygote individuals. This and other evidence suggest that the two IDDM associated genes in the HLAD region may predispose individuals to IDDM by different mechanism.

NIDDM is not HLA associated. In the search for a genetic marker of NIDDM susceptibility, restriction fragment lergth analysis has revealed a large DND fragment flanking the insulin gene on chromosome 11. The has been found to be associated with NIDDM or a form of NIDDM by some researchers. Evidence is accumulating that the insulin response to glucose is genetically controlled and may serve as one of the marker for NIDDM susceptibility. (Galton DJ and Hitman GA). Polymorphism and the insulin gene disease associations.

Evidence for genetic predisposition comes from studies in twins that demonstrate a higher concordance rate for type-I diabetes monozygotic twins (25.30%) then in dizygotic twins (5.10%) Skyler J. Immune intervener in type-I diabetes mellitus. The risk of type-I diabetes is increased in first degree relatives of probed with the disease. In USA among whites the overall risk is 0.2-0.4%. However in Siblings of probed with type-I diabetes, the risk is about 5%, while offspring's of diabetic parents have a 2-3% risk of the mother has the disease and 5-6% risk if the father has the disease. About 95% of individual of European origin with type-I diabetes one DR3, DR4 or DR3/DR4. Predisposition is also related to HLA DQ alleles and these associations are consistent across all ethnic groups. Thus the specific predisposition to type-I diabetes in those of European origin is associated with HLA DR3, DQW2 (also known as DQB1 0201) and with HLA DR4, DQW8 (also known as DQB1 0302) on the other hand some alleles of the major histocompatibility complex confer protection against the development of type-I diabetes. These include HLA DR2 and HLA DQB1 0602. Protective alleles appear to have dominance over susceptibility alleles.

NIDDM shows strong familial aggregation. Twin and family studies have provided firm evidence that the role of the genetic component is relatively strong. NIDDM appears to be the consequence of an interaction between this genetic susceptibility and exposure to environmental factors.

Peter gorec raised antisrum to erythrocytes from pure strain mice and by careful cross absorption with red cells from different strains, he identified the strain specific antigen II. Now known as H2. Subsequently george smell introduced the term histocompatibility (H) antigen to describe antigens provoking graft rejection and emonestrated that of tall the potential H antigen, differences at H2 locus provoked the strongest graft rejection seen between various strains. Far from representing a single gene locus, H2 proved to be a large complex multiple genes, may of which were highly polymphic, have the term major histocompatibility complex (MHC).

Table 4

Association of HLA with disease

Disease	HLA allele	Relative risk (%)
Class II associated		
Hasshimotos disease	DR5	3.2
Rheumatoid arthritis	DR4	5.8
Dermatitis herpetiformis	DR3	56.4
Chronic active hepatitis (autoimmune)	DR3	13.9
Coeliac disease	DR3	10.8
Sjogren's syndrome	DR3	9.7
Addisons disease (adrenal)	DR3	6.3
IDDM	DR3	5.0
	DR4	6.8
	DR3/4	14.3
	DR2	0.2
Thyrotoxicosis (Graves)	DR3	3.7
Primary Myxoedema	DR3	5.7
Goodpastures syndrome	DR2	13.2
Tuberculoid leprosy	DR2	8.1
Multiple Sclerosis	DR2	4.2
Class I HLA B27 Associated		
Ankolysing Spondylitis	B27	87.4
Reiter's Disease	B27	37.0
Post salmonella arthritis	B27	29.7
Post shigella arthritis	B27	20.7
Post yersinia arthritis	B27	17.6
Post gonococal arthritis	B27	14.0
Uveitis	B27	14.6
Amyloidosis in RA	B27	8.2
Other class-I association		
Sub-acute thyroiditis	BW35	13.7
Psoriasis	CW6	13.6
Idiopathic haemochromatosis	A3	8.2
Myasthenia gravis	B8	4.4

HLA typing for the detection of antigens of the HLA-A,B and C loci using the modified microlyrophocytotoxicity test was performed in 20 MRDM and 10 malnourished control. The frequency of was significantly high in MRDM compared controls (Rao PV, Ushabala P, Ahuja MMS).

In Indian IDDM, there is strong link with the HLA system emphasis the inheritance of susceptible diabetic genes, specially the DR3 and DR4 alleles and possibility environmental factors in a predisposed individual to initiate an immune response to cause β–cell damage and destruction, on the other hand NIDDM has no clear HLA link and environmental factors (race, ethnicity, sex, age, diet, activities, obesity and life style) have an important influence on the clinical expression of the disease an the severity of complication in a genetically predisposed individual.

By and large genetic studies on diabetics suggest that diabetes is about 50% inherited, and other 50% acquired or environmental. Because of the heterogeneous nature and multifactorial inherita pattern of diabetes, accurate genetic counselling is not possible as yet. However, data to date suggest that it is crucial to advise prospective patients not to procurate, since the overall risk of the development of clinical DM in offspring is extremely low. One of the earliest studies on HLA from the AIMS, New Delhi was in fifty four North Indian Type I diabetics. The frequencies of HLA BW21, BW35 and –A28 were reported increased and that of HLA –B7 was reduced, wherease HLA. B8-B15 (Commoner with western IDDM populations) and B18 were not found associated with IDDM in this series of patients.

J. Todd (Stanford, Oxford) reported his collaborative work with H.O. Mc (Devitt Stanford) on the relationship of MHC structures to autoimmune disease susceptibility, particularly insulin dependent diabetes mellitus (IDDM), where a food correlation between DR3 and/ or DR4 and in particular, certain DQ molecules (mostly DQW 3.2) and DQW2) has been identified.

Janice S. Dorman from USA states that the HLA region of the short arm of chromosome 6 contains genes known to be related to susceptibility to autoimmune disease, including IDDM. These genes encode class I (HLA-A,B,C) class II (HLA-DR, DQ, DP) and class III molecules, as well as tumour necrosis factor and complement. From an epidemiologic perspective, there are three unique features of the HLA system which make it an excellent marker for studies of host susceptibility: 1) the high degree of polymorphism at each locus, particularly within the complex, and 3) geographic and racial variations in the frequencies of specific HLA antigens).

Associations between HLA and IDDM began to be documented in the mid 1970's when it was observed that individuals with the disease were significantly more likely to be positive for HLA-B8 and B 15 than nondiabetic controls.

With rapid changes in HLA serology and the discovery of class II molecules, associations between DR3 and or DR4 and IDDM apparent. Advances molecular biology are permitting studies of the associations between HLA and IDDM are now being conducted at the DNA Level. Thus, it is now evident that the presence of DNA sequences coding for an amino acid other than aspartic acid in the 57th position of the DQ beta chain (non-Asp-57) is highly associated with susceptibility to IDDM, where as a aspartic acid in this position (Asp-57) appears to confer resistance to the disease.

Although most studies of IDDM susceptibility have been conducted in Caucasian populations, there have been a number of evaluations in other racial groups. The results of these investigations were generally consistent with those observed for Caucasians. Among the Blacks and Chinese, associations to DR3, DR7 and or DR9 were also reported. In the Japanese, DR4 and DR9 were highly related to IDDM susceptibility.

The genetic factors involved in NIDDM are so far not known. There were some suggestions that HLA might play a small role in NIDDM too. In diabetic Xhosas, a Black tribe living in South Africa a slight increase in HLA-A2 was seen. Also in the American Pima Indians, who are of Mongoloid origin, an increase of HLA-A2 was found in NIDDM. Pima Indians show a high degree of homozygosity and a restricted HLA polymophism (only four HLA-A locus antigens are found of which A2 and A2A are the most frequent ones). BW61, which is a subgroup of B40, was shown to be slightly increased in Asian Indians living in Fiji and in South Africa. In these Caucasoids BW61 is the most frequently found HLA-B locus antigen. A high frequency of CW4 was reported in Finnish haplotype. Whether these reported weak HLA associations with NIDDM are really meaningful needs to be verified in carefully designed studies one has to bear in mind that in all the above mentioned studies the most frequent HLA seen in the background population were also found to be increased in the NIDDM patients).

Only particular HLA haplotypes are increased in IDDM patients. In northern European Caucasoids and in populations descending from them the haplotypes A 1, CW7, B8, DR3 DQW2 (DQA 1- arginine, DQB1 – alanine- and A2, CW3, BW62, DR4, DQW8 (DQA1-arginine, DQB1-alanine) are clearly increased in IDDM, In Finland, in addition to these two usually seen haplotypes a new susceptibility haplotype A2, CW1, BW56, DR4, DQW8 (DQB1-alanine) was found which has so far only been seen in this population. Finland has the highest incidence of IDDM in the world which was in 1987-88, 35 per 1,00,000. The population with the nest highest inncidence lives in Sardinia 24 per 1,00,000. There, in addition to the usual Southern European IDDM susceptibility haplotype-A30, CW5, B18, DR3, DQW5 (DQB 1 serine). Both in Finland and in Sardinia population specific "Whole" haplotypes have been found which confer strong susceptibility to IDDM and party explain the high incidence of IDDM in these countries.

In the Japanase where DR3 and B8 are virtually absent (Less than 1%) first an increase of DRW8 was found, then an increase of DR9. It is now generally accepted that in Japanese IDDM patients two haplotypes are increased. One carries DR4, DQW4 and is mainly associated with A24, CW1, BW54 and the other carries DR9, DQW9. Both usually have aspartic acid inposition 57 of DQB1 which therefore clearly not protects against the development of IDDM in the Japanese. The A3 allele of the DQA1 Locus (DQA1*301) which is associated with IDDM in Caucasoids is also associated with IDDM in the Japanese.

A search for patients fitting the published criteria for Malutrition diabetes was made among 773, patients of diabetic clinic in Addis Ababa, Ehtiopia, a country where poverty and malnutrition are common. Only 4 cases who fit the criteria where found, none were convincing cases. It is concluded that although many young patients are thin and undernouished, the Ethiopian diabetics can generally be classified in to IDDM (Type I) and NIDDM (Type II), the latter usually non obese with on need to invoke a third syndrome.

HLA study was done in ten South African MRDM, 10 IDDM patient and 45 control subjects. The DR7, DQW9 haplotype was found to be frequent in MRDM patients (P 0.01). The Drw17 Dqw2 haplotype was over represented in Type 1 diabetes compared to control subjects (P 0.05). This study has clearly shown that the genetic background or MRDM is different from that of type 1 diabetes.

There are few reports on genetic, Immunological and nutritional characteristics of insulin using youth onset diabetes mellitus, IDDM and MRDM in Korea. Among 1266 hospitalised Korean diabetes 29(2.3%) Were IDDM, 84(6.6%) were MRDM. A diabetes history of first degree relatives 28.6% was more frequently found in MRDM group than in IDDM (14.8%) and NIDDM groups (19.0%). HLA DR4 was more common in IDDM (54.2%), MRDM (52.4%) and controls (26.3%). HLA DR3 was more among only iDDM patients (29.2%) than

control (10.9%) (Conventional islet cell antibodies were detected in 8 of 15 (53.3%) of IDDM patients tested and in 11 of 22 MRDM (50.0%) patients. MRDM patients had higher serum basal (1.02+0.51 ng/ml) and peak (1.44+0.76ng/ml) peptide concentrations than IDDM patients, but fewer than NIDDM patients. Before the onset of diabetes the calorie intake of 21 MRDM patients assessed was 63.1% of the daily requirenent and the intake of carbohydrate, protein & fat was 71.7, 55.9 and 39.8%. In summary our data suggest that IDDM in Korea is associated with HLA DR3 or HLA DR4, indicating a risk for IDDM in western society. Further more MRDM has history of under nutrition at the preonset period and is also associated with HLA DR4. It might be concluded that MRDM in Korea is another expression of IDDM caused by the storage of some nutrients for the structural/and or functional maintenance of pancreatic beta cells (Sanjeeve CB et al. 1992).

Thirty Ethiopian MRDM patients were HLA typed and their HLA antigen frequencies were compared to those of 31 previously typed IDDM patients and to 84 controls from the same ethnic background. In comparison to controls, a striking association between MRDM and HLA DR3 (X=15.15,P= 0.0001) was observed, whereas the frequency of HLA DR4 was non significantly increased (RR= 1.72). The frequency of DR2, Dqw1 and Dqw6 was decreased among MRDM. In comparison to IDDM that is associated with both DR3 and DR4 in this population, MRDM showed no significant differences in HLA class II antigen frequencies. Therefore the genetic basis of susceptibility to MRDM and IDDM in Ethiopia is at least partially identical (Huh KB et al. 1992).

HLA Association and Diabetes.

Epidemiological studies of HLA in IDDM have been found to vary among different diabetic populations. Among the Chinese HLA DR3 was shown to be significantly high in those with IDDM in Beijing and Shanghai. A similar association was observed in Chinese in Taiwan. But in Chinese with IDDM in Singapore HLA-AW33, B-17 and DR3 were significantly high. In the Thai, IDDM HLA DR3 was significantly high. Among Indians three studies showed

significant association with HLA B4 and Aw21 and DR3, In Koreans with IDDM the incidence of HLA BW54 was reported significantly high. In Japan association of IDDM with HLA BW54, DR4 and DRW9 and in Caucasian and Mongols HLA DR3 DR4.

A limited study of the HLA pattern in MRDM patients has shown a significantly high frequency of HLA DR3 than in non-diabetic control subjects and similar to that in type I diabetes in the same population (Kadir AJ et al. 1990).

4.7. ABO and Rhesus (D) Blood Group and MRDM

Blood group antigen is genetically detected and is unchanged throughout the life from birth to death except in some acquired cases of leukaemia where there is loss of A or B antigen which might be due to mutation (Thompson RB). There are many different types of blood group are paracticed for example Kell, Lewis,, Duffy, etc. but the most commonly performed grouping system is ABO blood grouping system. Among the rhesus group there are three different types of antigen namely D or d, C or c E or e. The D is the predominant form of rhesus blood group and is widely practiced.

The distribution of ABO and rhesus blood group system is different in different parts of the world (Hossain M, Jandy CK, Kali KM, Haque KMG, Toyklor GL and Prior AM, Sachs H, Hartman O, Halad K, Macarthu, and pensose LS, Macfunlar EWE and Sarker SS, Rahmnan M). A table is shown on next page showing the normal ABO blood group and Rh in different world population. The distribution of ABO and rhesus (D) blood group systems in greater Chittagong, Noakhali and Comilla (South East Zone of Bangladesh).

Table 5: Blood group distribution among different study group

Blood group	Caucasians	Chinese	Negrol	Indian	Britain	Rahim	Bangl-adesh Nandy	Hoss-ain
O	45.8	45.6	50.0	40.0	46.68	33.97	34.33	36.86
A	39.0	27.2	22.0	22.0	41.71	22.44	23.71	24.80
B	12.6	22.3	23.5	35.0	8.56	45.20	34.15	31.04
AB	4.6	4.5	5.0	3.04	8.39	7.79	7.33	7.30

Within past two decaes it has been shown there is an association between the ABO blood group and certain disease, this has been most clearly demonstrated in the case of disorders of upper GI tract where the secretion of the blood group substance is highest. The strongest relationship is between duodenal ulceration and group "O" but appear to play no role with gastric ulcer. Duodenal ulcer is three times more common in first degree relations of ulcer patients than in general population. Fifty percent concordance for duodenal ulcer has been observed in monozygotic twin as compared with 14% in dizygotic twins. Individuals having blood group O are about 37% more likely to develop these lesions than those of the other blood groups. Non secretors of blood group antigen are 50% more prone to duodenal ulcers than are secretors.

There is strong association of ABO blood group antigen with cancer of stomach. Gastric cancer have a high risk of developing in individuals with blood group A than in groups O or B. Also there is evidence of an association between pernicious anaemia and group "A" and diabetes mellitus seem to be associated with the same group (Thompson RB, Robbins Cotrim and Kumar). There is strong association of blood group 'O' for cholera in Bangladesh but no association with ABO blood group exist for ETEC diarrhoea.

Blood group antigens found on uroepithelial cells and in the secretions may affect bacterial adherence and thereby prediposes to urinary tact infection. (Lichodziejewska NM, Niemierko JM, Malinowska A, Semethowska JE, Manit A, Ruthowski B). Blood group, secretion status and susceptibility to assympatic abcteriuria in diabetes.

Many non malignant diseases may be associated with elevated serum CA19-9 levels, DM is one of them. Blood group secretor status was found to be a contributory factor among patients with NIDDM but not among those with IDDM. (Aly F2, Blackwell Co, Mackenzie DA, Weir DM, Elton RA, Cumming, Sofaer GJA, Clanka FE) chronic atrophic oral candidacies among patients with DM role of secretor status.

The changes in serum concentration of these (CA19-9, CA50) antigens might have some relationship not only to Lewis phenotype, but also to diabetes. (Shinmojo N, Naka K, Hakajima C, Petit JM, Vaillant G, Olsson NO, Guignier F, Collignons VB, Brun JM.

The predominant ABO groups in Rahim's study belong to B (45.20%) an O(33.97%) group while AB factors are 7.79%. The RhD was positive in 96.44% and in negative in only 2.56%.

Rahim MA, Rahman MH, Shahidullah M and Sarma SK studied 1067 patients with malignant neoplasm. Under the term malignant disease they included carcinoma, sarcoma and other malignant neoplasm as defined by World Health Organization. They found magority of the patients O(31.86%) or B(34.77%) respectively, group was 25.77% while least number of patients belonge3d to AB(7.59%). These figures were similar to those of control population of Bangladesh.

Studies have been made to determine possible between blood groups and different disease including cancer of stomach (Aird et al. 1953; Billington 1956; Buckwalter and Seoy 1961),

duodenal and gastric ulcers (Aird et al. 1954; Roberts 1957; Wallace 1958; Clanke et al. 1959; Buckwalter and Seoy 1961) pernicious anaemia (Callender et al. 1957), rheumatic fever (Glyun et al. 1956, Clarka et al. 1960), salivary gland tumour (Cameron 1958) and DM (Mcconnel et al. 1956). Rahman studied ABO groups in 2312 confirmed diabetes from Bangladesh and compared the results with normal controls subjects (8936). He found no statistically significant ABO blood group and diabetes.

With this background I tried to find if there is any association between the MRDM patients and ABO blood group. I did the ABO blood grouping using anti A & B and RhD antigen and patients blood and the results are tabulated below.

Table 6:

ABO and RhD of MRDM patients

Total No. ABO MRDM Blood Group		RhD + ve n(%)	RhD – ve n(%)
n = 38	A 7(18.42%)	6	1
	B 13(34.21%)	13	Nil
	O 16(42%)	16	Nil
	AB 2(5.26%)	2	Nil
Control	A 12(60%)		Nil
	B 2(10%)		Nil
	O (5(30%)	+ve (100%)	Nil
n = 20	AB Nil	Nil	Nil

Group

X2 = 9.9073 dt = (4-1) (2-1) = 3

p = <0.025

RhD

x2 = 0.5356 dt = (2-1) (2-1) = 1

p = <0.4

4.8.Renal function and MRDM

Diabetes nephropathy is an important cause of morbidity and mortality among both types of diabetes.About 30% of patients with type ! diabetes have developed diabetic nephropathy after 20 years.(Davidsons Medicine,2006).Incidence of Diabetes Mellitus is increasing globally and in some countries is the single most common cause of endstage renal disease and majority of them requires long term dialysis and subsequently transplantatation.The predominant cause being glucose and glucose degradation products like AGE.(SteinG,Funfstuck R,Schiel R,2004)

Abouna GM et al,1983 suggested that diabetic nephropathy is generally attributed to uncontrolled hyperglycemia with its associated glomerular hyperfiltrution. In man various workers have tried to prevent progression of the disease by strict glycemic control, functional improvement being reported by some, continued deterioration by others. They reported oversal of diabetic nephropathy in two cadevanic kidney after transplantation in to non diabetic recipients.

Recent studies in man and animals strongly support the concept that the primary responsibilities for diabetic nephropathy rests with the metabolic derangent of the diabetic state. It is unlikely that hyperglycemia person produces al of the nephropathic influences of diabetes. Alterations in microvascular haemodynemics in diabetes probably contribute to glomemlar pathology. These alterations may be based upon disturbed vasoactive control mechanisms regulating angiotersis and prostaglandin secretion and metabolism. In approximately 50% of the children with Juvenile onset of insulin dependent diabetes, renal failure will develop within an average of 20 years after its onset.

Diabetic nephropathy and its and result renal failure is a vast problem for diabetic patients. Newly 40% of the insulin dependent diabetic (type I IDDM) patients will develop renal failure on average about 20 years after onset of diabetes. Together diabetes related kidney failure all for approximately 25% of new end stage kidney disease patients in the united states. In UK in 1979 33% of diabetic patients under the age of 50 years develops uremia with evidence of nephropathy.

Renal structural and functional changes have been recognized to occur from after onset of IDDM. Renal hypertrophy occurs in early diabetes mellitus and in animals with experimental diabetes. In both patients and animals kidney enlargement is noted shortly after the onset of hyperglycemia. Both glomerulus and tubular size are significantly increased with a 30% increase in total glomerular volume, an increase in glomerular filtration surface area, podocyte slow hypercellularity and proximal and distal tubular cellular hypertrophy and hperplasia. They based this augment on the accompaniment of increased GFR by demonstrably increased tubular reabsorption rates from sodium, glucose and calcium. They proposed that elevated plasma and utrofiltrate stimulates tubular reasorbtion of sodium by the sodium glucose contrusper mechanism thus producing increased solute in water reabsorbtion and a net increase in GFR and FF. Others have proposed addition factors which may influence hyperfunction in IDDM. Although glucagon administration has been shown to increased GFR in animals, normal man and well controlled diabetes, the mechanism of this rise in GFR is unclear. It has been proposed that growth hence may influence the hyperfunction of diabetes, based on the finding that administration of growth hence to diabetics while maintain usual glycemic results in an elevation of GFR and RPF over base line values. Thus the growth hence elevation usually found in type I diabetes usual metabolic control may contrute enhanced GFR and RPF. Overt protein long been reorganized as one of the hallmarks of clinically apparent diabetic nephropathy. Recent work has focused on the microalbumin which can be detected earlier in the disease process. Microalbumin can be defined as persistant elevation in the urinary albumin excretion to 20-200mg/ml when using early morning urne.Diabetic nephropathy is a frequent and serious secondary complication of diabetes mellitus leading to increased morbidity and mortality and to impaired quality of life in persons affected.(Rahman & Tahmin,2006).Early diagnosis of microangiopathy and treatment with angiotensin converting enzymes inhibitors with tight glycaemic and blood pressure control reduces the

risk of CVD by 53%,nephropathy by 615 and retinopathy by 58% compared to conventional treatment.

Hyperfunction of the kidney is well documented early in IDDM and is the subject of an extensive review, glomerular filtration rate (GFR) renal plasma flow (RPF) and filtration fraction (FF) are increased in newly diagnosed patients prior to insulin treatment GFR is elevated nearly 50% over normal prior to insulin treatment and remains 20% higher achieved near normal blood glucose values. Patients with good metabolic control appear to have lower GFR than patients with poor metabolic control, but GFR remains elevated by 20-30% in diabetics on standard insulin treatment, unless the patient develop clinical nephropathy. This increased GFR is closely correlated with the enlarged kidney size and both newly diagnosed diabetics and in those with longer duration without evidence of nephropathy.

The mechanism of renal hyperfunction in diabetes is unclear, however, vascular volume expansion has been excluded as a possibility, glucose infusion alone has been shown to increase GFR by 6% in normal man. In diabetic a rise in blood glucose from normoglycemic levels to moderately hyperglycemic levels also results in a 5% increase in GFR. Micropuncture studies has shown that increased GFR is secondary to increased osmolar plasma flow and transcapillary hydrostatic pressure, the letter appearently secondary to alterations in the balance of afferent and afferent glomerular arteriolar resistances. Dizel and Brochuer-Mortensen have proposed that these are result from changes in altered tubuloglomerular function.

Parameters of nutritional status including serum albumin,serumcreatinine and body mass index(BMI) are powerful predictors for mortality and hospitalization of patients with endstage renal disease.

Depression is most common associated psychological problems and may increase mortality in chronic hemodialysis patients due to poor oral intake and proinflammatory cytokine secretion.(Cano NJ,2002)

Many patients with end stage renal disease(ESRD) are malnourished and cross sectional studies show that markers of malnutrition may predict death.The commonest marker is serum albumin,because it is closely related to the effects of inflammation and other non nutritional factors.(Stenvinkel 2002)

Higher incidence of malnutrition was observed in peritoneal dialysis patients than hemodialysis patients in one study in Korea. (ParkYK, 1999) Cardiovascular is the leading cause of morbidity and mortality in ESRD.Cause include Diabetes, hypertention, anemia, hypotension, hypoalbuminimia, malnutrition, dyslipidemia, dialysis modalities etc. (Zabetakis PM, Nissenson AR,2000)

4.9. Immunology and MRDM

MRDM is a complex disease of new entity and multificatorial etiology. It pathogenesis has not been completely elucidated. It is assumed that besides genetic factors, other factors may be involved. Recently greater attention has been paid to the problem of immunodeficiency and inadequate immunoreactive responses. The presence of insulin antibodies and immune complexes and deficiency of T lymphocyte count in diabetic patients (specially in those with juvenile onset insulin dependent type) lead to the assumption that abnormalities of cellular and humoral immunity may play a certain role in genesis of diabetes. Immunodeficiency has been found by many authors in juvenile onset diabetes. (Unger B et al. 1985; Irvine JW et al. 1978; MacCuish AC et al. 1974).

The data Suggests either genetically induced deficiency of cellular and humoral immunity or acquired deficiency of complete immunity to be involved. Other factors such as stress,

infection, inadequate nutrition only potentiate disorders present contribute to the deficiency of immune responses. They studied 10 Juvenile onset diabetes, 20 adults onset diabetes and 10 healthy controls. In 80% of patients with Juvenile onset diabetes a significant deficiency (below 25%) of T. Lymphocytes was found, while in adult onset group a less severe deficiency of T. Lymphocytes was found. A decrease of C3 complement was found in 80% of the Juvenile onset diabetes, while it was 40% decreased in adult onset insulin dependent diabetes with nephropathy. Adult onset insulin dependent diabetes with nephropathy C3 was decreased in 20%. In adult onset diabetes without complication the C3 level was normal in all patients. C4 was more static but a decrease was found in two patients with Juvenile onset diabetes and in few with adult onset diabetes.

IgG was decreased in 4(80%) patients with Juvenile onset diabetes while IgA and IgM were mostly stable. These results showed an abnormal immune response in diabetes, specially in Juvenile onset diabetes and in adult onset insulin dependent diabetes with complications. These observations points in favour of assumption that within the genetic predisposition of DM a deficiency of cellular and some deficiency of human immunity either congenital or acquired may be present.

The clinical and subclinical associations between IDDM and autoimmune endocrinopathies (mainly thyroid) together with the pathoanatomical findings in the islets of Langerhans at the time of diagnosis suggest that autoimmune mechanism may be concerned with pathogenesis of IDDM. (Gupta S1984). Immunobiology of clinical and experimental diabetes, New York, London, Plenum Publishing company 1984). Cell mediated autoimmunity directed against as yet unidentified antigenic components of the endocrine pancreas has been demonstrated in IDDM. In addition, a variety of autoantibodies reacting with antigens in the islets of Langerhans have been identified; these include islet cell cytoplastic antibodies that react with all endocrine cell types in the islets, islet cell surface

antibodies react predominantly with β-cells complement dependent cytotoxic antibodies and an antibody that immunoprecipitate a 64 k protein present in islet cells.

Islet cell cytoplstic antibodies are the most extensively studied, they can be demonstrated in 60-80% of patients with IDDM at the time of diagnosis and in 95% of their first degree relatives, but in only one percent of patients of NIDDM and non diabetic controls. Furthermore islet cell cytoplastic antibodies and the other antibodies may be present for years in a prediabetic phase of IDDM, in some NIDDM patients developing insulin dependency (Mario U et al. Immune abnormalities in diabetic patients not requires insulin at diagnosis.

The pathogenomic role of islet cell cytoplasmic antibodies and the other IDDM specific antibodies remain to be elucidated. However, when they occur in individuals with a diminished early insulin response to intravenous glucose stimulation and a IDDM associated with HLA DR allele, they are more susceptaible to β-cell destruction that may eventually lead to IDDM. Antibodies to the insulin receptor have been identified in a rare form of diabetes associated with severe insulin resistance and Acanthosis Nigiricans.

Although, pancreatic β-cell destruction has immunological association, the immunological mechanism concerned have not yet been clearly defined. The cells and pathways involved in the initial or primary attract are not yet known. Further there may be several different pathogenic sequences that lead to β-cell destruction. Some appear to be antigen specific, involving T-cell mediated e.g. macrophage production of cytokines that induce the release of free oxygen and nitric oxide radicals, to which β-cells may be particularly vulnerable. (Paulsen MT et al). Cytokines and free radicals as effect molecules in the destruction of pancreatic β-cells in: Baekkeskov S, Hansen B eds. Human diabetes genetic, environmental and antoimmune etiology..

IgG is the most abundant immunoglobulin in the serum of normal humans. It is also found in the tissue fluids, and it can cross placenta from the maternal to fetal circulations. It has antibacterial, antiviral and antitoxic activities in vivo, and in virtro it is moderately to strongly active in agglutination and precipitation, is moderately effective in complement fixation reactions (IgG and G3) and has opsonic properties. IgG1 displays skin sensitizing activity, and IgG2 is cytophilic, e.g. Fc region can combine with macrophages, which may then react with antigen against which the antibody was raised (half life 23 days).

IgA is the second most abundant immunoglobulin in human serum and is the chief immunoglobulin in exocrine secretions, including milk and colostrum, tears, nasal fluid, bronchial fluid, gastrointestinal secretion, bile and urine (half life 5-6 days). Two sub-classes IgA1 and IgA2 are found in all sera. Most of the secretory IgA is apparently produced by plasma cells beneath the epithelial surface of mucous membranes and exocrine glands. Serum IgA is synthesized both in the lymphoid tissues, such as the lymphnodes and spleen and in the exocrine glands and mucosa.

IgM is found predominantly in the intravascular pool rather than in tissues or secretions, presumbly because of large molecular size. For the same reason it does not tend to cross the placenta the concentration in fetal blood is only about 10% of that in maternal blood. IgM is usually the first antibody to appear in animals or human following immunization. It is then gradually replaced by IgG. It serves as an antigen receptor sites on lymphoid cells and that being pentavalent to decavalent, they may more readily be triggered to respond to antigenic stimulation than lymphoid cells being IgG molecules receptors. This might account for the more rapid initial IgM response to immunization.

Complement:

In addition to the abundant data obtained with in vitro experiments, three lines of evidence indicate that complement mediation plays a central role in a spectrum of human disease.

a) Localization of complement at the site of injury.

b) Hypercatabolism of components.

c) Decreased component of concentration/or presence of activation fragments in the circulation and extravascular fluids.

Over 60 years ago Gunn reported decreased haemolytic component in two children with post scarlatial glomerulonephritis as compared to uncomplicated Scarlet fever. Earlier von pirquet and Cchick had postulated that the interaction of equine antigen and host antibody produce toxic factors i.e. circulating immune complexes which caused symptoms of human serum sickness and decreased haemolysis was demonstrated in these patients. C is required for the initiation of neutrophil vascular injury in human immune complex disease where activation of C3 and C5 via either the classic or the alternative or both can result in increased vascular permeability, ingress of inflammatory cells, phagocytosis of immune complexes with concomitant release of lysosomal enzymes and tissue injury.

Disease association:

Classic pathway

(a) SLE > The three criteria for C participation in disease are conclusively satisfied in SLE. The prototype human autoimmune disease in which soluble immune complexes are deposited in vascular and other basement membrane, activate complement and evoke tissue injury. Deposition of C3 was first demonstrated in glomeruli, C3 and C4 are detected on erythrocytes, platelets and leukocytes. Circulating immune complex are present in 100% patients. Hypercatabolism of C1q, C3, C4, C5 p and factor B.

(b) HBV infection – a symptom complex resembling acute serum sickness occurs approximately 20% patients with acute type B viral hepatitis. Typically urticaria with or without weeks before any clinical signs of hepatitis and then the extra hepatic symptoms

cease with development of Jaundice. Transient glomerulonephritis and cutaneous vasculitis also occur. Consistent decrease of C4, circulating Ab immune complexes.

(c) Dengue haemorrhagic shock – profound C activation occurs in dengue haemorrhagic fever which is caused by infection with any of the four antigenitically similar groups of B Arbor viruses. This occur only in children experiencing a second infection with a different type of dengue virus decrease in serum C3, C4, C5 and factor B is found.

Alternate pathway

(a) Post streptococcal acute glomerulonephritis: An immune complex mechanism exists. Streptococcal M protein and plasma membrane antigen has been documented in damaged glomeruli, while host IgG and C3 in irregular granular pattern along capillary wall an subepithelial regions. In addition P is associated with granular C3 deposits in 100% while C1q and C4 are detected in 60-80% biopsies. Decreased C2 and C4 levels are occasionally present at the onset of haematuria but C3, C5, p are uniformly decreased for extended periods and parallel direction of clinical involvement.

(b) Chronic MPGN with hypocomplementa: Selective decrease in C3 as one distinctive marker along with the pathological picture of lobulated membranoproliferative with extensive measugial hyperplasia and deposition of C3 and IgG in the peripheral capillary loops.

Haematological disorder

Autoimmune hemolytic anemia (AIHA): The Coombs antiglobulin test is positive for C3 and C4 in the majority of patients with idiopathic AIHA and cold agglutination disease, serum C3 level is normal.

Paroxysmal nocturnal haemoglobinuria (PNH): An acquired abnormality of blood cells occurs in PNH which renders affected platelets, neutrophils and erythrocytes and extremely susceptible to lysis by terminal C5b-9 membrane attack unit of C. Alternate pathway activation is most likely involved in anemia of PNH.

Low serum complement levels

Low serum complement levels – Particularly low C3 – are encountered in antigen antibody complex diseases such as SLE, AGN and in cryoglobulinemia.

DIC – Decreased concentration of serum C3 occurs in the majority of patients with DIC associated with septecaemia, obstetrical disease and malignancy. The relationship between C and coagulation system not been well defined.

Lymphoma

An unusual C profile occurs in some patients with lymposarcoma and increased serum 7S IgM. Extremely low concentration of C1q and C4 are present with normal C3 and C9.

Inherited C deficiencies

Selected inherited deficiencies will be emphasised which highlight both the relative importance of an intact C system in defense against infection and paradoxically the increased association of immunopathogenetic disease with those deficiency. Heriditary deficiency of certain complement components (e.g. C2,C3,C4,C5 and C8) may lead to increased susceptibility to infection. Hyh KB et al. 1992; studied 1266 hospitalized Korean diabetics among which 29(2.3%) IDDM and 84(6.6%) were MRDM.

It is well known that in Type I diabetes mellitus there are abnormalities in serum lipid and lipoprotein levels, these abnormalities consists of an elevation of triglycerides and prebetalipoproteins and sometimes of cholesterol and betal poproteins. It has been claimed that high carbohydrate/ high fibre/low fat diets for diabetic subjects can improve metabolic control. The authors compared the lipid and lipoprotein serum levels in a group of 19 diabetic children who first followed a conventional diet defined as carbohydrate 50% protein 20% fat 30% of total energy intake and after 12 months of a normal carbohydrate/low fat diet. There was a significant difference of lipid parameters after two months. Cholesterol- 175.66±36.81 vs 165.1±21.66 mg/dl. LDL- 115.4±16.91 VS 104.1±10.01 mg/dl; p 0.05. Triglyceride-91.6+20.9 US 121.4+ 28.0 mg/dl; p 0.05 no significant difference was observed between insulin requirement and HbA1c (Effect of normal carbohydrate/low fat diet on lipid metabolism in insulin dependent diabetes mellitus in childhood. Charelli F, Verrotti A, Tumini S, Morgese G.

The offspring of type 2 (non insulin dependent) diabetic patients have a higher incidence of the disease when compared with general population. Recent studies have demonstrated a higher prevalence of subtle metabolic abnormalities in glucose tolerance, lipids and lipoproteins and gluconeogenic precursors in genetically predisposed, non diabetic off spring of type II diabetic patients. It has been suggested that these early metabolic abnormalities could represent either early marker's of the disease or deteriorate in to future diabetes.

4.11. Diet and MRDM

Both the association of malnutrition diabetes with food cyanogens, and our laboratory observations support a role for cyainde in its pathogenesis. In recent years much evidence has been marshalled to suggest that diabetes is divided into two basic patterns in the temperate zone. Individuals who develop diabetes rather suddenly and who are predisposed to ketone formation regularly require insulin. They are usually young but not always. An islet autoimmune response is often detectable early in the disorder. In the second form an elevated post absorptive blood sugar is found in mature individuals, who are often without symptoms, ketone bodies are not found and insulin is not required usually. A familial pattern is commonly seen and overweight appears to be predisposition.

A form of diabetes that does not fit into either temperate zone categories has been recognized in tropical countries for more than two decades. Affected individuals are usually adolescents or young adults, characteristically under nourished. who require considerable amount of insulin to maintain or increase body weight but who does not develop ketoacidosis. This condition without other findings is often referred to as type J diabetes because of its initial description in Jamaica.

The association between the geographic distribution of malnutrition diabetes and cassava consumption supports a hypothesis that the combination of cyanide exposure and low protein intake may play an etiologic role in malnutrition diabetes.

A link between cyanide ingestion, protein calorie malnutrition and diabetes is supported by both geographic distribution analysis and animal studies, firm support for the concept that cyanide ingestion, combined with malnutrition, causes youth onset diabetes would complement the evidence for an environmental of youth onset insulin dependent diabetes produced by analysis of identical twin study. (McMillan E and Geevarghese PJ, 1966, 1968, & 1977).

Incidence of complications: Hypertension was the most frequent complication with high prevalence in Thailand, the Philippines, Hong Kong and Japan. Retinopathy, Nephropathy and Neuropathy were also frequent. Retinopathy was found with high prevalence in Iraq, Indonesia, Taiwan and Japan, whereas neuropathy was the most frequent complication in India. Indonesia and Taiwan, peripheral vascular disease was rare. Diabetes ketoacidosis although not as frequent as in the west, occurred in many countries. Pulmonary tuberculosis and infection remain high in most Asian Countries.

The causes of death in people with diabetes different countries are varying. Diabetic coma ranks high in India, Thailand and Japan. Ischaemic heart disease accounts for high mortality in the Philippines and India, whereas cerebrovascular disease figures prominently in Indonesia. Gangrene as a cause of death still remains high in Thailand and Indonesia. Infection is a frequent cause of death in Thailand and Japan.

Cases of malnutrition related DM conforming to the description of the protein deficit pancreatic diabetes type in Ethiopian patients were compared with type I (insulin dependent) and type 2 (non insulin dependent) diabetic. Fourteen of 39 MRDM patients had fat malabsorption compared with only two of ten type I diabetic patients and one of nine control subjects. Xylose absorption was normal favouring a pancreatic cause for the malabsorption. Plasma C peptide during oral glucose tolerance test was significantly lower than that in type 2 diabetic patients and normal control subjects and was also consistently but not significantly higher than in type I diabetic patients glucogen secretion patterns were similar in malnutrition related and type I, diabetic patients. Out of 23 newly diagnosed MRDM patients 14 remain ketosis free for our eight days while another six developed ketoacidosis or significant ketonuria within two days during the trial.

The similarity of the malnutrition related and type I DM in age of onset, insulin requirement for diabetic control and appearance of ketosis progress in some cases, together with similarity of C peptide and glucagon secretion pattern suggest that the protein pancreatic diabetes, a variant of malnutrition related DM may be Type I DM modified by the background of malnutrition rather than an aetiologically separate entity (Abdulkadir CJ, et al 1979). The clinical and hormonal (C peptide and glucagon) profile and liability to ketoacidosis during nutritional rehabilitation in Ethiopian patients with MRDM.

Cyanoglucosides are important chemical of cassava and its seems that excessive cassava intake combined with a low intake of proteins, deficient in certain aminoacids, provides an essential moity for the accumulation of cyanide in the body with result at toxicological effects. Alternative source of dietary cyanide include sorgum, yet, millet, maize, land linseed. There possibly be other toxic factors, especially food toxins, which may interact with malnutrition to produce similar clinical and morphological changes? We need much more information about other factors which either singly or in concert with protein energy malnutrition, may lead to FCPD syndrome.

As cyanoglucosides in cassava have also been implicated in the etiology of tropical ataxic neuropathy and of endemic goiter in several regions of Africa. Protein deficient diabetes mellitus PDDM) has been described as J-type, K-type or M-type of diabetes. There is considerable evidence that protein malnutrition in early childhood initiated functional impairment of pancreatic β–cells in the case of PDDM. It seems that nutritional injury, in the form of protein malnutrition in early infants and childhood, results in partial failure of β-cell function. A outline low level of protein intake may make this process progressive and Irreversible, resulting in the clinical onset of DM at an early years of age.

There is an urgent need to plan interesting strategies for diabetes care and control in developing countries, based on sound epidemiological and dermographic perspective. Only

then can these countries move towards primary prevention of diabetes – a disease affecting a large segregates of the young population. (Jasbir S, Bajaj, 1988).

Records of 489 consecutive diabetic Ethiopians revealed that 171 had type I diabetes, 462 type II on obese, 210 type II obese and four drugs induced. Undernutrition (BMI <18 kg/m^2) was present in 12.9% of patients.

Abdominal radiographies have been done for 189 patients mainly in the young thin and insulin requiring. Pancreatic calcification has been found in only two cases, both middle aged men with a history of alcohol intake. Only one patient with parotid enlargement was seen, cassava is not eaten in Ethiopian. DM was induced in one patients by steroid, in three by pentamidine therapy for leishmaniasis a known cause of diabetes, DM followed viral hepatitis in four cases. France T et al.1984).

Adrenocortical activity was investigated in experimentally induced protein malnutrition in Rhesus monkeys. Control studies were carried out in the same animals before inducing protein malnutrition, plasma cortisol levels were elevated in the protein malnourished state. There was a total abolition of the dirunal rythm of cortisol secretion. Fasting hypoglycaemia was also observed in the protein malnourished state. It is concluded that increased adrenocorticoid activity as sustained steroidogenesis result from protein deficiency. Hypoglycaemia may be an important stimulus in addition to the metabolic stress imposed by protein deprivation. The organization of increased adrenocorticoid activity is important in a protein deficient host, since the disease against infections might be impaired in such a solution (Khasdo SR et al. 1979).

A complex interplay exists between magnesium and glucose metabolism hypomagnesaemia has been reported in both IDDM & MRDM patients. It has even been shown that the DM is the chronic disease most frequently associated with hypomagnesaemia.

The importance of hypomagnesaemia is inversely related to the quality of blood control, largely results from hypermagnesaemia, and may reflect a substantial depletion of body stores of magnesium. On the other hand magnesium also influence glucose homeostasis. Circumstantial evidence has been presented that hypomagnesaemia could cause insulin resistance during treatment of diabetic ketoacidosis. This suggestion is in keeping with in vitro studies, which ascribe to magnesium an important role in the action of insulin. Magnesium may also be involved in the regulation of the β-cell function. In vitro variations of extracellular magnesium concentration modulate glucose induced insulin release and insulin biosynthesis. Moreover, several insulin secretogogues markedly affect magnesium fluxes in islet cells (Legrand C, et al. 1987).

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a pancreatic cause for the mal absorption. Plasma C-peptide during oral glucose tolerance

test was significantly lower than that in type 2 diabetic patients and normal control subjects and was also consistently but not significantly higher than in Type I diabetic patients. Glucagon secretion patterns where similar in malnutrition related and type, 1 diabetic patients. Out of 23 newly diagnosed MRDM patients 14 remain ketosis free for eight days while another six developed ketoacidosis or significant ketonuria within 2 days during the trial.

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Protein deficient diabetes mellitus PDDM) has been described as J-type ,K-type or M-type

of diabetes. There is now considerable evidence that protein malnutrition in early childhood initiated functional impairment of pancreatic beta cells in the case of PDDM. It seems that nutritional injury, in the form of protein malnutrition in early infants and childhood, results in partial failure of beta cell function. An outlining low level of protein intake may make this process progressive and irreversible, resulting in the clinical onset of diabetes meilitus an early years age.

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A complex interplay exists between mangnesium and glucose metabolism. Hypomgnesemia has been reported in both IDDM and NIDDM patients. It has even been shown that the diabetes mellitus is the chronic disease most frequently associated with hypomagnesemia. The importance of hypomgnesemia is inversely related to the quality of blood glucose control, largely results from hypermagnesemia and may reflect a substantial depletion of body stores of magnesium. On the other hand magnesium may also influence glucose homeostasis. Circumstantial evidence has been presented that hypomagnesemia could cause insulin resistance during treatment of diabetic ketoacidosis. This suggestion is in keeping with in vitro studies, which ascribe to magnesium an important role in the action of insulin. Magnesium may also be involved in the regulation of the B cell function. In vitro variations of extra cellular magnesium concentration modulate glucose induced insulin release and insulin biosynthesis. Moreover , several insulin secretogogues markedly affect magnesium fluxes in islet cells (Legrand CW et al. 1987).

Helgason and Janasson in a comprehensive survey in Iceland of ketosis phone diabetes found 29% preponderance of males and a trend for the time of diagnosis to coincide with epidemics of viral diseases They found a significantly increased incidence between July and January in the age group diagnosed as D-14 years. The incidence of diabetes of this group of boys was very much higher than would be expected ($P<0.00001$). HLA histocompatibility types and virus infections were considered as possible causes of the finding but there seemed to be at least one additional season factor acting prenatally.

Circumstantial evidence suggests, that this additional factor is the N nitrosamine compound content of processed mutton traditionally consumed in Iceland in the two weeks from December 23. Recently produced Icelandic smoked/ cured mutton contains considerable concentrations of N nitrosamine compounds. This work implies that a common food additive contributes to the production of ketosis prone diabetes, not in the consumer but in the progeny (Helguson T et al. 1981).

4.12. Histopathological finding of pancreas in diabetes and MRDM

The pathological appearance of the islets of Langerhans is compatible with that of an autoimmune lesion. The typical finding in IDDM is so called insulitis. The term insulitis was coined by von Meyenburg, but it was already known to the first pathologist who performed systemic studies of the pancreatic gland in diabetes and pointed out that the lesion was specific for Juvenile diabetes mellitus. Gepts has recently confirmed these findings. Insulitis has been described in few cases of IDDM of late onset and also in spontaneously diabetic animals.

In detail insulitis consists of mononuclear infiltration of the islets of Langerhans together with a very selective destruction of β-cells, leaving α- and delta cells intact. The infiltration is made up mainly of small lymphocytes and is often rather discrete. Severe lymphocytic infiltration distorting the whole architecture of the islets can be seen. Not all the islets of a diabetic pancreas are involved. In a recent series 10-75% of the islets were found to be affected. In this series the duration of DM was very short (a few weeks). Insulin has not been described in juvenile diabetes with a duration of disease of more than one year. Thus insulitis is a feature of IDDM of short duration, it is tempting to speculate that the lymphocyte infiltration causing the β-cell destruction has been present in the months or perhaps only weeks before diabetes become on clinically manifest.

The cause of insulitis in man is so far unknown. Several animal models have been produced. Since the animal models have many features in common with IDDM in man eg. genetically determined susceptibility, involvement of virus, lymphocytic insulitis, cell medicated and possibly also humoral autoimmunity they have important implications for the study of the pathogenesis of the human disease. (Nerup J, Christy M, Deckert T and Egeberg J. Diabetes Mellitus in Textbook of Immunological disease. Vol. I & II, Ed. Max Samter Publication. Little Brown and Comapny 1978. p. 330).

Chronic pancreatitis:

Chronic pancratitis characteristically present with abdominal pain, which can be very severe. Two major anatomic forms have been described, one associated with obstruction of the major pancreatic ducts either by calculi or stone and the other accompanied by extensive parenchymal calcification.

Microscopically the main features are dilatation of ducts and acini, squamous metaplasia, intramural eosinophilic mucoprotein plug which often calcify, acinar atrophy and perilobular and intralobular sclerosis.

Chronic pancreatitis can result in a marked proliferation of islet cells, which may grow in cords and small cluster. (Geldof AA et al. 1992).

Histopathological changes in rat pancreas were induced by cyclic periods of experimental malnutrition or by cassava (manioc) feeding for 11 weeks. A marked decrease in pancreatic weight in the cassava fed group was collected with shrinkage of acinar structure and degenerative features in exocrine pancreas. In the malnutrition group vacuolization and loss of tissue architectures were observed in some parts of the organ. No sign of ductal obstruction as a tentative cause of pancreatic pathology after malnutrition could be detected. Loss of islet tissue was occasionally seen in degenerative areas. It is concluded that histopathological changes in exocrine pancreas result from malnutrition and cassava

feeding differentially and precede ultimate degenerative process of pancreas endocrine tissue.

4.13 Distribution of MRDM and Control Subjects:

Distribution of MRDM patients and control subjects from different comers of Bangladesh who have been attending BIRDEM daily are included in this study. It is a unique advance to study these subjects reflecting different geographic areas of Bangladesh. Bangladesh is divided into 64 district division and 464 upazillas administratively.

Histopathology of pancreas:

Von meyenburg (1940) noted mononuclear infiltrate in and around islet of Langerhans of diabetic children dying with ketoacidosis. Similar lesions were produced by Rynold et al. (1964) in experimental animals by immune process. Autoimmunity has been suggested to play an important role in the pathogenesis of diabetes particularly in the insulin dependent group.

Microscopically the most typical features are diffuse interlobular and periductular pancreatic fibrosis with progressive acinar and islet replacement by fibrofatty tissue, there is little or no evidence of inflammatory reaction. Although the viscid material in the main pancreatic duct and its branches is almost always bacteriologically sterile, this does not entirely exclude the possibility of fibrocalculous pancreatic diabetes being initiated by a non bacterial infective process. (WHO technical report series 1985; p. 22).

Histologically there was a decrease in volume density of endocrine cells compared to age-matched diabetes resistant control rats. In a 200 day old non diabetic prone BB rats 55.3±4.0% of islets contain immunocytes and the number of immunocyte per 1000 of islet tissue averaged 53.8+12.8 compared to 12.2 ± 0.8% in age matched diabetes resistant BB controls (p.0.05).It was concluded that diabetes prone BB rats that escape event diabetes may nevertheless exhibit a marked increase in immunocytes associated with subtle loss of

endocrine volume and function. Thus in diabetes prone BB rats disorder rates for insulitis

defined here as a statistically significant increase in immunocytes, are less than those for overt diabetes. This may mean that an event subsequent to the development of insulitis determines the extent of β-cell destruction (Morphometric and functional studies of islets in diabetes prone BB/W rats that are discordant for event diabetes I komiya, (Baelens D Inman L, Perrelet A, Orci L and Unger RH.)

Biochemical tests: Venous plasma true glucose was estimated by glucose-oxidase method using technicon auto analyzer II. HbA_1c was measured by auto Analyzer (The Hemoglobin A_1c was Analyzer, HA-8110) which was set up with high pressure liquid chromatography (HPLC) with column filter. Serum total protein and serum albumin were measured on the basis of Biuret and Bromo-Cresolgreen methods respectively using the BM/Hitachi System 704. Serum total amylase, triglycerides and cholesterol were determined by enzymatic colorimetric, enzymatic UV test, enzymatic colorimetric tests respectively using BM/Hitachi System 704. Immunoglobulin estimation was done by radial immunodiffusion technique and HLA by lymphocytotoxicity test pancreatic biopsies from FCDP and chronic pancreatitis patients.

Radiological Support: Finding of plain x-ray of abdomen in erect posture already done to detect pancreatic calcification, ERCP and CT Scan of pancreas already recorded in the guide book of the MRDM subjects were noted. Pancreatic biopsies from FCDP and chronic pancreatitis patients were processed for light microscopic examination and studied with routine H and E stain for evaluation.

Statistical Methods: All values were expressed as mean ± SD. For analysis of variance among and within different classes, ANOVA calculation was adopted using Scheffe procedure. Pearson's correlation coefficients (r) was calculated to study the correlation of different variable among themselves. Association of relevant parameters with different

classes were done using Chi x^2 test. Unpaired "t" test was applied when required. To identify relative risk (Odds ratio) multivariance analysis was done. In all cases $p<0.05$ was considered significant. All analysis were done using SPSS/PC+ package.

Forty five 'under 30' diabetic subjects reported during our study period from June 1990 to June 1993. Of the 45 MRDM patients males were 27(60.0%) and female constituted 18(40.0%) male and female ratio 1.5:1 55.85% subjects came from urban areas and 44.15% were from rural areas. The control group compared of 20 subjecs of which male 16(80.0%), female 4(20%) the male and female 4:1.

Age and Sex: 28(62.22%) resides in urban and sub-urban areas and the rest 17(37.78%) in city areas. Among the 45 MRDM patients 30(66%) are from Dhaka and its neighbouring districts and the rest 14(34%) are from different districts covering all 6 divisions of Bangladesh. Among 20 control subjects 80% are resident of Dhaka and its neighbouring districts and the rest 20% for other division. 15(75%) leaves in urban and semiurban areas where 5(25%) resides in rural areas.

Materials & Methods

Study subjects:

A total of 45 MRDM patients (M = 27, F = 18) attending BIRDEM out patient department between the period June 1990 to June 1993 were selected randomly as and when found basis. The age range is between 12-29 years. Their height and weight was taken and BMI was calculated using the formula kg/ht in M^2. Present or past stigmata of malnutrition was searched for and noted. Their detail clinical history was recorded in a prescribed proforma with reference to age, sex, income, education, occupation, dietary history, family history of diabetes etc. were recorded and coded data sheet (annexure-I).They were explained about collection of blood for the following examination and 15 ml blood was collected aseptically from a suitable capital vein after a verbal consent. The blood was placed in five different test tubes for the following tests. The selection criteria for MRDM is shown in annexure[1].

Control subject:

Twenty controls were selected randomly from the staff of BIRDEM and also outside BIRDEM. The age range is between 20-29 years (M=16, F=04). All similar tests as mentioned for study subjects were done for the controls and the same procedure followed for them. However no biopsy sample could be collected from them. Test procedure followed is described below. Blood sample were treated as follows. For lipid estimation 4 ml of blood samples was taken in a plain test tube and was separated by centrifugation and stored at 4°C until analysis within one week.

Distribution of MRDM and Control Subjects:

Control subjects are taken from staff and their relative in BIRDEM and some other private diagnostic Laboratories located at Dhaka. MRDM subjects are below 30 years of age and reported to BIRDEM and diagnosed on the WHO criteria of 1985. The study period is between June 1990 to June 1993.

Detail history was recorded in a preformed case sheet. Age, sex, local district, rural or urban areas, education, occupation, annual family income, excreta disposal, water supply,

housing facilities, habits, past history of viral disease and malnutrition, symptoms of DM, family history of DM, anthropometric, clinical examinations and biochemical results were included. Details of each of the parameters are given below:

Table 7: Distribution of MRDM and control subjects.

Patients	
Dhaka	9(20.0%)
Mymensingh	3(6.36%)
Comilla	4(8.89%)
Sherpur	1(2.22%)
Narshingdi	4(8.89%)
Shariatpur	3(6.36%)
Gaibandha	1(2.22%)
Laksham	1(2.22%)
Patuakhali	1(2.22%)
Noakhali	2(4.44%)
Pabna	1(2.22%)
Madaripur	1(2.22%)
Naogaon	1(2.22%)
Barishal	1(2.22%)
Gafforgaon	1(2.22%)
Laxmipur	1(2.22%)
Kishoregonj	2(4.44%)
Gazipur	2(4.44%)
Jaydevpur	1(2.22%)
Narayangonj	1(2.22%)
Sirajgonj	1(2.22%)
Tangail	1(2.22%)
Manikgonj	1(2.22%)

Control	
Dhaka	2(10.00%)
Mymensingh	1(5.0%)
Comilla	1(5.0%)
Narayangonj	3(15.0%)
Munshigonj	3(15.0%)
Brahmanbaria	1(5.0%)
Noakhali	1(5.0%)
Gazipur	1(5.0%)
Jamalpur	1(5.0%)
Patuakhali	1(5.0%)
Barishal	1(5.0%)
Manikgonj	1(5.0%)
Goffargaon	1(5.0%)
Narshingdi	2(10.0%)
Jaydevpur	1(5.0%)
Sherpur	1(5.0%)

20

Past History

Among the 45 MRDM patients 20 (22.22%) gave past history of fever, diarrhoea, abdominal pain, 8(17.78%) cold, cough, fever , 4(8.89%) each of chronic suppurative otitis media and scanty hair, gingivitis ,angular stomatitis (stigmata of Malnutrition), Burning feet and urinary problem, 2(4.48%) each of multiple Abscess burning inside head, and the rest 10(22.22%) gave no important past history.

Family History:

Out of 45 MRDM patients 7(15.56%) gave family history of diabetes. Rest 38(84.44%) did not give any family history of diabetes. On enquiring typical symptoms like polydypsia, polyphagia, polyuria was present in 40 (88.89%) of the MRDM patient, the rest 5(11.11%) complains of isolated symptoms.

Age:

Age of the MRDM subjects ranging from 21 to 29 years were included in this study while for control subject age range is from 20-29 years.

Education:

subjects were asked whether they had attended any educational institute. If attended upto which level of education they had completed. Then they were grouped into four class intervals i.e. No education or illiterate, class I to X (secondary level) class V, class XI to class XII (higher secondary level) degree or and class XIII and above.

Occupation: Subjects were asked about types of occupation they were engaged. Occupation was then categorized into five groups. These were-unemployed/beggar, unskilled labour, skilled person, sedentary worker and housewife. Unskilled labour included day labour, servant, hotelbody, farmer, factory worker, fisherman, peon, guard, hawker, cleaner and sepoy. Driver, operator, carpenter, mechanic, goldsmith, tailor, typist, barber, welder, cook, family welfare visitor were included into skilled person group, whereas lawyer, manager, research assistant, teacher, officer, engineer, clerk, accountant, salsman, imam,

businessman and student were included in sedentary group of occupation. Housewife was categorized into sedentary group.

Annual family income: Both MRDM and control subjects were asked about their monthly income.. Annual income in the family was expressed in taka per annum. In case of farmer this was calculated from maunds of paddy or rice and cash crops like jute, cotton they obtained per year. Income was then grouped 500 into three class intervals i.e. income Tk 500-5000 per month or Tk..6000-60000 per annum was categorized as poor class, monthly income between Tk 5001 to Tk10000 ie annual income between Tk. 60,012 to Tk. 120,000 per annum as middle class and monthly income of Tk10000 or more ie annual income of Tk.1,20,000 and above as higher income class. US$ 1.00 is considered Tk. 70.00 approximately.

Environmental and Housing Conditions: Both MRDM and control subjects were asked about the method of excreta disposal, whether they had pucca sanitary latrine or kuccha latrine made of bamboo or wood or thy used open fields. Subjects were asked about the source of drinking water whether from the ponds, tubewell, well or municipality water supply. They were also asked about their houses,whether those were made of bricks, tin, leaves, and bamboos or mud. Sanitary latrines were categorised as good, and others as bad. Similarly municipality water and tubewell were considered as good water supply and others as bad. Pucca house was considered as good housing and others as bad. Types of excreta disposal, water supply and housing were summarized together. They were classed as poor environmental conditions (bad), good environmental condition (good) and moderate environmental condition (intermediate).

Habit: Both study and control subjects were asked whether they were smokers or non-smokers and whether they took alcohol occasionally or regularly. Regular taking of betel, panta (stal) rice, dry fish were included into the history of habit.

Past History: History of measles, mumps, chickenpox, jaundice, helminthiasis, enteritis, respiratory tract infection (RTI) in the past and near recent were taken from both MRDM the subjects and control accompanied parents and near relatives. Special enquiry was done about abdominal pain suggestive of pancreatitis and large bulky loose stool suggestive of steatorrhoea. Past history of malnutrition and vitamin deficiency were noted with specific questions about puffy face, oedema, ascities, skin and hair changes, teeth and ulcers in gums, tongue and mouth.

Symptoms: MRDM subjects were asked which typical symptoms of DM, such as polyuria, polydipsia, polyphagia, weight loss and weakness were taken along with the duration. DM with mild or atypical presentation were confirmed by asking how it was diagnosed.

Family History of DM: Study MRDM subjects were particularly asked about history of DM in the family upto second generations and second degree of relatives, which included father, mother, both parents, siblings, grand parents from both paternal and maternal sides, uncle and aunts from both paternal and maternal sides, cousins. Patients, accompanied parents and near relatives were asked whether any member of the family in above levels were suffering from or died of DM. This information was also included how the diagnosis and treatment obtained. DM in first degree of relatives was considered when diabetes was present in father or mother or parents along with siblings. Definite autosomal dominant was considered by the presence of DM in father or mother or parents along with corresponding grand parents either from paternal or maternal side. Possible autosomal dominant was considered by the presence of DM in father or mother or parents along with uncle and grand parents from either side.

Anthropometric Study: BMI were calculated from body weight in kg by standardized weighing machine, height in cm by Harpenden stadiometer for both MRDM and control subjects.

Table 8: Collection of blood for different biochemical tests

Tube No.	Tests	Amount	T. Tube used	Remarks
Tube No. 1	Glucose (F/R)	of blood	Flurate Oxalate Mixture tube	In all cases
Tube No. 2	Amylase Creatinine Urea STP Lipid profile	5 ml	Plain test tube	
	Immunoglobulin			In selected cases
	C3, C4			Do
	Group & Rh			Do
Tube No. 3	Electrolytes	2 ml Paraffin containing tube		
Tube No. 4	HLA	1 ml		In selected case
Tube No. 5	HbA_1C	5 ml		(Heparinised tube)

Some biochemical data and radiological data were collected from their diabetic guide book already recorded.

Montaux test was done in some cases after intradermal injection of PPD 0.1ml and induration/non in duration was measured with a scale between 48-72 hours after injection.

Biopsy slides and blocks from 20 FCPD cases other than these 45 study subjects were collected retrospectively reviewing the medical records, 2 cases of chronic pancreatitis were also taken for comparison. These were stained with routine H&E special stains like gomoris chromium haematoxyline. Massons trichrome and PAS stain and examined under light microscope. The results were recorded. Also histological slides from two non diabetic patients suffering from chronic pancreatitis were found out and these were compared with the findings of the FCPD patients.

For glucose estimation 1 ml of blood was placed in a tube containing fluoride. The plasma was separated and analyzed within a few hours of collection.

Plasma glucose and serum lipid (triglycerides, total cholesterol and HDL-cholesterol) were measured in the BIRDEM biochemistry laboratory, Dhaka by enzymatic methods and were mentioned briefly below. The LDL-cholesterol was calculated from observed triglycerides, total and HDL-cholesterol by using Firedwald's formula.

5.1.Estimation of plasma glucose:

Plasma glucose was measured on a Technicon Auto-analyzer using glucose oxidase enzymatic colorimetric method.

Test Principle:

In this methods the aldehyde group of β-D glucose is oxidizes by glucose oxidase to give gluconic acid and hydrogen peroxide.

$$\beta\text{-D- Glucose} + H_2O + O_2 \rightarrow \text{gluconic acid} + H_2O$$

The hydrogen peroxide may be broken down to water and oxygen by a peroxidase and if an oxygen acceptor is present, it will be converted to a coloured compouned which can be measured.

The oxygen acceptor is four aminophenazone which with phenol, give a pink coloured complex which is read colorimetrically. The absorbance of the complex measured at 510 nm is directly proportional to the concentration of D-glucose present in the sample.

4.2. ESTIMATION OF SERUM TRIGLYCERIDES:

Serum triglyceride was detected by Hitachi 704 Autoanalyzer using enzymatic method.

Principle

Triglycerides lipase Glycerol + fatty acids.

Glycero + ATP GK glycerol 3 phosphate + ADP.

ADP + PEP PK pyruvate + PTP.

Pyruvate + NADH+H+LDH Lactate+NAD

GK= glycerol kinase

PEP= phosphoenol pyruvate

PK= pyruvate kinase

LDH= Lactate dehydrogenase.

The triglycerides were detected after enzymatic hydrolysis with lipase with the liberation of glycerol and fatty acid, Glycerol, in presence of ATP and the enzyme glycerol kinase produce glycero,-3-phosphate and ADP, ADP then reacts with phosphoenlol pyruvate in

presence of pyruvate kinase and liberate pyrevate and ATP. Pyruvate acted upon by lactate dehydrogenase on NADH++ H+ and produce Lactate and NAD+.

The decrease in absorbance at 340 nm is proportional to the concentration of glycerol. ESTIMATION OF SERUM TOTAL CHOLESTEROL: Serum total cholesterol was detecte by Hitachi 704 Auto-analyzer by using enzymatic procedure involved clevage of the cholesteryl ester by cholesterol esterase and oxidation of free cholesterol by cholesterol oxidase.

Cholesterol ester + H_20 CE Cholesterol + Fatty acid.

Cholesterol + 0_2 Co 4 cholesterol + H_20_2

CE= Cholesterol esterase.

Co= Cholesterol oxidase.

The reactions will be quantified photometrically by the use of H_20_2 dependent colour *forming reactions-* $2H_20_2$ dependent colour forming reactions- $2H_20_2$+ phenol + 4 aminophenazone Peroxidase

Spectrophotometric determination was done in the absorbance at 505 nm which is Aproportional to the concentration of cholesterol present.

4.3. ESTIMATION OF HDL CHOLESTEROL

PRINCIPLE: The lipoproteins of chylomicron, VLDL and LDL in the serum were precipitated by the addition of phosphotungstic acid in the presence of magnesiumtions. The supernatant obtained after centrifugation contains HDL from which cholesterol was estimated by using "cholesterol enzymatic reagents".

Method of precipitation

Composition of HDL- cholesterol reagent is

Phosphotungstic acid- 40 gm/L

Mg C12, 6 H_20 -------- 100 gm/L

500 ul of userim and 50 ul HDL- cholesterol reagent was mixed in a test tube and was let stand for 10 minutes. Then it was centrifuged for 15 minutes at 3000 rpm. Then detection of HDL – Cholesterol was done from the supernatant using enzymatic enzymatic reagent and Auto-analyzer.

DETERMINATION OF LDL- CHOLESTEROL

LDL- Cholesterol was calculateed form the estimated werum triglycerides, total and HDL-Cholesterol by using the Friedwald's formula (137)

$$\text{LDL- Cholesterol} = \text{Total Cholesterol} - \frac{(\text{Triglycerides} + \text{HDL- Cholesterol})}{5}$$

4.4.Determination of HbA1c by auto analyzer (AUTO A1c HA-8110)

Sample material : I ml of venous blood was drawn and transferred in a heparinised glass tube and was shaken gently. It was the ready for analysis.

Reagents : 1) Eluent A 2) Eluent B 3) Hemolyzing reagent and 4) Washing solution

Method : The HBA1c auto analyzer is designed to measure both HbA1c and HbA1 with pressure liquid chromatographh, using a column filter developed especially for separation of HbA1c.

Principle : The stationary phase used in the column is a hard porous polymer containing appropriate amount of hydrophobic and hydrophilic function group. It employed a unique separation system incorporating cation exchange chromatography and reverse phase partition chromatography by a hydrophobic reciprocal action to attain high separation, short throughput and long live of the column. Eluted fraction from the column detected by a dual wave length photometer and processed by the build in microcomputer to identify HbA1c and to calculate the area of the peak.

Procedure : Sample was added with hemolyzing reagent to analyzer, each components eluted within 13 minutes. Data was obtained as printed matter.

BUN- It was estimated by Diacetyl monoxime method. Reagents used were-a) Diacetyl monoxime and b) BUN acid, Reaction temperature and wave length were 80^0 C and 520 nm respectively, Principle diacetyl monoxime reacts with BUN (Blood urea nitrogen) in the presence of BUN acid at 40^0 c and forms a purple color which is read at 520 nm and is directly proportional to the concentration of BUN present.

Creatinine- Creatinine in serum reacts with picric acid in the presence of sodium hydroxide solution and form a complex colored substance (alkaline picrate) and picrate derivative which is read at 505 nm. The color produced is directly proportional to the concentration of creatinine in the study sample.

4.5. Ion selective electrode (ISE) system for estimation of electrolytes

The ISE unit consists of three ion selective electrodes, a reference electrode, dilution vessel and three pipettors. For electrolyte estimation 20 ul of sample serum was aspirated by the sample probe, and the probe moved to the ISE dilution vessel. The electrical potential generated by sodium, potassium and chloride was compared with the electrical potential generated at the reference electrode. Electrical information was sent to the instrument computed and results were computed and displayed. ISE reagents were used for the test. CO_2 was measured in a CIBA corning CO_2 analyzer.

4.6.Estimation of Creatinine

Jaffe method :

Reagent- 1. 32 m. mol picric Acid
2. 2 N NaOH
3. 2 mg/dl standard

Procedure	Blank	Standard	Test
Standard	-	200 ul	-
Sample	-	-	200 ul
Picric acid	3 ul	3 ul	3 ul

Shake well and wait 5 minutes

Then centrifuge 10 minutes

Then take supernatant 2 ml in Blank, Standard, Test, Add 100ml NaoH

Shake well for 25 minutes

Then Read 530 nm

Test-Blank X Consentrations Acid

Standard -Blank

Normal : 0.67 – 1.58 mg/dl

4.7.Estimation of Total Protein

Rcommended Method : Biuret method.

Principle – Copper in alkaline solution reacts with the peptide bonds in proteins, Producing a violet colour, Which is proportional to the amount o protein present.

Reagent – Biuret reagent (For 2 Litre).

Crystalline copper sulphate- 3'0 gm (or 20ml 15% ou so)

Sodium potassium tatrate – 12'0 gm

Potassium Iodide – 2'0 gm

Place in a 2 litre flask and dissolve in about 1 litre distilled water with constant swirling add 600 ml 10% NaoH and make up to volume with distilled water.

Procedure :

1. For each sample, standard and blank pipette in to test tubes 5'0 ml of biuret reagent.
2. Add 50ul of sample, 50ul of standard and 50 of distilled water to the corresponding
3. Mix all tubes and allow to stand at room temperature for 30 minutes.
4. Measure the absorbance of the reagent blank and tests at 540 nm, setting the spectrophotometer to zero with water or reagent blank.

Calculation:

$$\frac{\text{Test absorbance}}{\text{Standard absorbance}} \times \text{Standard Value} = \text{gm Protein/dl}$$

4.8.Immunoglobulins and Complement tests

Quantitative determination of specific proteins by radial immunodiffusion

Principle: The determination of specific human serum proteins, without dilution, by radial immunodiffusion (RID) is based on the formation of an immunoprecipitin ring in an agarose

gel. Identical volumes of serum samples and standards are dispensed into calibrated well cut into a gel containing a specific antiserum.

Procedure: routine assay

Dispense standard no. 2 and the serum samples into the wills.

Allow to diffuse completely in the airtight zip bag.

-Determine the concentrations according to the diameters using the table of reference valves supplied with the kit.

The results obtained with the serum samples are only valid if the diametter obtained for standard no.2 is included in the confidence range given at the bottom of the table of reference valves.

Reagents : Stability and storage : at 2-8'C until the expiration date shown on the packaging

Reference	Immuno- kit
7 602 2	IgG Immuno-kit
7 601 2	IgA Immuno-kit
7 600 2	IgM Immuno-kit
7 607 2	C3(B1C/B1A) Immuno-kit
7 610 2	C4(B1E) Immuno-kit

Quality contorl Immunotrol (Ref. 7 630 1)

Equiupment Humilton or SMI type micropipette (5 ul).
bioMerieux measuring ruler (available on request) and
suitalbe viewer.

Sample Freshly collected, undiluted serum.

Table 9:Concentration range of the plates

	g/l	IU/ml
IgG Immuno-kit	3- 30	35-350
IgA Immuno-kit	0.7- 7	43-430
IgM Immuno-kit	0.3- 4	35-460
C3(B1C/B1A) Immuno-kit	0.3- 3	26-264
C4(B1E) Immuno-kit	0.1- 0.8	41- 326

RADIAL IMMUNODIFFUSION

PRODEDURE 1. Preparation of the plates

Removed the Immuno-kit and serum samples from the refrigerator.

Leave at 18-25^{0}C for 15 minutes, Opened the aluminium bag. Removed the 4 lid by depressing the lock slots on the under side of the plate. Incubate the plates without their lids for up to 15 minutes at 18-25^{0}C to remove any condensation.

2. Assay

Procedure A

Dispensed exactly 5 ul of standard no.2 into well no.1 and 5 ul of each serum sample into the following wells. Replaced the lid and reurned to the zip bag. Marked the sample codes on the label. Closed the zip bag and incubated at 18-25^{0}C on a level surface for 48 hours (72 hours for assay of IgM, IgD and C4).

Referred to the table of reference values. The protein concentrations were read directly from this table.

Table 10: Normal adult values (serum)

	mg/dl	g/l	IU/ml
IgG	600-1800	11.3 (6-18)	X 11.5=130 (79-207)
IgA	100-460	2.1 (1-4.6)	X 6.1= 128 (61-280)
IgM	50-350	1.4 (0.5-3.5)	X 115= 161 (58-402)
C3	70-170	1.2 (0.7-1.7)	X 88= 106 (67-150)
C4	20-50	0.3 (0.2-0.5)	X 408= 122 (82-204)

4.9.ANTI-HLA-ABC SERA

Lymphocytotoxicity Test

Directions Use

Lyphoilized serum has to be reconstituted before use with the required volume of distilled water as stated on the label. The reconstituted is to be kept deep frozen during storage.

Principle of Procedure

Anti-HLA sera react with corresponding lymphocyte antigens. The addition of rabbit complement results in a structural change of the lymphocyte cell membrane. Thus eosin is able to penetrate into the lymphocytes and permits absorption of the dye (positive reaction). Non-reacting lymphocytes do not absorb the dye (negative reaction).

Material

1. Anti-HLA-ABC sera
2. Control-HLA (positive control)
3. Control-HLA (negative control)
4. Complement (rabbit)
5. Hank's Solution (Ca-and Mg-free)
6. Lymphoflot (density gradient for isolation of lymphocytes)
7. Lymphostabil (Mc Coy's Medium 5A, modified according to Park and Terasaki, for storage of lumphocytes; Ca- and Mg-free)
8. Eosin 5% in distilled water , merck, Art No. : 15935, filter
9. Formaldehyde solution for use in histology, 37%, acid-free, merch, Art. No. 3999 (filter and adjust pH7.2 with 0.1 N s9odium hydroxide)
10. Microtray

B. Lymphocytotoxicity Test

1. Filled the wells of the microtray up to the brim with cover oil. The reagents to follow were placed under the surface of the oil.
2. Dispensed into each well 1ul anti-HLA-ABC serum and 1 ul of the adjusted cell suspension and incubated for 30 min at room temperature (approx. 22^0C)
3. Added 5 ul of rabbit complement to each well and incubated for 60 min at room temperature (approx. X 22°C)
4. Added 3 ul eosin to each well and allowed 5min for staining.
5. Added 6 ul of formaldehyde solution to each well for fixation.

6. Reading was taken with an iverted phase contrast microscope for up to 2 hours.

11. Cover Oil
12. Inverted microscope with phase contrast
13. Microliter syringes (Hamilto, No. 705 and 725 with volume dispenser No. PB-600)
14. Cover slips, 50X 75 mm

A. Isolation of Lymphocytes

1. Approx. 5 ml of fresh heparinized blood specimen (approx. 10 units heparin per ml blood) were mixed with an equivalent volume of Hank's Solution. The blood specimen were stored at room temperature (approx. 22oC)
2. Piptted Lymphoflot into a test tube and then gently laid on an equal volume of the diluted blood. Avoided mixing the layers.
3. Centrifuged for 20 min at 2800 rpm (1000 X g) without brake. Remove the lymphocytes which appear as a white ring on the border between the plasma and lymphoflotand place into a new tube and filled with Hank's Solution.
5. Washed 2 times with Hank's Solution, centrifuged for 10 min at 1500 rpm (320 X g). Decanted the supernatant. Resuspended the lymphocytes and filled with Hank's Solution. Centrifuged for 10 min at 1000 rpm (150 x g) and decant the supernatant. The lymphocytes were suspended in Lymphostabil. The cell suspension contain 2000 cells/ul.

4.10.Serum Albumin

Method: Bromcresol green

STD- 6.0 g/dL

Procedure:

	Blank	Standard	Test
STD	-	10ul	-
SAMPLE	-	-	10ul
Reagent	3ul	3ul	3ul

Mixed well and waited 5 minutes.

Real samplel and standard against blank at 630 nm (600- 650 nm)

(Normal : 3.5 – 5.7 l/dL)

Urea

Cleavage with urease, Berthelot's reaction

Test Principle

Urea + 2 H O Urease 2 NH + CO

Ammonium ions react with phenol and hypochlorite to give a coloured complex.

Normal Values

Serum : 10-50 mg/ 100 ml

1.7- 8.3 mmol/l

(Reference: Mackay, e.M. and L.L. Mackay (1927) J. Clin Invest 4: 295.)

Urine: 20 – 35 g/24 hrs

333-583 mmol/24 hrs

(Reference : Sarre, H. (1959). Nierenkrankheiten. Geory Thieme Verlag, Stuttgrat.)

Sample material

Serum, EDTA plasma, urine

Reagents

Contents		Initial concentrations of solutions:
1.	Buffer/Urease	
	Phosphate buffer	50 mmol/l
	Urease	10 u/ml
2.	Standard	
	Urea	3 mg/ 100 ml (= mmol/l)
3.	Phenol	0.106 mol/l
	Sodium nitroprusside	0.17 mmol/l
4.	Hypochlorite	
	Sodium hypochlorite	11 mmol/l
	Sodium hydroxide	0.125 N

Quality control

In the normal range : Precinorm U, Precinorm UBS,
Precinorm S

in the pathologic range: Precipath U, Precipath UBS,

Precipath S

For precision : Precinorm UPX

Preparation and stability of solutions

1. Use suspension undiluted. Shake before use.
   Stable up to the expiry date specified when stored at + 2 to + 8 C

2. Use solution undiluted.
   Stable up to the expiry date specified when stored at + 2 to + 8 C

3. Cat. No. 124 770: Dissolve contents in 500 ml redist water
   Cat No. 124 788. Dissolve contents in 1500 ml redist. Water Rinse bottle well when preparidng the solution.

Any undisclosed sodium nitroprusside will dissolve completely when the specified amount of water is added.

4. Cat No. 124 770 : Dilute contents with 500 ml redist. Water
   Cat No. 124 788 : Dilute contents with 1500 ml redist water.

Stable for six months at + 2 to 8^0 C.

Sample preparation

Hemolysis interferes with the test.

Serum or plasma can be stored upto three days at + 4^0 C

Dilution:

Dilute serim 1 + 9 with 0.9% NaCi solution.

Dilute Urine 1 + 1000 with redist water.

Procedure

Wavelength : Hg 546 nm (530-570)

Spectrophotometer : 55 nm

Cuvette :1 cm light path

Incubation temperature : 37^0 C or 50-60^0 C

Measure against reagent blank.

One blank and one standard are sufficient for each assay series.

Whwn using undiluted surum, pipette 1.0 ml redist. Water into each test tube (including reagent blank and standard) before adding the sample.

Pipette onto bottoms of test tubes			
	reagent blank	standard	sample
Suspension 1 solution 2 diluted serum or diluted urine or undilduted serum	0.10 ml - - -	0.10 ml 0.20 ml - -	0.10 ml - 0.20 ml 0.02 ml
Mis, close test tubes with clean stopper or Parafilm,* Incubate for 10 min at 37 C or 5 min at 50-60 C Add.			
solution 3 solution 4	5.0 ml 5.0 ml	5.0 ml 5.0 ml	5.0 ml 5.0 ml
Mis immediately after addition of solution 4 and incubate for 15 min at 37 C or 10 min at 50-60 C. Read absorbances dof sample (A sample) and standard (A standard) against blank	429946		

If the urea concentriation exceeds 200 mg/ 100 ml (33/3 mmol/l) in serum or 20 g/ 100 ml (3.33 mol/l) in urine repeat the assay using half of the volumes given in the pipetting table (result X 2)

Calculation of the concentration (c) of urea and urea- N in the sample :

		urea	urea-N
serum	(mg/100 ml)	c= 30x A sample / A standard	c= 14x A sample / A Standard
	(mmol/l0	c= 5x A sample / A Standard	c= 5x A sample / A Standard
urine	(g/100 ml)	c= 3x A sample / A Standard c= 500x A sample / A standard	

4.11. Ethical Issues:

The research design was explained to the patient or his /her guardian.He/she was also informed about the physical risks, publication of data, ability to withdraw anytime from the research and maintaining confidentiality. As at that time no ethical committee was existent in BIRDEM the verbal consent taken after explaining the project was taken as patients consent after which the samples were taken after all aseptic precautions. However written consent from some control and MRDM patients were also taken. Moreover permission from the BIRDEM authority ie Director General of BIRDEM was also taken (Copy enclosed, annexure 4).

Results

&

Observations

5.0. RESULTS, OBSERVATIONS

Table – I

: Showing mean ± SD of Height, Weight and BMI of MRDM & Control subjects

	*Height (cm) Mean ± SD	**Weight (kg) Mean ± SD	***BMI Mean ± SD
Patient n = 45	153.27 ± 10.53	35.42 ± 10.05	14.98 ± 2.72
Control n = 20	160.25 ± 7.07	40.35 ± 10.20	17.27 ± 1.79

* p <0.003 Table – I shows that all the variables of height (cm) [153.27 ± 10.53, p <0.003].

** p< 0.079 Weight (kg) [35.42 + 10.05, p <0.079] and BMI (kg/MI).

*** p <0.000 (14.98 ± 2.72, p <0.000) of patients were significant lower than there of control subjects (160.25 ± 7.07; 40.35 + 10.20 and 17.27 ± 1.79 respectively).

Table – II

Showing mean ± SD of Monthly income*

Income	<500	500-5000	5001-10000	10000	
Patient n = 45	17 E= 12.4615	24 E= 27.00	2 E= 2.0769	2 E= 3.4615	45
Control n = 20	1 E= 12.00	15 E= 12.00	1 E= 0.9231	4 E= 1.5385	20
Total N= 65	18	39	3	5	N= 65

x^2 = 8.4702 dt = (4-1) x (2-1) = 3 p <0.05*

Table – III

Showing mean ± SD of Educational level**

		Class-X	SSC/HSC	Degree	Total
Patient n = 45	23 E= 15.9231	21 E= 22.1538	- E= 2.7692	1 E= 2.7692	45

x^2 = 35.3404, dt (4-1) (2-1) p <0.005**

Table IV

Diet & personal habits:

Control subjects (n=20)	**Diet among MRDM**
Daily Rice	Daily Rice
Daily Dal (lentil)	Daily Dal (lentil)
Green and leafy vegetables like cucumber, papaya etc.	Green and leafy vegetables
Small fish	Small fish
Egg	Egg
Weekly/ twice/thrice or more	**Monthly once /twice or more**
Meat	Meat
Large Fish	Large fish
Milk ,Egg and Other dairy products	Milk, egg, other dairy products
Habitat	
Rented	Slum in city
Sublet	Semi urban areas
Semi urban	Rural
Majority uses Sanitary Latrines, Some Kuccha latrine, Some open spaces	Majority uses Kuccha latrine Some open spaces, Some Sanitary Latrines
Use of safe drinking water	
Majority uses tube well, ponds,	Most uses tube well and water supply in lakes, river water.

Table – V:

Showing mean ± SD of BUN, STP, Creatinine

	BUN* Mean ± SD	Creatinine** Mean ± SD	STP *** Mean ± SD
Patient n = 45	27.27 ± 14.09	0.92 ± 0.21	7.39 ± 0.12
Control n = 20	24.73 ± 2.85 P<0.251	0.75 ± 0.16 P<0.001***	7.82 ± 0.64 P<0.018**

As displayed Table – V, BUN (27.27 ± 14.09, US 24.73 ± 2.85; $p < 0.251$) as well as creatinine (0.92 ± 0.21 vs 0.075 ± 0.16; $p < 0.001$***) of patients were higher.but STP was lower (7.39 ± 0.12 US. 0.12 vs 7.82 ± 0.64; $p < 0.018$**) than the control subject.

Table – VI:

Showing mean ± SD of Serum Electrolyte

	Na Mean ± SD	K	CL*	CO_2
Patient n = 45	135.71 ± 3.86	4.61 + 0.73	95.63 + 6.21	24.59 + 3.78
Control n = 20	137.26 ± 3.57 p<0.173	4.34 ± 0.29 p<0.096	111.73 ± 18.26 p<0.001*	25.62 ± 1.47 p<0.228

As depicted in Table – VI, serum K was higher p<0.096) where as Na (p<0.173), CL (p<0.001*) and CO_2 (p<0.228) were lower in the patient than control subjects

Table – VII:

Showing mean ± SD of Serum Amylase level

	Serum Amylase Level *
Patient n = 45	150.04 + 55.48
Control n = 20	171.60 + 19.26 (P<0.024*)

Serum amylase (Table VI) of the patients (150.04 + 55.48) was significantly lower (p <0.024*) than that of control subject (171.60 + 19.26).

Table – VIII

Showing mean ± SD of Immunoglobulin IgG, IgM, IgA

	IgG Mean + SD	**IgM**	**IgA***
Patient n = 17	1515.26 ± 12.80	137.59 ± 74.57	313.39 ± 22.25
Control n = 10	1555.19 ± 335.92 p<0.787	117.12 ± 60.99 p<0.447	206.89 ± 42.66 p<0.004*

Table – VII shows the contraction of IgG, IgM and IgH, IgH p< and IgM were statically same between the patient and controls subjects (p= 0.787 and p= 0.447 respectively). But IgA of the patient (313.39 + 22.25) was significantly higher (p<0.004)* in patient, than control subjects (200.89 + 42).

Table – IX:

Showing mean ± SD of Compliment 3, 4

	C_3	C_4*
Patient n= 17	C3 (Mean ± SD) 134.29 ± 46.76	C4 (Mean ± SD) 41.41 ± 23.21
	p value< 0.8	p value< 0.05*

Table – X :

Showing mean ± SD of Blood group & RhD*

	A	B	O	A	B
Patient n= 38	8 E= 13.440	13 E= 8.7692	16 E= 12.8615	1 E= 1.3103	38
Control n= 20	11 E= 6.5517	2 E=5.174	6 7.512	1 E= 0.6897	20
	19	15	22	2	58

x^2 = 9.9073, dt (4-1) (2-1) = 3, p <0.025*

Table showing RhD positive and negative

	Positive	Negative	
Patient	37 E= 37.345	1 E= 0.6552	38
Control	20 E= 19.6552	- E= 0.3448	20
	57	1	n= 58

x2 = 0.5356, df (2-1) (2-1) = 1, p <0.4

Table XI

HLA-A

Patient n = 20	A1 2(10%)	A2 8(40%)	A3 2(10%)	A4 1(5%)	A9 4(20%)	A11 2(10%)	A28 2(10%)	A29 1(5%)	A30 2(10%)	A34 1(5%)	A31
Control n = 10	4(40%)		1(10%)		4(40%)	4(40%)				1(10%)	

HLA-B

Patient n = 20	B5 6(30%)	B7 4(20%)	B12 4(20%)	B13 2(10%)	B15 5(25%)	B27 3(15%)	B42 2(10%)	BW4 2(10%)	BW6	BW4
Control n = 10	5(50%)				3(30%)				3(30%)	2(20%

HLA-C

Patient n = 20	CW5 4(20%)	CW6 4(20%)	CW7 4(20%)	CW3 2(10%)	CW2 2(10%)	CW1 2(10%)	CW4
Control n = 10				1(10%)	1(10%)	2(20%)	3(30%)

Table XII

Showning Mean±SD of FBS, PPS, HbA1c in MRDM and Control subjects

	Mean±SD*** FBS(mmol/l)	Mean±SD*** PPS(mmol/l)	Mean±SD*** HbA1c(%)
MRDM Patient n=43	21.24±6.20	30.28±7.65	13.46±2.56%
Control N=20	4.70±0.49	5.76±0.43	5.12±0.30%
	P<0.000***	P<0.000***	P<0.000***

Table – XIII:

Showing mean ± SD of lipid profile in MRDM & central subjects

	TG* Mean ± SD	HDL** Mean ± SD	Cholesterol*** Mean ± SD
Patient n = 45	178.58 ± 77.21	33.07 ± 4.60	141.21 ± 23.28
Control n = 20	145.89 ± 55.83 P<0.060	50.85 ± 6.08 P<0.000***	159.42 ± 37.63 P<0.056*

As shows in Table II, TG was higher (p <0.060) in patients (178.58 ± 77.21)than that of control (145.89 ± 55.83) however, HDL and cholesterol of patients (33.07 ± 4.60 and 141.21 ± 23.28) were significantly lower (p <0.000***, and p <0.056*) than those of control subjects (50.85 ± 6.08 and 159. 42 ± 37.63 respectively).

Table XIV:

Histopathological findings of pancreas (FCDP patients)

Age group 13-30 years n = 20 (M=7, F=13)	Pancreatic biopsy			
	Fibrosis + ++ +++	Chronic inflammatory cell infiltration + ++ +++	Dilatation of pancreatic duct present Absent	Infarction Present Absent
N = 20	11 1 8	10 6 4	15 5	5 15
%	55% 5% 40%	50% 30%20%	75% 25%	25% 75%

+ = mild , ++ = moderate, +++ = severe/marked.

Table XV:

Histopathological findings of Pancreas (chronic pancreatitis patients)

Age group 31-65 years n = 19 (M=8, F=11)	Pancreatic biopsy			
	Fibrosis + ++ +++	Chronic inflammatory cell infiltration + ++ +++	Dilatation of pancreatic duct present Absent	Infarction Present Absent
N = 19	15 2 28	11 4 4	10 9	5 15
%	78.95% 10.53% 10.53%	57.89% 21.5 21.5%	75% 25%	25% 75%

+ = mild , ++ = moderate, +++ = severe/marked.

Table XVI

IHC of four pancreatic biopsies

Total no.of pancreatic biopsies	CD3(T cell)	CD20(Bcell)	P53	Bcl-2	
4	Positive- 4 Strog +ve(100%)	Positive-4 Strong +ve(100%)	Negative-4 (100%)	Negative-4 (100%)	

Discussion

A total of 45 under 30 diabetics (MRDM) subjects and 20 age and sex matched control reported during this study period. Their detail personal,family,social,other parameters were recorded in a prescribed proforma (annexure 1) and blood were taken for different tests (as described in annexure 2).An extra 20 pancreatic biopsies from FCPD patients were processed for light microscopy and immunohistochemistry (IHC) with markers for T & B and apoptotic markers. All the results are shown in Result section(Chapter 6,pages 95-102).

7.1 Height, weight and BMI in MRDM and control:

we have assessed the height, weight and BMI in all 45 MRDM patients and 20 controls. The results are shown in Table 6.1, page 95. The lowest vs highest height, weight and BMI for MRDM patients and controls are 130 cm, 171 cm vs 151 cm vs 172 cm, 20 kg vs 37 kg, 52 kg and 9.8, 21.25 vs 13.5, 19.7 respectively. The mean $\pm$ SD of height, weight, BMI in MRDM vs control are 153.27$\pm$10.53 cm vs 160.25$\pm$7.07 cm $p<0.003$, 35.42$\pm$10.05 kg vs 40.35$\pm$10.20 kg $p<0.079$, 14.98$\pm$2.72 vs 17.2$\pm$1.79 $p<0.000$ respectively. The results revealed all the variables of height, weight and BMI of MRDM patients are significant lower than those of control subjects. This is because of poverty, malnutrition, illiteracy and impact of socioeconomic status of these patients. The results are similar with the findings of some studies where MRDM patients were found to have either underweight(BMI<19) or normal BMI (between 19-25).Logistic studies from these studies found low BMI, jobless and signs of malnutrition had higher risk of developing MRDM.(Tjokroprawiro A 1990;Sainani GS etal,1985;Thandanand S,1987;Ahuja MMS 1965)

7.2 Income, Level of Education and Diet and MRDM

Economic status, education level and diet are important epidemiological factors that affect different disease process. This is particularly true for diabetes where these factors need to be specifically assessed and asked for. For this we have asked about these parameters and recorded the findings in a prescribed proforma.The results are shown in table6.2, 6.3, page 95 and 96.

After analyzing the data we found that majority of MRDM patients were in the poor economic group monthly income <500 17,(37.78%) and between 500-5000 24, (53.33%). Only 2(4.44%) MRDM subjects were in 5001-10000 group and another 2(4.44%) in the income group of >10000. Whereas majority of control group belong to 500-5000 15,(75%) and only 1,(5%) belong to <500 group, 1(5%) to 501-10000 group and the rest 3,(15%) >10000 group. The economic difference between MRDM and control group was statistically significant ($p<0.05$). So poverty is an important factor in the genesis of MRM.

Regarding level of education there is statistically significant difference between MRDM and control group ($p<0.005$), 23(51.11%) of MRDM subjects were illiterate, 21(46.67%) had primary to secondary level education, only 1(2.22%) had degree. Whereas 11(55%) of control group had primary to secondary level of education, 6(30%) has higher secondary level and 3(15%) has degree level of education. It is evident from the data that level of education is an important factor in the pathogenesis of MRDM.

7.3 Diet & personal habits: We have taken detail dietary history of all the MRDM and controll subjects. It is evident from analysis that economic status, literacy level and health are important in maintains the disease status. Both MRDM patients and control subjects are not very economically sound, have different level of education but these showed statistical difference interms of literacy and income between them. This is because the MRDM patients are undernourished because they can not afford to buy rich protein food so they had to depend on low protein food and as the carbohydrate is the main source of their food

either as rice, bread, suji they are dependent different type of pulses (Dal) and leafy green vegetables to supplement their daily need. Rarely they took meat, large fish, milk and dairy products. The results are shown in Table 6.4, page 96.

As such their food is deficient of protein, fat and other essential elements required for normal development. These foods also contain cyanides and may be important in the destruction of pancreatic tissue. The use of unsafe water from ponds, haour, Bil, river and arsenic polluted tube well not only causes different water and food borne diseases like diarrhea, dysentery, worm infestations, GIT diseases leading to malabsorption and development of diabetes as well., skin disease and also lead to their poor health condition. Also the diabetes itself and its consequence, lack of proper treatment due to inability to buy insulin unless it is supplied free aggravates their clinical condition.

Illeteracy predominant in MRDM patients support their lack of health awareness, poor socioeconomic status and lack of knowledge regarding healthy foods leading to malnutrition specially in mothers and infants. The control group on the other hand some how manage to get satisfactory diet in comparison to the MRDM patients because of a slight higher income, literacy and consciousness about health. These findings are similar with the findings of some studies in India and Africa (Mohan V 1986;Mohan V etal 1985, Winter WE etal 1987,Mohan V etal 1989).

7.4. Renal Function and MRDM

As impairment of renal function is usually associated with both type I and II diabetes we decided to see if there is any association with MRDM and renal disease. For this we did the renal function tests like serum urea, creatinine, electrolytes, total protein of these MRDM patients and control subjects. The results are shown in Table 6.5, page 97.

As depicted in Table – VI, serum K was higher p<0.096) where as Na (p<0.173), CL (p<0.001*) and CO_2 (p<0.228) were lower in the patient than control subjects

It is seen that lowest vs highest creatinine value of MRDM patients vs control subjects are 0.6, 1.4mg% vs 0.5, 1.1mg% respectively. The mean ± SD of the creatinine value for MRDM patients and control subjects are 0.92 ± 0.21 mg% respectively. It is seen that lowest vs highest urea value of MRDM patients vs control subjects are 8.0, 93.0mg% vs 20.0, 28.0mg% respectively. The mean ± SD of the urea value for MRDM patients and control subjects are 27.27 ± 14.09mg% vs 24.73 ± 2.85mg% respectively.

It is seen that lowest vs highest serum total protein (STP) value of MRDM patients vs control subjects are 6.2, 8.5mg% vs 6.96, 9.1mg% respectively. The mean ± SD of the STP value for MRDM patients and control subjects are 7.39 ± 0.12mg% vs 7.82 ± 0.64mg% respectively.

It is seen that lowest vs highest Na, K, Cl, CO_2 value of MRDM patients vs control subjectsare 135.71±3.36, 4.61±0.73, 95.63±6.21, 24.59±3.78 meq/L vs 137.26±3.57, 4.34±0.29,111.73±18.26, 25.62±1.47 meq/L respectively.

It is evident from the data that although the urea and creatinine levels are within normal reference range however both values are higher in MRDM patients compare to control subjects particularly the creatinine values shows significance between the two groups p<0.001. Serum total protein value is significantly lower in MRDM patients than control group p<0.01. These indicate impaired renal function in MRDM subjects which may be an effect of malnutrition and hyperglycaemia.

The electrolyte analysis shows that although the value of electrolytes are within normal reference range still there is high K value in the MRDM subjects than control and low Na,

CO_2, value in MRDM than controls. The significant low value of Cl_2 in MRDM patients

p<0.001 may be some sort of metabolic acidosis.

7.5. Pancreatic function:

To assess the exocrine pancreatic function in MRDM patients and compare it with controls we did the serum amylase level estimation. The lowest and highest serum amylase value in MRDM patients were 48% mg and 355 mg%. The serum amylase value for control was 125 mg% and 210 mg%. The mean ±SD of serum amylase was 1500.04± 55.48mg% in MRDM patients and 171.60+9.26 mg% in control. There is significant difference between MRDM patients and control group (p<0.02). This indicates exocrine pancreatic abnormal function in MRDM patients. The results are shown in Table 6.7, page 98. Other studies showed variable results in serum amylase value indicating low specificity of the test in chronic pancreatitis(Wiyono P, 1988, Pitchumoni CS 1984, Kakami AL 1985).

Histopathological examination of pancreatic biopsies from FCPD patients showed marked fibrosis, dense chronic inflammatory infiltrate, ductular dilatation and stone formation in these patients indicating an immunological destruction of their pancreatic beta cell mass. These findings are similar to some studies (Sutradhar Sr 2004;Saraya A et al 1999,Mohan V 1998) and dissimilar to other studies (Soto Blanco B 2001)

7.6. Immunological Tests and MRDM

Immunological abnormalities are well studied in two major types of diabetes. Immunological destruction of beta cells is established cause of type I diabetes leading to insulin deficiency. Also there is insulitis in pancreatic beta cells in type II diabetes where there is some destruction of beta cells a happen also. Whether there is any immunological association with MRDM we have analyzed the serum immunoglobulin levels and complement level in MRDM and control subjects. The results are shown in Table 6.8,6.9, page 98.

It is seen that lowest vs highest IgG, IgM, IgA value of MRDM patients vs control subjects are 1515.26±412.80, 137.59±74.57, 313.39±12.25 vs 1555.19±335.92, 117.12±60.99, 206.89±42.66 respectively. The mean ± SD of the IgG, IgM, IgA value for MRDM patients and control subjects are 134.29±46.74,41.41±23.21vs 137.32±30.78, 28.16±10.70 respectively.

The results reveal that the IgG and IgM level are not much different in MRDM and control group however there is statistical significant difference in IgA value between MRDM and $p<0.004$. This reflects associated immune abnormalities in MRDM patients. Similarly there is no difference in C_3 level between MRDM and control but significant difference is seen in C4 concentration between MRDM and control $p<0.05$. This also indicates abnormal complement active in MRDM patients which may be responsible for islet cell destruction.

Most of the work on Immunology and MRDM were based on islet cell antibodies (ICA) which we could not do because of lack of facilities showed increased ICA 30.9%(Verma IC 1989) and no ICA in MRDM patients in other study (Wiyono P 1989,Dabadghao P 1996).

7.7. ABO Blood Group and MRDM

After analyzing the blood group and Rh data (The results are shown in Table 6.10, page 99) it is seen that the common blood group in MRDM subjects are 0(16, 42.11%), B(13, 34.21%), A(8, 21.05%) an AB(1, 2.63%) whereas the common blood groups among control subjects are A(11, 55%), 0(6, 30%), B(2, 10%), AB(1, 5%) respectively. The difference is statistically significant ($p<0.02$). The RhD for MRDM is positive for 37, (97.37%) and negative 1(2.63%) whereas in control group RhD is positive in all 20 (100%)cases. There is no statistical difference in RhD between these two groups. It is evident from these data that ABO blood group antigen particularly those with group B,O,A are at increased associate with MRDM. Many studies showed association of different diseases particularly different

malignancies with blood group and Rh (deGruchy's clinical hematology,2004) but we could not find any study involving blood group and RH association with MRDM patients.

7.8. HLA and MRDM:

A total of 20 MRDM patients and 10 controls were subjected to HLA ABC by lyphocytotxicity test. The results are shown in Table 6.11, page 100. It was found that among the MRDM patients 8(40%) showed positivity for A2, A9, A11 in 4(20%),A1,A30 in 2(10%).Among control A1,A9,A11 in 4(40%) cases and A3,A34 in 1(10%) of controls. Among HLA-B, MRDM patients showed 6(25%)HLA-B5 positivity, B15 positive in 5(25%)B27 in 3 (15%) and B7,B12, in 2(10%) of MRDM. Among the control HLA-B positivity were B5 in 5(50%),B15 in 3(30%),BW6 and BW4 in 3(30%) control subjects. Among HLA-C positivity in MRDM patients were ,CW5,CW6,CW7 in 4 (20%) each, CW3,CW2,CW1 in each 2(10%) whereas in control subjects the HLA-C positivity were CW4 in 3(30%),CW1 in 2(20%) and CW3,CW2 in 1(10%) subjects. It is evident from the HLA studies that there is some association of MRDM and HLA

There is some limitation of this study as the number of samples were small and further study on HLA association will have to be undertaken with large number of samples in future studies.

Similar studies in other parts of the world showed increase allele 9 of MICA positivity and allele 4 negativity associated with MRDM (Sanjeevi CB 2002,Kanungo A 2002) however DR7-DQ9 and DR3-DQ2 positivity in both NIDDM and MRDM patients indicate it may be a slow onset IDDM(Sanjeevi CB 1999, KanungoA 2002,Huh KB 1992)

7.9.Hyperglycaemia and Glycosylated Hb:

Hyperglycaemia itself is a putative agent and cause pancreatic beta cell and other cell injury by oxidative stress and apoptosis. The level of hyperglycaemia and glycosylation

of sugar and other proteins vary in different types of diabetes. To throw some light in

these factors we also measured the fasting postprandial blood glucose level and also HbA_1c of MRDM and control subjects. The results are shown in Table 6.12, page 100.

The lowest value of FBS, PPS and HbA1C in MRDM subjects were 9.0 mmol, 18.2 mmol, 9.4% and the highest value for the same were 34 mmol, 50 mmol, 17.9%. The lowest and highest value of FBS, PPS, HbA1C for control subjects were 5.6 mmol,5.2 mmol,4.6% and 5.6 mmol, 6.8 mmol, 5.3% respectively.

The mean ±SD of the FBS, PPS, HbA_1c for MRDM patients and control subjects are 21.24±6.20 mmol, 30.28±7.6 mmol, 13.46±2.5 % vs 4.70±0.4 mmol, 5.76±0.4mmol, 5.1±0.3% respectively. It is evident from the data that the mean sugar and HbA_1c level was much higher in MRDM than the control and is statistically significant. This implies the importance of hyperglycaemia in the genesis of MRDM and advocacy for strict glycemic control to prevent the long term complications of diabetes in MRDM patients.

Majority of the MRDM patients live in semiurban, rural and slum areas where the living condition is unhygienic.More over due to increase number of family members in the family the diet distribution is unequal. But the control subjects in contrast earns more, live in rented or own house in a slightly better hygienic condition than the MRDM patients.

Similar results were found in other studies (Ramachandran A 1988, Tjokroprawiro A 1990,Sainani GS 1984, Ratnam VJ 1984, Mohan V 1992) who found severe beta cell damage in FCPD, IDDM and PDDM patients. Another study showed increased incidence of complications in different type of diabetes including FCPD and the high blood glucose and increased glycosylated hemoglobin level (Kanta barman K 2004)

7.10. Lipid Profile and MRDM

Dyslipidemia is proved to be associated with different type of diabetes including MRDM. To see this association we have done fasting lipid profile (Triglyceride, LDL, HDL total cholesterol) by biochemistry autoanalyzer using regent from Boeringher manheim of MRDM and control subjects (The results are shown in Table 6.13, page 101). Triglyceride value ranged from lowest 64 mg% to highest value of 264mg% in MRDM subjects (mean±SD 178.58±77.21mg%) while for control the values are 95mg% to 339mg% (mean±SD 145.89±55.83%). The value of HDL are 20mg% lowest vs 40mg% highest (mean+SD 33.07±4.60mg%) in MRDM subjects while for control the lowest HDL value is 42mg% and highest 58.9mg% (mean±SD 50.85±6.08). Total cholesterol lowest 67mg% and highest 187mg% (mean±SD 141.21±23.28mg%) in MRDM subjects and for control lowest value is 106mg% and highest 178mg% (mean±SD 159.42±32.63mg%). It is evident from the values that TG is higher in MRDM patients compared to control ($p<0.06$) which is not significant. However HDL and total cholesterol were significantly lower $p<0.000$ and $p<0.056$ in MRDM than control. These results reflects dyslipidimia in MRDM subjects. The results are similar with other studies (Mohan V 1985, Samal KC 1990, Banwell JG 1967,Das S 1984) .

7.11. Histopathology of Pancreas and MRDM

A total of 20 FCPD patients pancreatic biopsy is evaluated. The age range varied from 13 years to 30 years, of these 7 are male and 13 females. The male to female rations is 1:1.86. These patients were referred for pancreatic biopsy due to clinical symptoms and radiological evidence of pancreatic calcification. We evaluated the histopathological finding based on routine hematoxylin and Eosin stain. the lympocyte infiltrate, amount of fibrosis, retrograde change like hemorrhage, infarction and dilatation of pancreatic ducts are also noted. The results are shown in Table 6.14, page 101.

We also did histopathological evaluation of pancreatic biopsies from 19 cases of patients suffering from chronic pancreatitis as evident clinical history and radiological findings. Their age range varies from 31-65 years (male 8, female 11). The male female ratio is 1:1.38. The results are shown in Table 6.15, page 102.

It is evident from the findings of the pancreatic biopsy of FCPD patients that immunological destruction of pancreas is the main cause of MRDM in these patients. This is supported by the fact that there is varying degrees of fibrosis, dilatation of pancreatic ducts, infarction and inflammatory infiltrate in the pancreas tissue which all supports this etiology.

Fibrosis: We defined fibrosis into mild, moderate and severe or marked depending on the percentage of fibrosis in the historical sections and denoted it as +, ++, +++ respectively. It is seen that FCPD patients vs chronic pancreatitis patients the amount of fibrosis varies by mild 55% vs 78.93%, moderate 10% vs 10.53% and severe 40% vs 10.53% respectively. It indicates increased moderate to severe in FDPD patients than chronic pancreatitis patient.

Chronic inflammatory cell infiltrate: Predominantly lymphocytes, monocytes, macrophages. The inflammatory infiltrate is also categorized as mild moderate and severe depending on the number of chronic inflammatory cells <100/hpf, upto 500 cells/hpf and >500 cells/hpf respectively. The degree of chronic inflammatory cell infiltrate did not vary between the two groups. Mild, moderate and severe chronic inflammatory infiltrate ranges from 50% vs 57.89,30% vs 21.05%,20%, vs 21.05% between FCPD vs chronic pancreatitis groups.

Dilatation of pancreatic ducts: Degree of dilatation of pancreatic duct as evidenced by histopathology which is due to chronic inflammation did not show any difference between the two groups. Both groups 75% dilatation of pancreatic duct are seen, rest 25% did not show any dilatation. In both groups there is dilatation of pancreatic duct as a sequele of chronic inflammation.

Infarction: Areas if infarction are seen in 25% cases of FCPD but not seen in chronic pancreatitis patients. The difference may be due to improper sampling i.e. sampling not taken from infracted areas. Infarction indicate area of ischaemic necrosis due to injury and consequence of inflammation.

we compare the FCPD and the chronic pancreatitis group there is difference in relation to fibrosis, chronic inflammatory infiltrate and infarction. All these changes are more marked in FCPD group than the chronic pancreatitis group. This difference may be due to difference in age group, nutritional status, immunological destruction, insulin requirement etc. which are more in MRDM patient i.e. younger group than the chronic pancreatitis i.e. older age group. However, this need to be substantiated by inclusion of larger number of subjects in future study and also taking proper histological sampling of pancreas.

In one study with 6 FCPD pancreatic biopsies seen light microscopically and using antibodies with insulin,glucagons,Pancreatic polypeptide(PP),somatostatin,vasoactive intestinal peptide(VIP),gastrin showed a spectrum of changes ranging from moderate to severe atrophy, fibrosis of the parenchyma and degeneration of the ducts similar to the present study (Govindrajan M 2001)

We did IHC staining by ABC method using four different markers of four pancreatic biopsies of FCDP patients. Markes used are from DakoCytomation,T cell(CD3) Polyclonal Rabbit anti human CD3(Code No N1580), B cell(CD20) Monoclonal Mouse anti human Cd20(ClonL26), p53Monoclonal Mouse antihuman p53 protein(Code No1581) and antiapoptotic marker bcl-2Monoclonal Mouse antihuman bcl-2 oncoprotein(code No1587).The stains run with positive and negative control supplied by the manufacturer.

It is evident from the IHC that there is T and B cell activation leading to both humoral anf cell mediated immunity in the etiopathogenesis of MRDM particularly the FCPD variant.Also there is indirect evidence of increased apoptosis as evidenced by complete negative bcl-2 staining and p53 staining. This corroborates that immunological destruction and increased apoptosis of pancreatic beta cells are responsible for the etiopathogenesis of MRDM.

Although pancreatic involvement is considered to be the hall mark of MRDM (Saraya A 2003), little reference were found in the light microscopic and IHC changes in pancreatic biopsy. The FCPD variant of MRDM was found to be associated with formation of calculi in the pancreatic system with fibrosis, dilatation of pancreatic ductular system and marked chronic inflammatory infiltrate with destruction of pancreatic cell mass.(Barman KK 2003).However it is evident from our study that immunological destruction of pancreatic beta cell mass, fibrosis and increased apoptosis is responsible for the development of MRDM. The results are shown in Table 6.16, page 102.

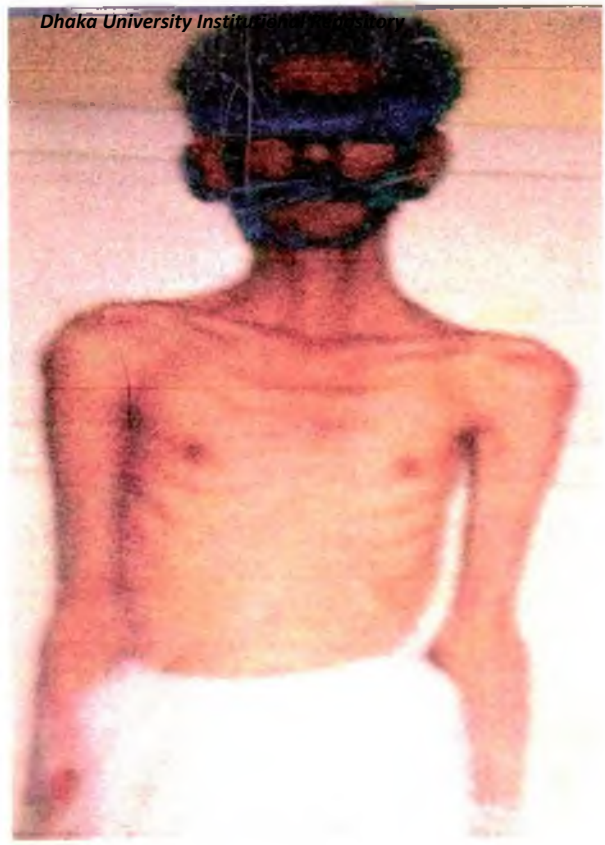


Fig: 1: MRDM Patient (Male)

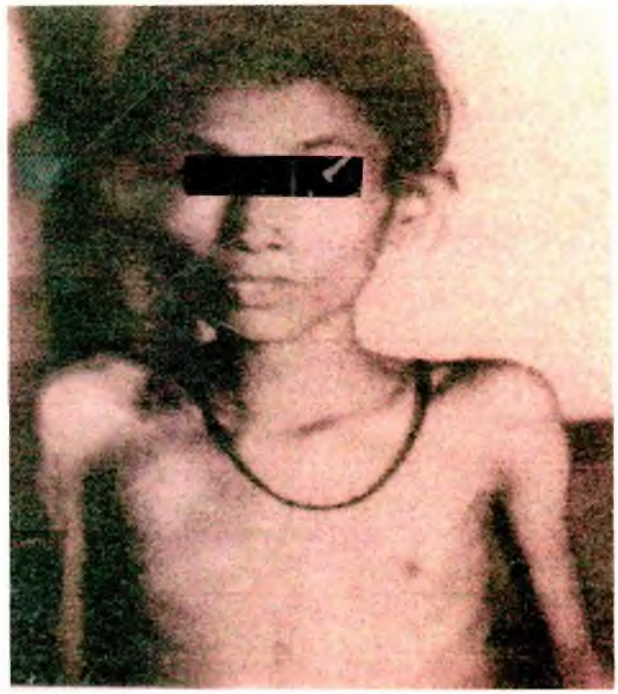


Fig: 2: MRDM Patient (Female)

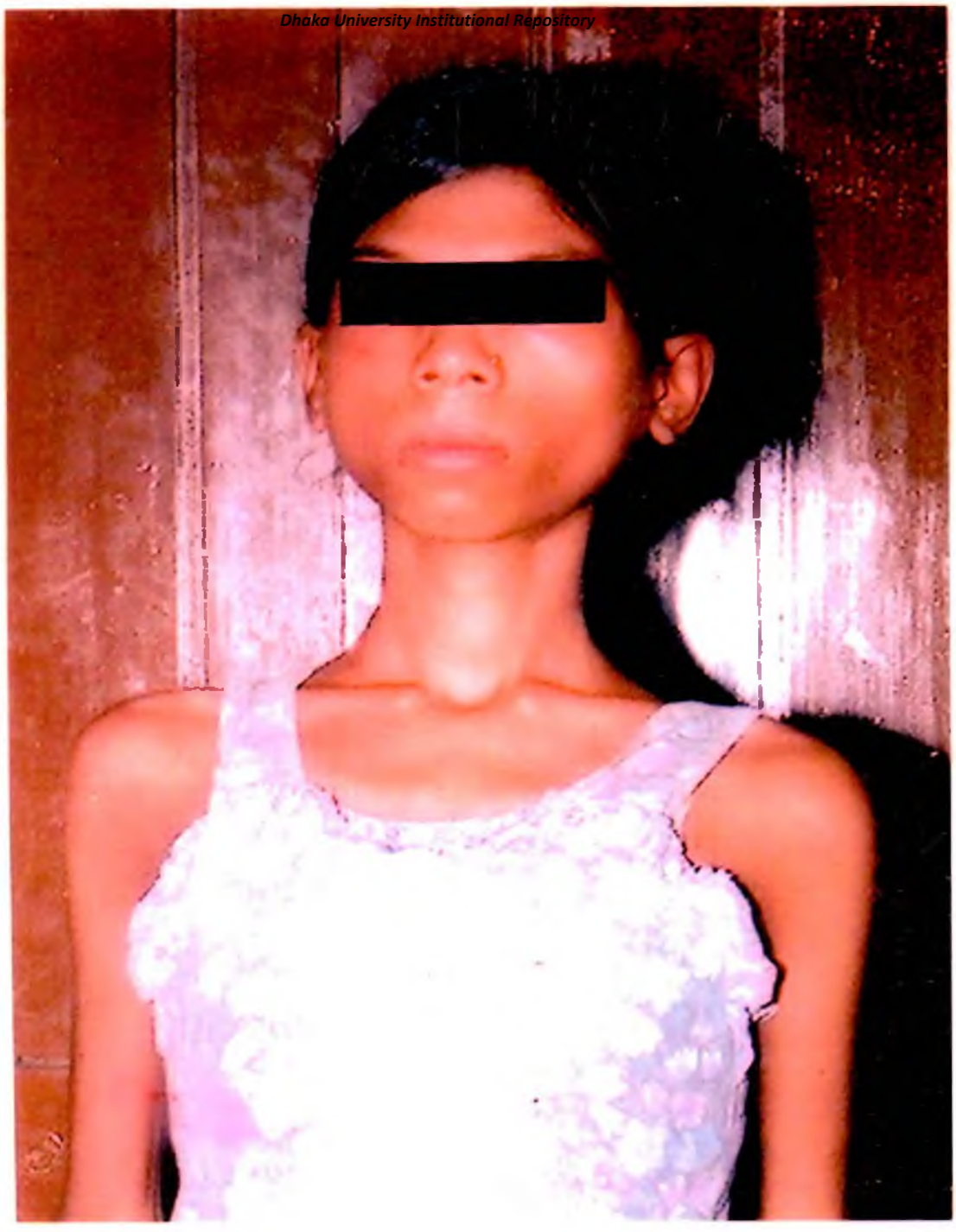


Fig: 3: MRDM Patient (Female)

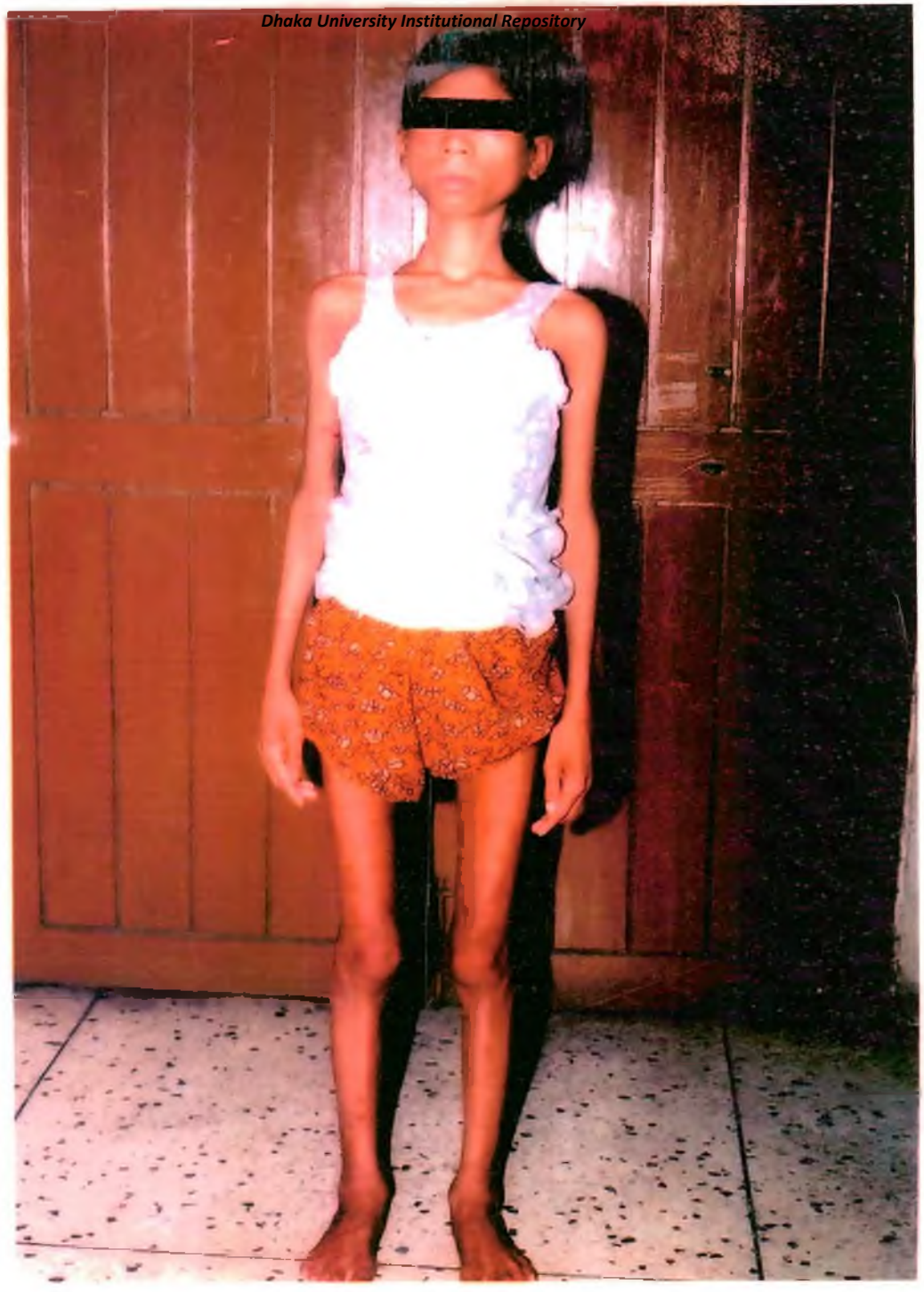


Fig: 4: MRDM Patient (Female)

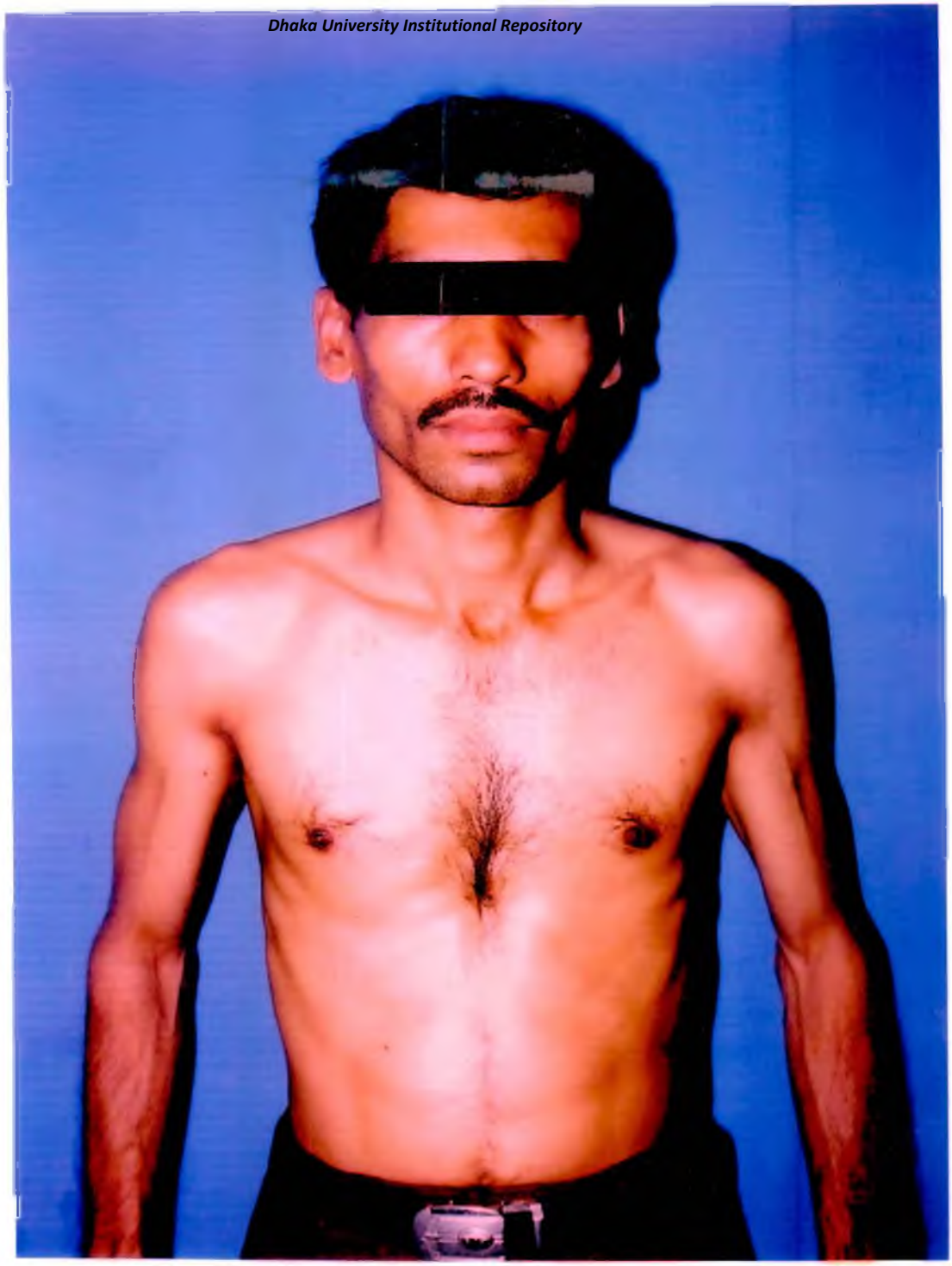


Fig: 5: Control (Male)

Fig: 6:

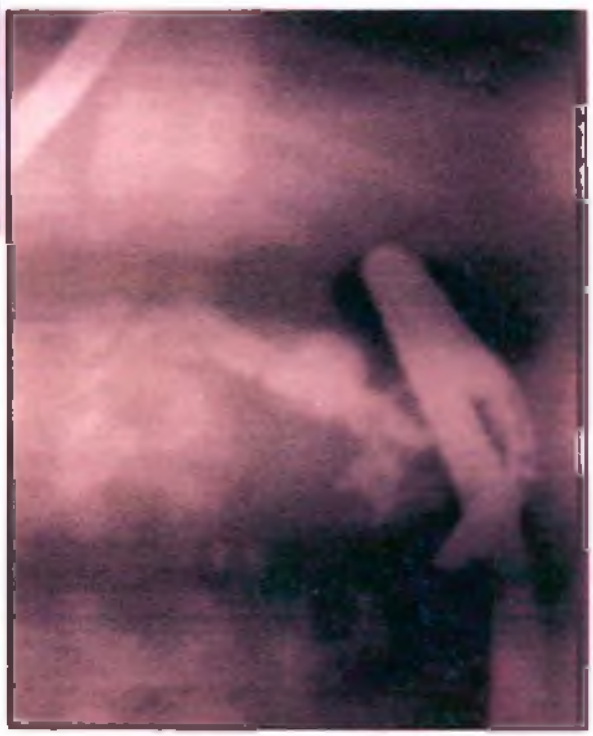


Fig: 7:

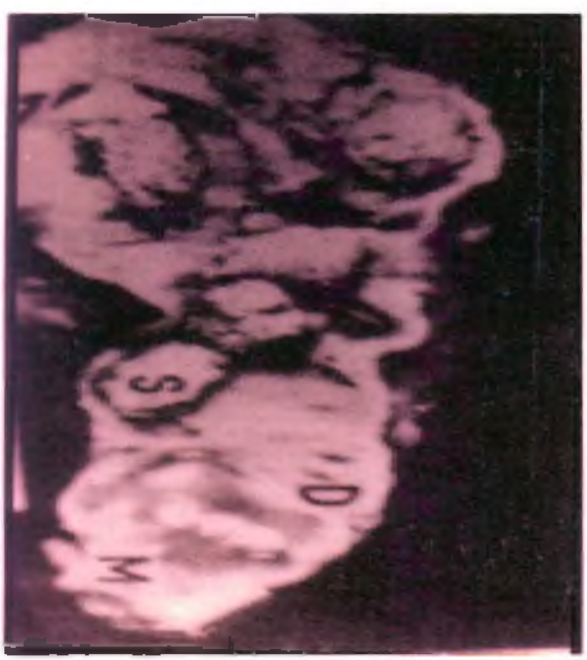
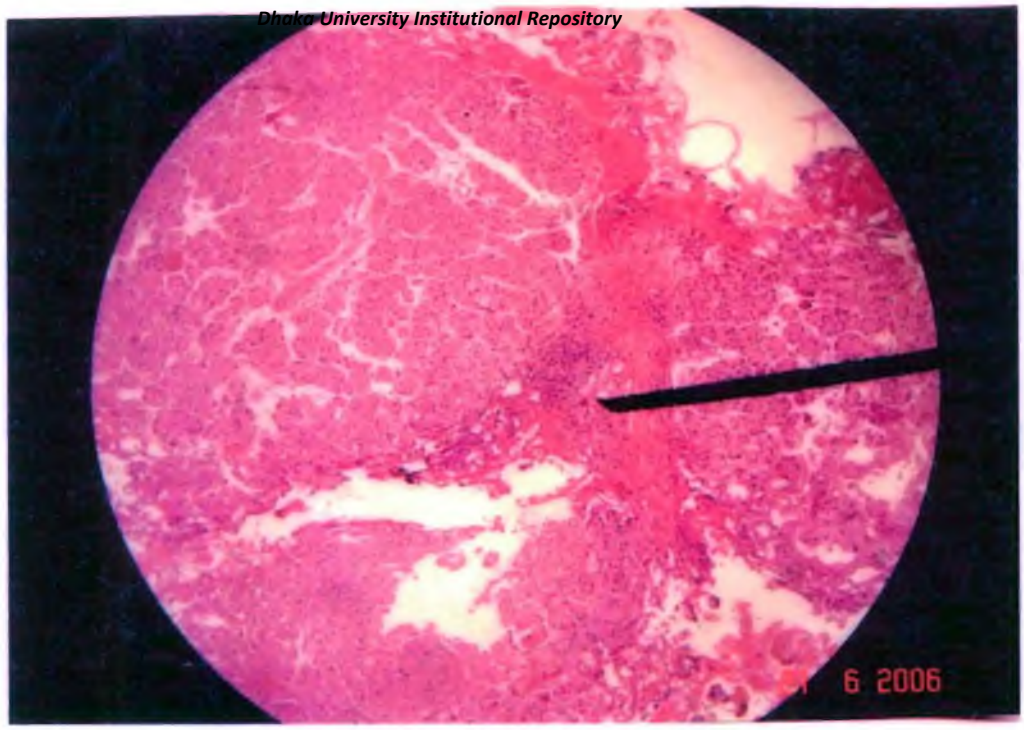
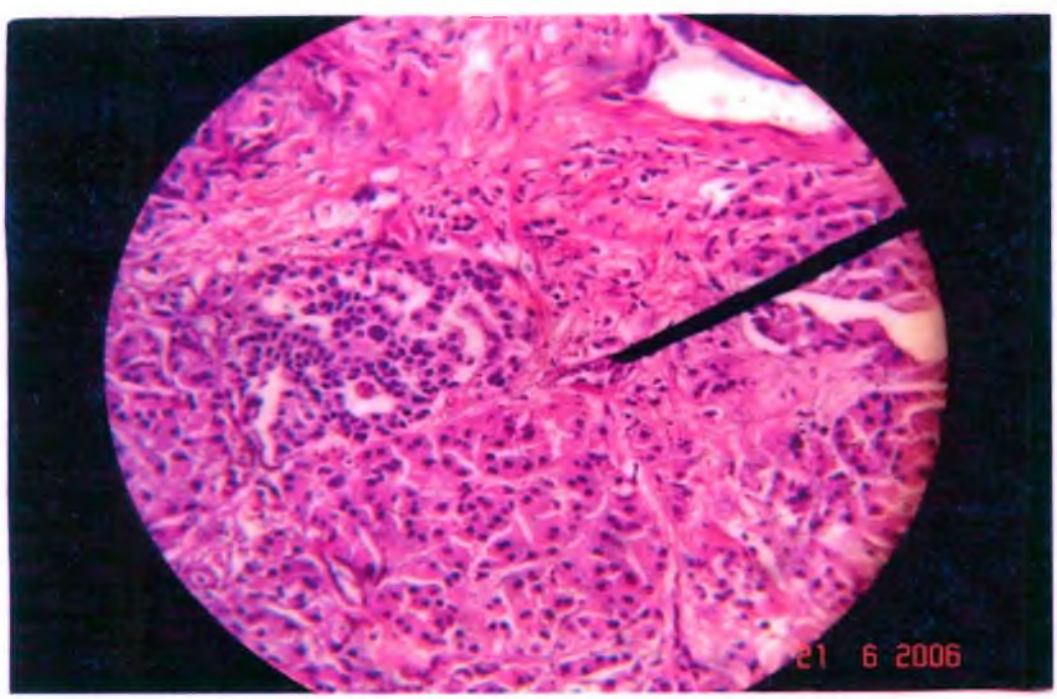


Fig: 8:

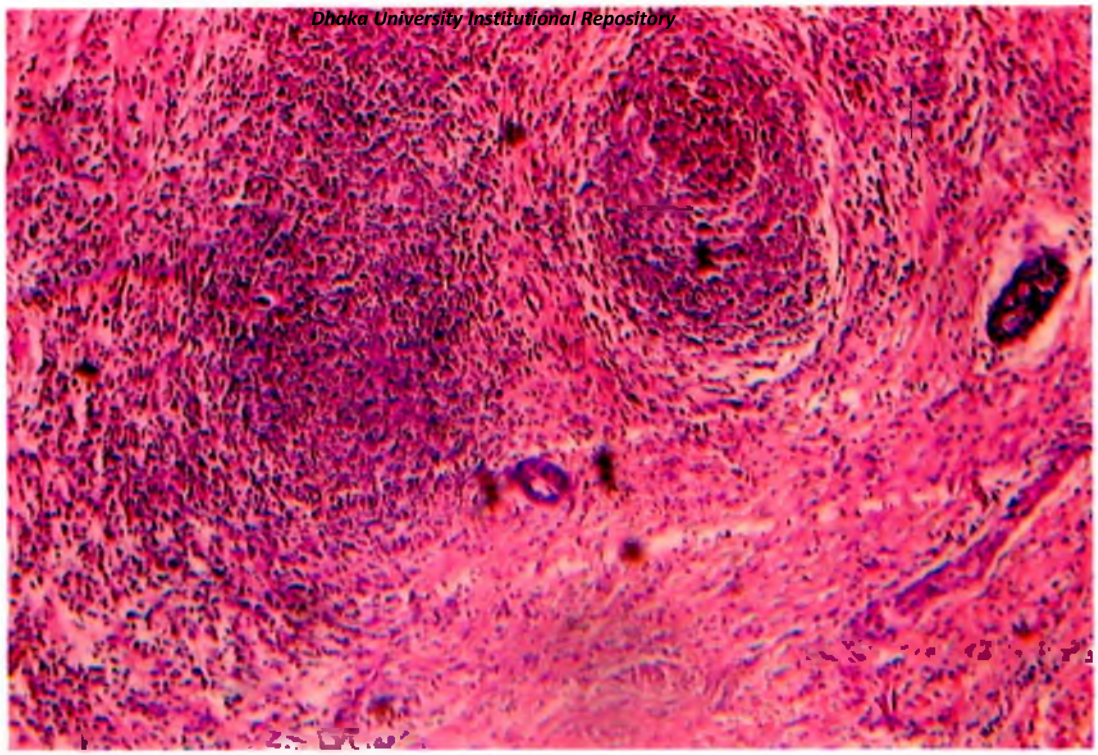
Photograph 6,7,8 : Plane X-Ray abdomen, ERCP, CT scan showing stone in the Pancreas of FCPD case



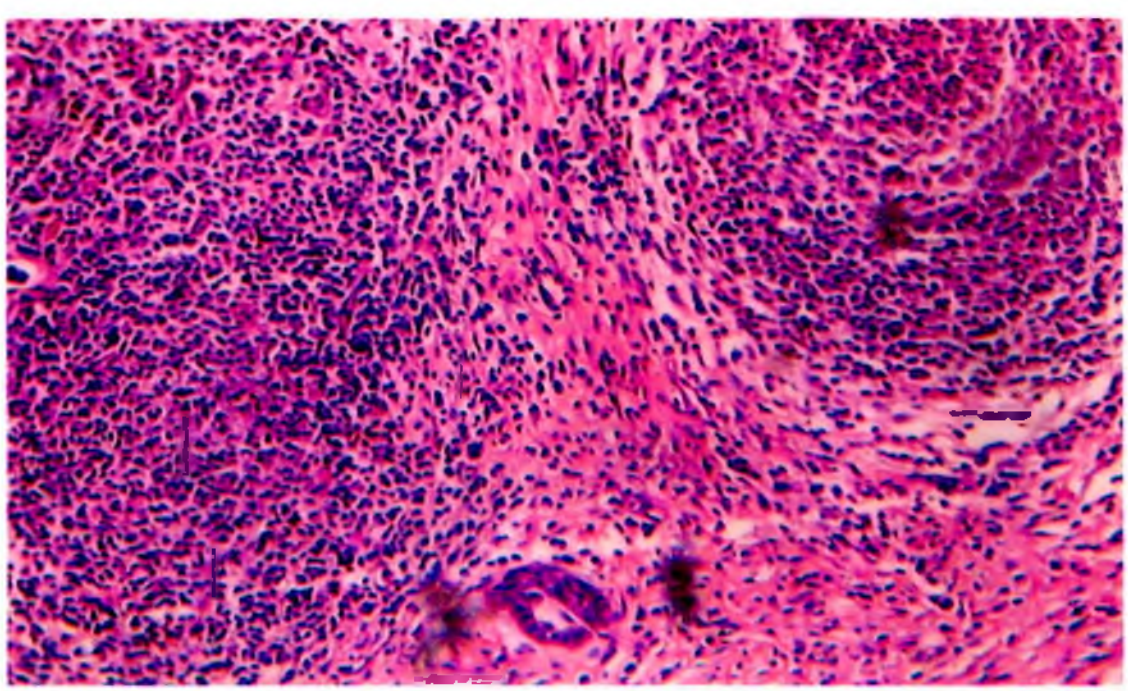
Microphotograph-I: Pancreatic biopsy, H&E stain, showing loss of pancreatic tissue, accumulation of chronic inflammatory cells, increased fibrosis. X 20



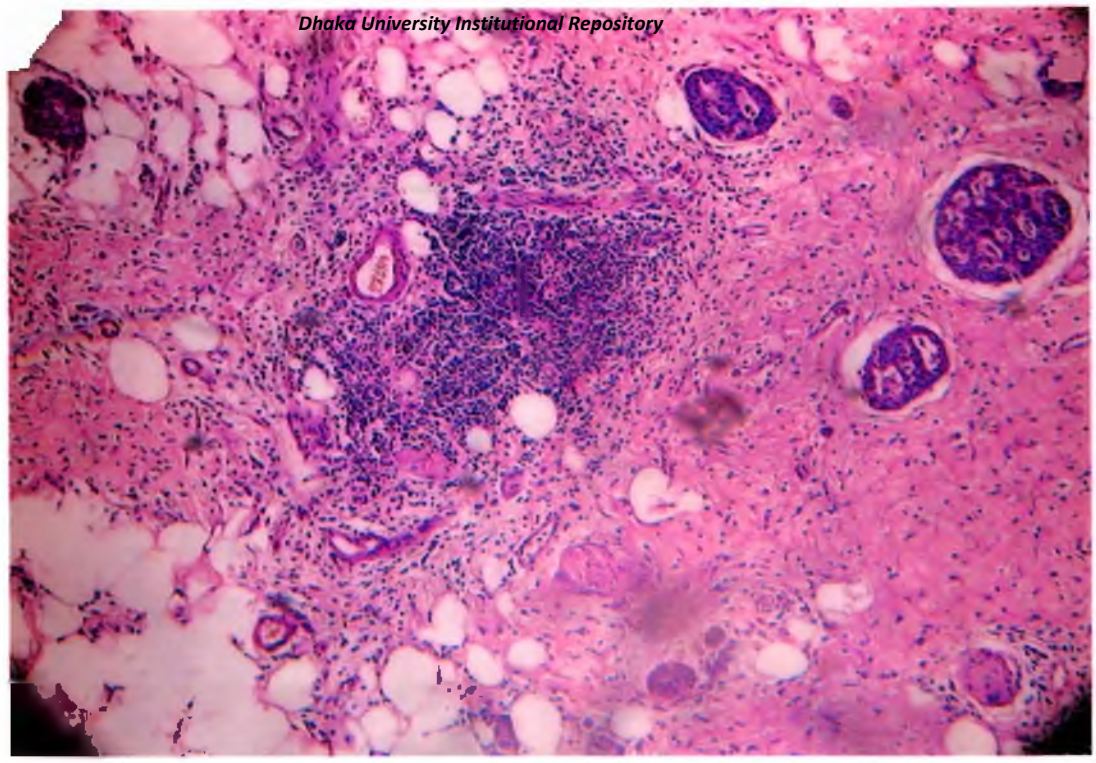
Microphotograph –II: Pancreatic biopsy, H&E stain, showing loss of pancreatic tissue, accumulation of chronic inflammatory cells, increased fibrosis. X 40



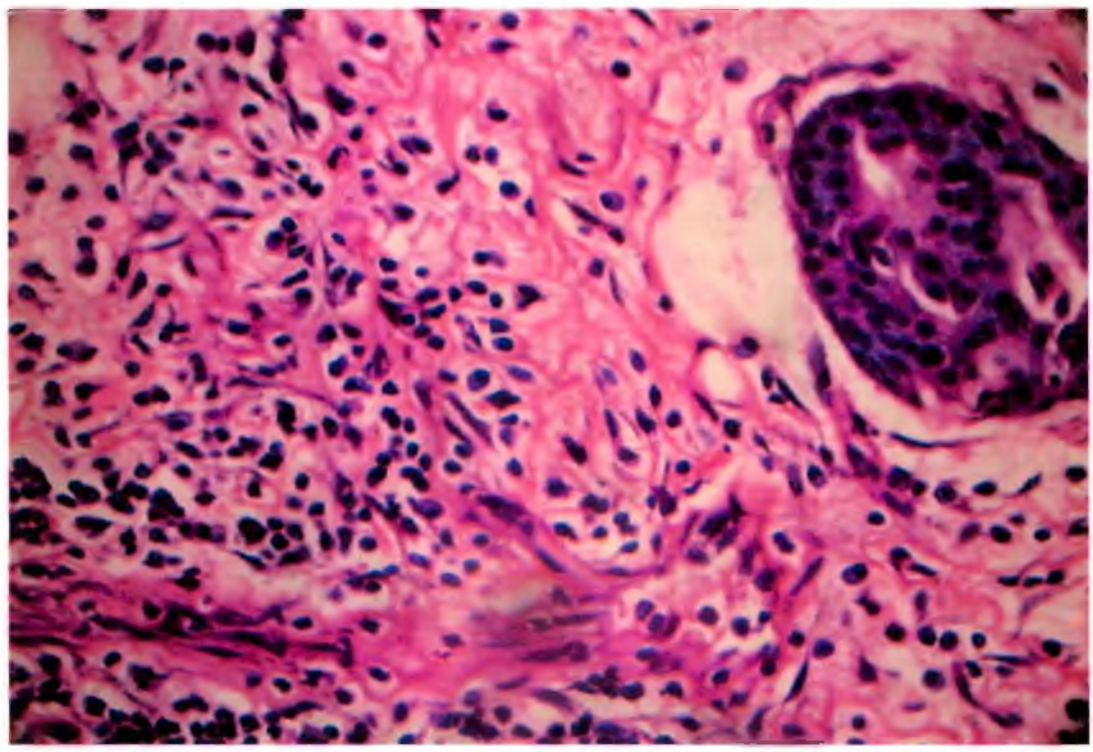
Microphotograph –III: Pancreatic biopsy, H&E stain, showing loss of pancreatic tissue, accumulation of chronic inflammatory cells, increased fibrosis. X 4



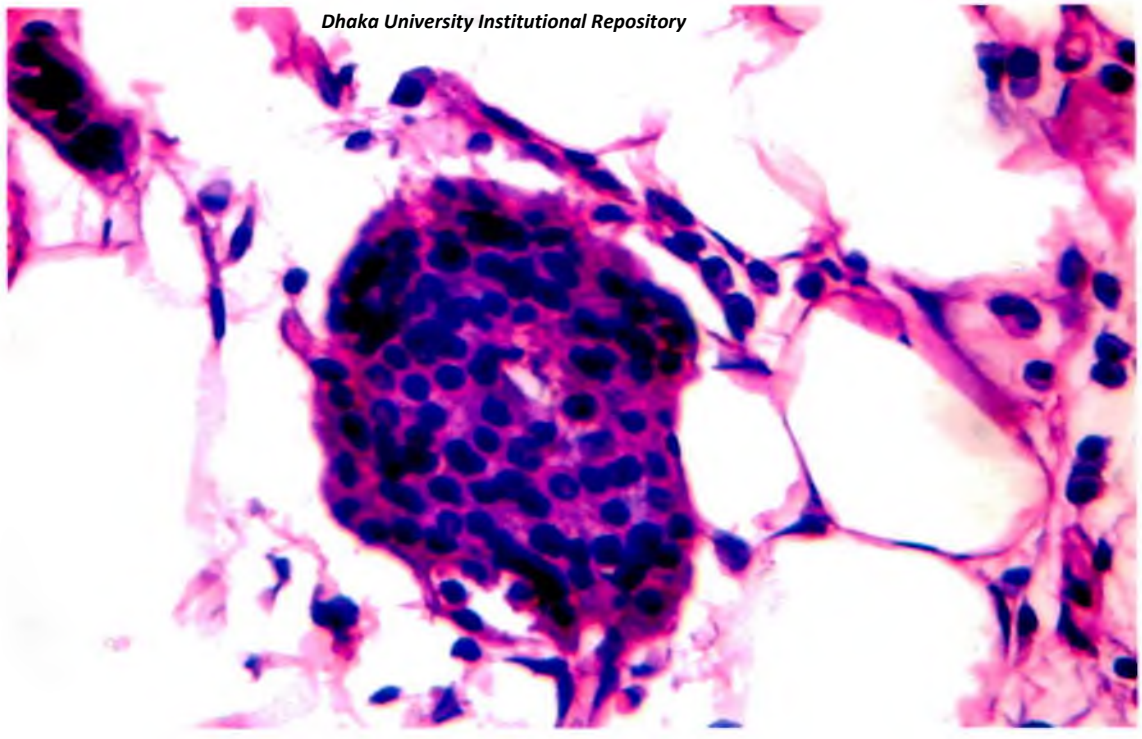
Microphotograph –IV: Pancreatic biopsy, H&E stain, showing loss of pancreatic tissue, accumulation of chronic inflammatory cells, increased fibrosis. X 10



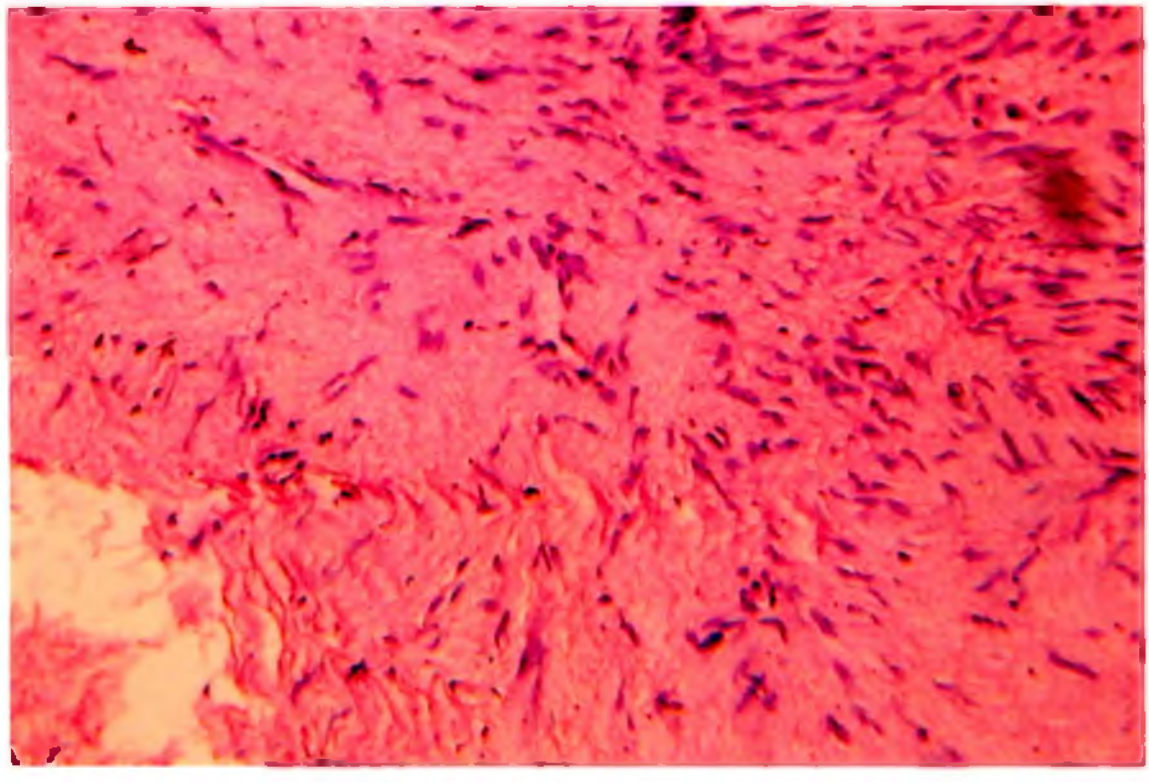
Microphotograph –V: Pancreatic biopsy, H&E stain, showing loss of pancreatic tissue, accumulation of chronic inflammatory cells, increased fibrosis & adipose tissue X 4



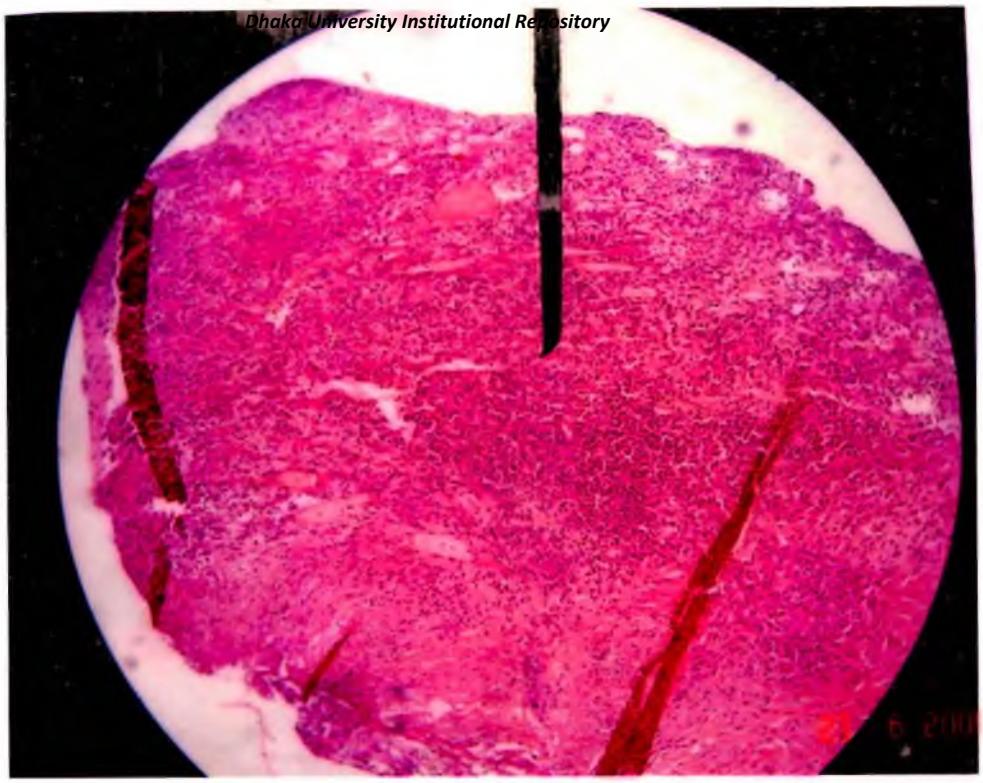
Microphotograph –VI: Pancreatic biopsy, H&E stain, showing loss of pancreatic tissue, accumulation of chronic inflammatory cells, increased fibrosis. X 40



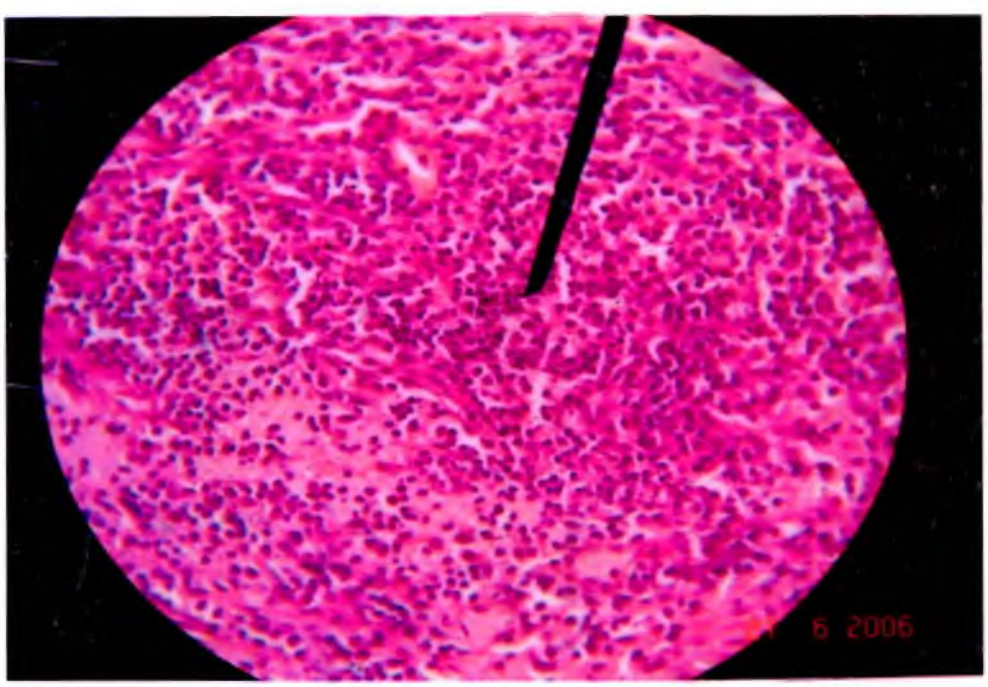
Microphotograph–VII: Pancreatic biopsy,H&E stain,showing a distorted pancreatic gland,accumulation of chronic inflammatory cells, increased adipose tissue. X 40



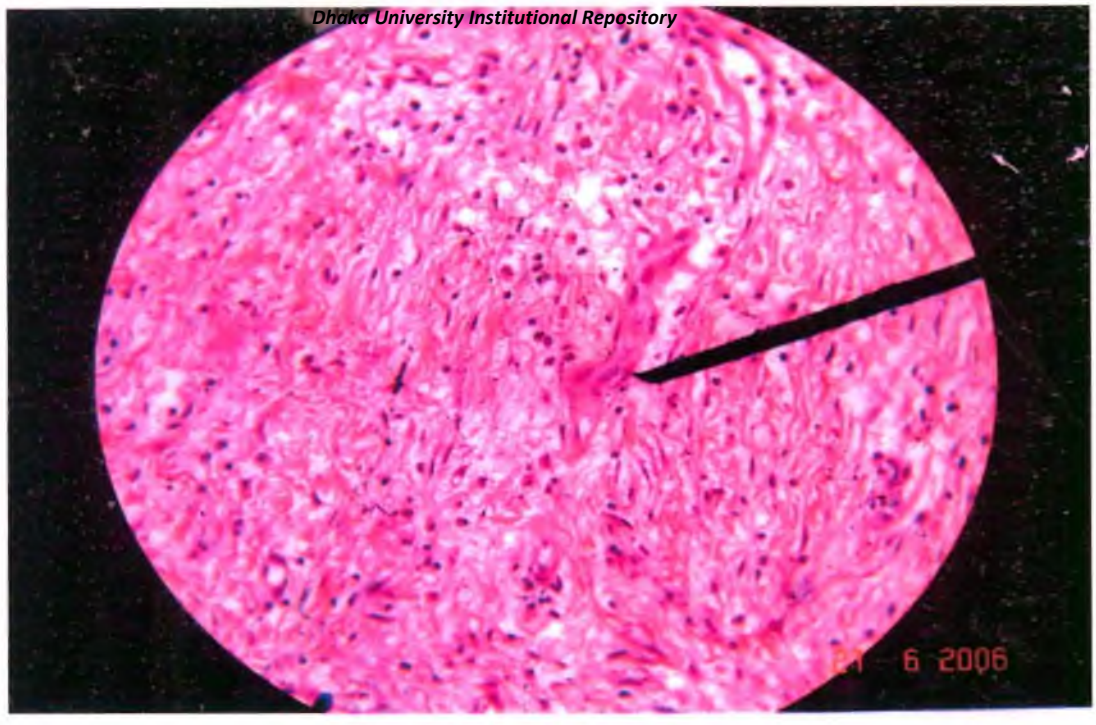
Microphotograph–VIII: Pancreatic biopsy,H&E stain,showing complete replacement of Pancreatic tissue by hyalinised fibrocollagenous tissue. X 10



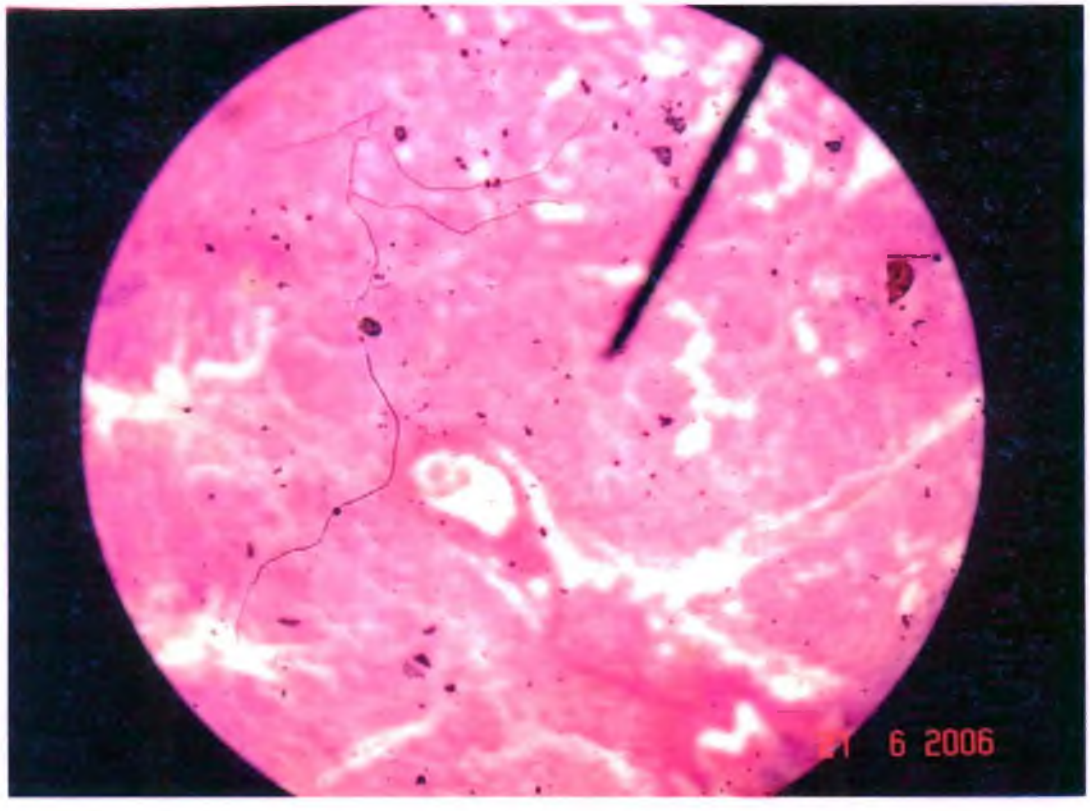
Microphotograph-IX: Pancreatic biopsy, H&E stain, showing dense chronic inflammatory infiltrates in pancreatic tissue. X 20



Microphotograph-X: Pancreatic biopsy, H&E stain, showing dense chronic inflammatory infiltrates in pancreatic tissuae. X 40



Microphotograph-XI: Pancreatic biopsy, H&E stain, showing areas of ischaemic necrosis. X 20



Microphotograph-XIi: Pancreatic biopsy, H&E stain, showing areas of ischaemic necrosis. X 40

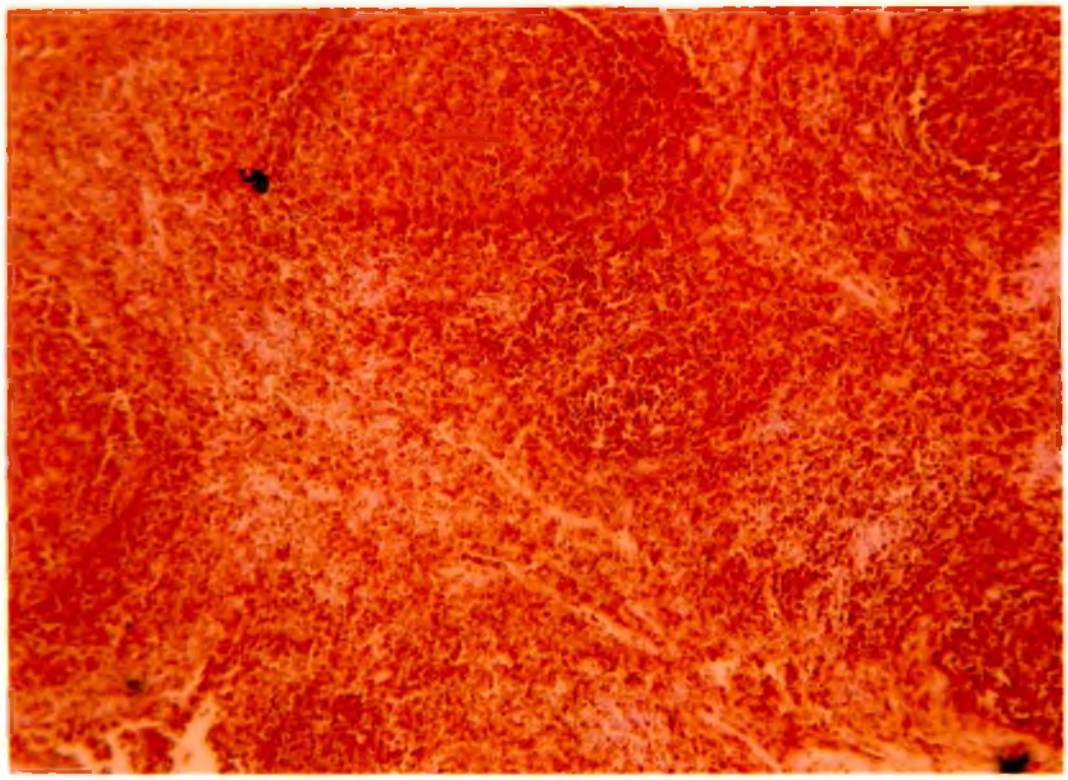


Fig-1: IHC, B cell marker (CD20) control showing strong immunopositivity of B cells X 40

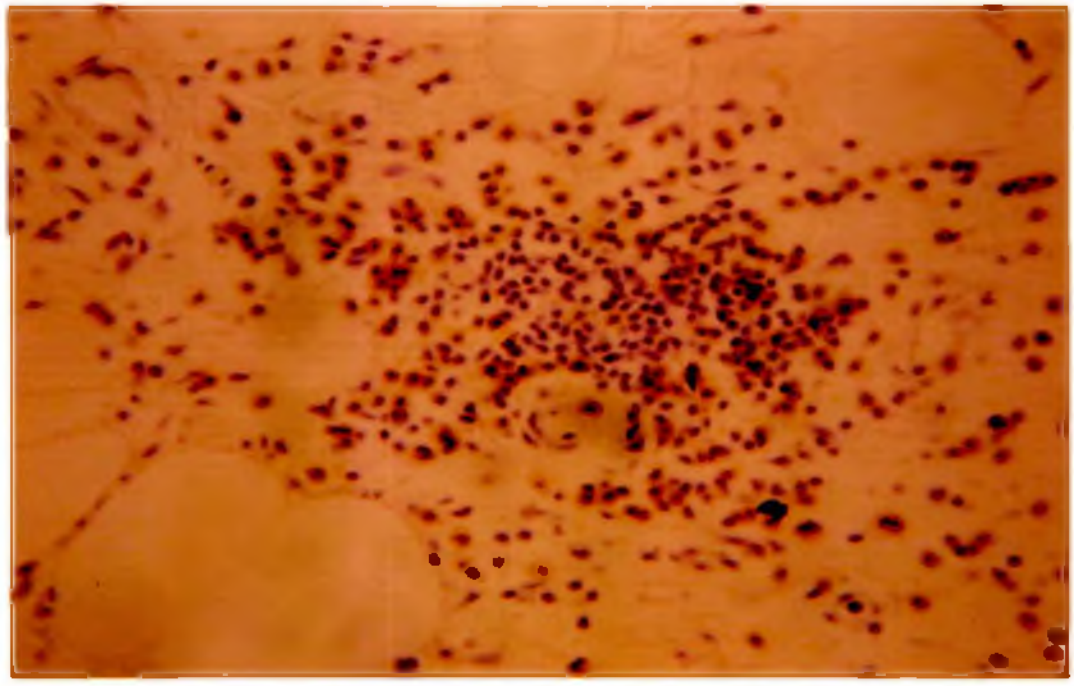


Fig-2: IHC, B cell marker (CD20), pancreatic biopsy of an FCPD patient showing strong immunopositivity of B cells X 10

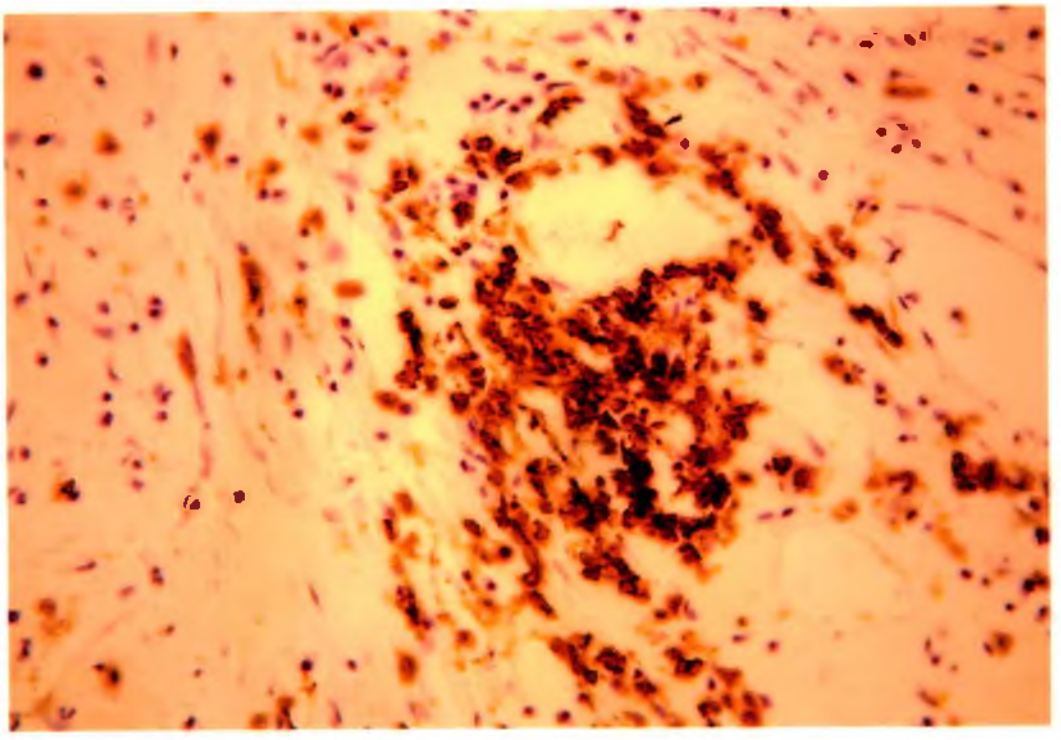


Fig-3: IHC, B cell marker (CD20) pancreatic biopsy of an FCPD patient showing strong immunopositivity of B cells X 40

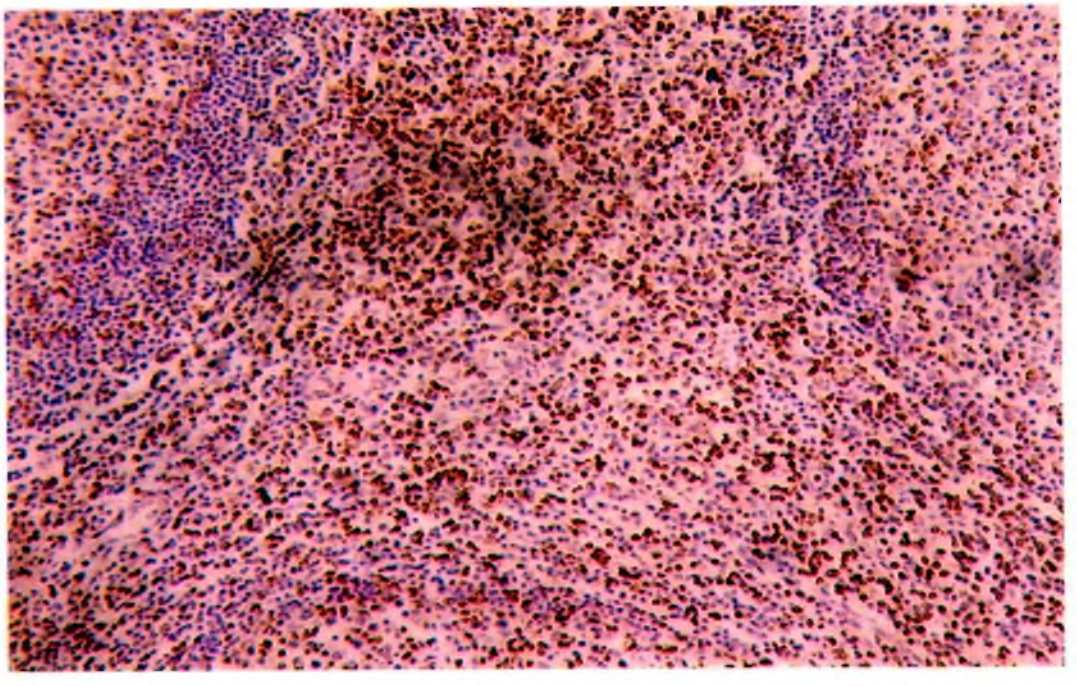


Fig-4: IHC, T cell marker (CD3) , pancreatic biopsy of an FCPD patient showing strong immunopositivity of T cells X 10

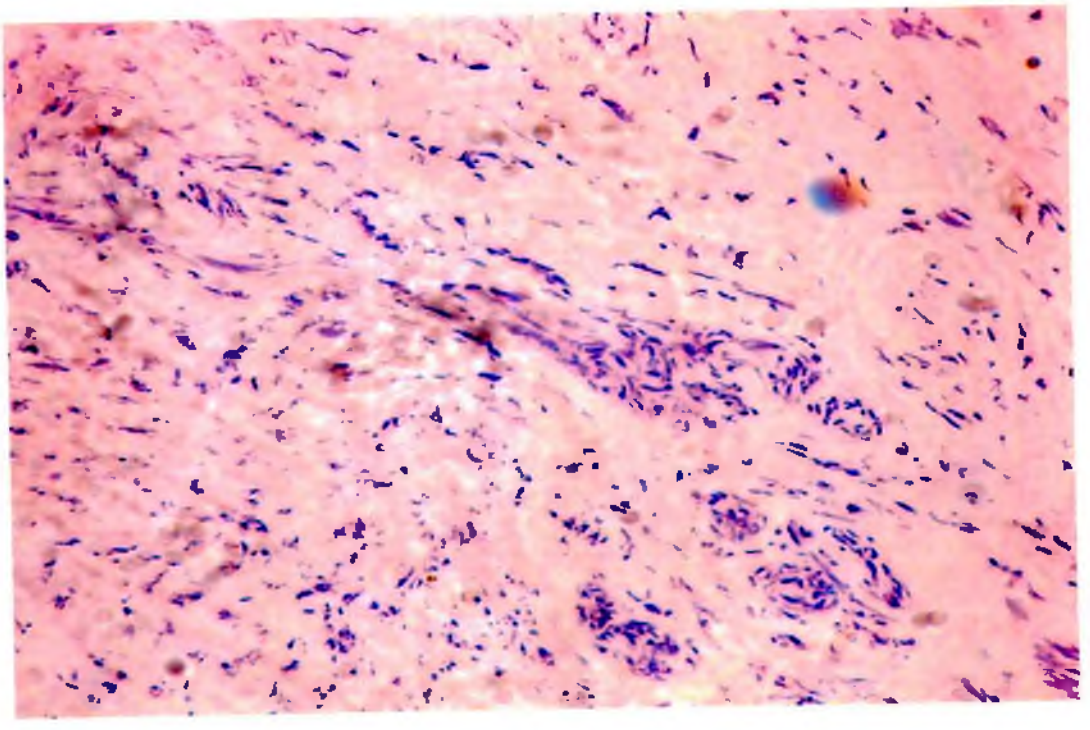


Fig-5: IHC, p53 staining of FCPD patient showing negative immunostaining X 10

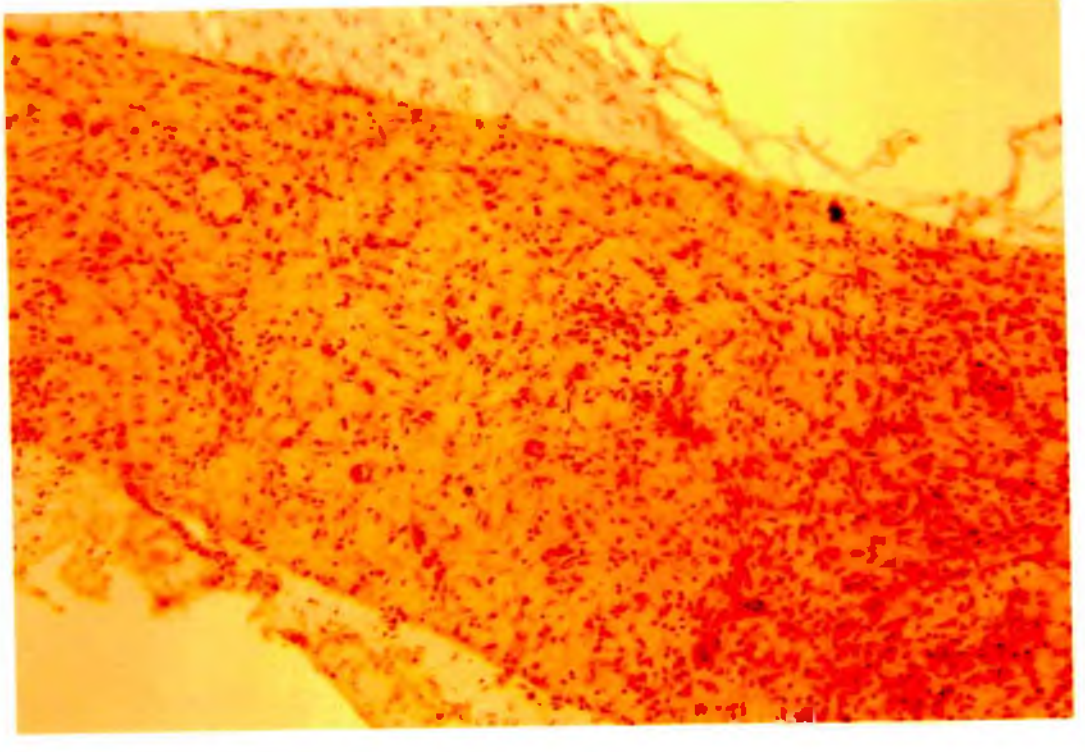


Fig-6: IHC, bcl-2 staining of pancreatic biopsy of an FCPD patient showing negative immunostaining X 10

An attempt was made to identify etiopathology of malnutrition related diabetes mellitus (MRDM) in Bangladesh perspective. A total of 45 MRDM and 20 age and sex matched control subjects were included in this study. Different parameters like literacy, economic, dietary status, height and weight and BMI, pancreatic function, renal function, HLA and immunogenetics,blood group and RhD, lipid profile, blood glucose, HbA_1c, immunoglobulin, complement and histopathology of pancreatic biopsies were assessed in these subjects. Statistically significant difference were observed between MRDM and control group in some parameters like glycaemic stataus, HbA_1c,urea, creatinine, immunogloblin, complements, exocrine pancreatic enzyme like serum amylase, lipid profile, height, weight, BMI, economic status, literacy, diet etc. indicating these factors are strongly associated with the etiopathogenesis of MRDM patients in Bangladesh. Pancreatic biopsies from FCPD patients , a variant of MRDM showed immunological destruction of islet cells, by both cell mediated and humoral immunity as evidenced by IHC positivity with T & B cell markers. increased lymphocytic and mononuclear cell infiltrate,increased fibrosis and collagen deposition in the pancreas and infarction necrosis with destruction of both exocrine and endocrine pancreatic tissue in this type of MRDM. All these findings indicate that MRDM probably represent a subtype of Type 1 diabetes or IDDM. However this needs further study with larger number of MRDM subjects. HLA, blood group and immunogenetic studies also revealed strong HLA, blood group association with MRDM which showed significant difference between MRDM and control groups.

Limitation:

This study is limited by the small sample size, number of MRDM and control subjects are 45 and 20 respectively. Future and further studies with large number of subjects should be included in this type of study to substantiate the findings of the present study. As IDDM is nearly absent and MRDM constitutes about 30% of our total diabetic population it is

essential to conduct this type of study in Bangladesh to find out its etiopathology. Particulars epidemiological data, more biochemical and genetic marker analysis are needed to draw any concrete conclusions regarding etiopathology of diabetes under 30 years leading to improve management and better preventive strategies.

Raw Data

Code : 1 – 2

Patient

NO	TG	HDL	Cholesterol	LDL
P-1	268	32	155.2	224.8
P-2	160	20	133.0	81.0
P-3	294	30.8	114.4	24.8
P-4	111	32	135.3	81.3
P-5	259	36	157.0	69.2
P-6	167	37	142.0	213.6
P-7	64	30	67.0	24.2
P-8	120	34	148.0	90.0
P-9	147	38	130.0	62.6
P-10	255	23	105.8	31.8
P-11	207	33	136.0	61.6
P-12	133	35	110.1	48.5
P-13	138	37	136.0	71.4
P-14	148	35	154.2	89.6
P-15	201	36	150.0	73.8
P-16	155	38	145.0	76.0
P-17	220	20	132.0	68.0
P-18	104	34	119.0	31.0
P-19	260	36	137.1	49.1
P-20	180	39	171.0	96.0
P-21	133	38	135.0	70.4
P-22	190	40	151.0	73.0
P-23	89	29	180.3	133.2
P-24	112	32	156.0	101.6

P-25	154	28	131.0	72.2
P-26	128	31	186.2	129.6
P-27	177	33	170.0	103.6
P-28	86	29	151.0	104.8
P-29	215	35	166.0	88
P-30	252	32	149.1	66.7
P-31	283	33	187.0	97.4
P-32	159	30	109.5	47.7
P-33	176	37	136.0	63.8
P-34	235	34	145.0	64
P-35	104	39	104.2	44.4
P-36	102	31	156.0	104.6
P-37	176	38	146.0	72.8
P-38	94	32	171.0	120.3
P-39	204	33	124.0	50.2
P-40	214	30	117.0	44.2
P-41	210	30	128.2	56.2
P-42	216	36	134.0	54.8
P-43	237	28	153.0	77.6
P-44	89	39	13.3	74.5

Control

NO	TG	HDL	Cholesterol	LDL
C-1	105	45	160.0	94
C-2	182	43	156.0	76.6
C-3	170	51	106.2	21.2
C-4	156.1	50	140.1	58.88
C-5	110	48	190.5	120.5
C-6	160	45	302.8	225.8

C-7	180.2	54	150.0	62.96
C-8	100.5	38	142.4	84.3
C-9	175.0	42	152.0	75
C-10	110.2	48	138.1	68.06
C-11	95.5	58.9	145.2	67.2
C-12	115.7	56.2	150.2	70.86
C-13	105.0	57.2	164.2	86
C-14	157.6	56.2	164.2	86
C-15	105.7	48.2	156.2	86.86
C-16	176.7	56.7	142.8	50.76
C-17	107.1	57.1	145.2	67
C-18	160.0	56.2	161.2	73
C-19	339.7	52.3	150.2	29.96
C-20	105.7	57.0	156.2	78.06

Non Paired t test

Code : 1 – 2

Patient

	Creatanine	B U	STP	Amylase
P-1	0.7	17.0	8.2	180
P-2	0.7	18.0	7.8	205
P-3	0.7	11.0	6.5	172
P-4	0.9	28.0	6.2	257
P-5	1.1	32.0	6.0	355
P-6	1.0	36.0	7.0	103
P-7	.08	27.0	7.5	98
P-8	1.0	22.0	7.3	184
P-9	.09	18.0	6.8	190

P-10	1.2	40.0	6.8	158
P-11	0.6	23.0	6.2	160
P-12	0.8	17.0	8.5	171
P-13	0.6	23.0	6.2	160
P-14	0.8	17.0	8.5	171
P-15	0.6	8.0	7.8	202
P-16	1.3	36.0	6.3	110
P-17	1.0	29.0	6.5	170
P-18	1.0	13.0	8.1	98
P-19	0.8	19.0	7.6	190
P-20	0.8	30.0	7.1	110
P-21	0.8	21.0	8.4	139
P-22	0.9	26.0	6.8	199
P-23	1.0	14.0	6.5	171
P-24	1.0	45.0	7.0	115
P-25	1.1	15.0	6.8	156
P-26	0.7	17.0	7.2	160
P-27	0.9	32.0	8.2	134
P-28	0.8	20.0	8.3	119
P-29	1.1	23.0	7.8	96
P-30	0.7	18.0	8.2	115
P-31	0.7	28.0	8.0	60
P-32	0.8	32.0	7.8	139
P-33	0.7	23.0	8.1	223
P-34	1.1	34.0	8.3	200
P-35	1.4	60.1	7.5	80
P-36	1.32	36.1	8.5	98

P-37	1.1	18.0	8.4	127
P-38	0.8	22.0	7.0	133
P-39	1.3	28.0	7.1	48
P-40	0.8	32.0	7.0	139
P-41	1.3	28.0	7.1	182
P-42	0.8	32.0	7.0	140
P-43	1.0	93.0	7.5	164
P-44	1.1	40.0	8.1	209
P-45	0.8	21.0	6.5	82

Control

	Creatnine	B U	STP	Amylase
C-1	0.7	25.8	7.2	158.0
C-2	0.8	28.0	7.7	180.2
C-3	0.9	20.0	9.1	160.1
C-4	0.7	24.0	8.6	208.2
C-5	0.6	25.4	8.4	158.0
C-6	0.7	22.0	7.5	210.0
C-7	0.7	28.0	8.2	160.1
C-8	0.5	29.2	9.1	190.2
C-9	0.8	27.0	7.6	187.0
C-10	0.8	23.4	8.4	160.5
C-11	0.6	22.0	7.09	180.9
C-12	0.9	24.1	7.32	175.2
C-13	1.0	22.0	7.74	165.2
C-14	0.8	24.1	7.4	125.9
C-15	1.1	26.2	7.7	165.9
C-16	0.7	21.3	7.72	125.9
C-17	0.8	27.4	8.07	172.1

C-18	0.9	26.0	7.71	181.3
C-19	0.6	28.2	6.96	162.5
C-20	0.5	26.5	7.02	178.2

Patient

SL. No.	IgG	IgM	IgA	C_3	C_4
1.	11763.1	192.1	413.7	132.8	62.5
9.	995.3	11.7	1.2.8	62.1	24.8
10.	1635.1	93.2	440.2	88.0	24.8
11.	1572.6	64.1	362.1	64.9	41.2
12.	915.3	113.7	145.5	126.1	34.0
20.	2104.1	111.8	529.6	116.1	20.0
21.	2608.5	88.4	243.9	178.3	26.1
22.	1272.0	47.2	273.3	122.5	47.4
23.	2441.1	129.7	325.3	142.2	26.1
36.	1871.4	240.9	196.7	129.1	32.9
37.	1029.6	158.1	284.0	170.9	64.1
38.	1809.6	139.0	431.0	249.9	110.9
39.	1344.2	263.9	243.7	142.9	22.9
40.	1289.7	207.7	196.7	178.3	42.4
41.	1080.0	207.7	507.6	142.6	24.3
42.	1628.9	51.3	305.0	79.8	64.1
43.	1399.0	218.6	326.6	156.5	35.5

Control **n = 10**

SL. No.	IgG	IgM	IgA	C_3	C_4
1.	1270.0	86.2	273.3	149.5	31.3
2.	1166.5	78.0	215.8	109.7	17.8
3.	1550.3	230.6	180.4	122.5	20.0
4.	1608.5	230.6	189.0	161.1	12.5
5.	1288.8	94.5	273.3	201.1	4207
6.	1688.3	118.2	253.6	91.4	21.6
7.	2127.1	83.2	153.4	156.5	37.5
8.	1688.3	75.0	263.6	129.1	21.6
9.	1997.6	83.2	196.7	135.8	40.7
10.	1166.5	91.7	169.8	122.5	35.9

Electrolytes Code : 3

Patient

SL. No.	Na	K	CL	CO_2
4.	138	3.8	99	25.4
5.	133	3.9	91	22.0
6.	131	6.7	89	25.6
7.	135	4.2	92	27.0
8.	138	5.1	102	20.0
9.	131	4.0	91	24.6
10.	138	5.1	102	20.0
11.	124	3.4	80	27.8
13.	136	4.1	96	24.3
14.	134	4.6	94	29.0
15.	135	3.7	96	20.0

18.	139	5.5	102	22.9
20.	141	5.2	109.2	19.0
21.	138	4.2	100	20.3
22.	138	4.5	105	33.5
23.	136	5.9	94	29.3
36.	142	4.2	103	22.1
37.	131	4.5	94	27.4
39.	136	4.8	92	17.3
40.	137	4.5	93	25.5
41.	133	4.1	90	27.2
42.	139	4.7	98	23.4
43.	137	5.2	96	26.2

Control

NO	Na	K	CL	CO_2
C-1	140.2	4.37	108.5	24.8
C-2	143.3	4.35	109.3	24.9
C-3	140.2	4.0	110.0	23.8
C-4	138.7	4.8	112.2	25.2
C-5	136.5	4.6	109.2	24.2
C-6	139.6	4.1	105.1	25.6
C-7	138.0	4.1	135.2	25.3
C-8	1387.9	4.4	103.7	26
C-9	137.6	4.2	112.2	28.2
C-10	140.1	4.30	105.8	25.3
C-11	130.9	4.8	99.2	23.0
C-12	134.2	3.9	100.9	25.9

C-13	135.2	4.6	105.2	25.7
C-14	133.2	4.6	102.5	23.9
C-15	136.2	4.09	102.5	25.9
C-16	136.2	4.12	105.1	26.1
C-17	139.2	4.32	102.6	27.1
C-18	128.2	3.39	102.6	29.1
C-19	140.2	4.02	103.8	25.2
C-20	138.7	4.31	117.0	27.2

Height (Wt), Weight (Wt), Basal Metabolic Index (BML) of the patients and controls.

Patient

NO	Height (cm)	Weight (kg)	BMI (kg/M^2
P-1	147	27	12.5
P-2	156	35	14.4
P-3	143	20	9.8
P-4	149	29	13.06
P-5	154	38	16.0
P-6	151	27	11.8
P-7	152	24	10.38
P-8	141	28	14.14
P-9	163	31	11.69
P-10	150	34	15.11
P-11	146	20	12.20
P-12	130	22	13.0
P-13	155	29	12.08
P-14	151	40	17.54
P-15	146	34	15.96
P-16	155	41	17.06

P-17	138	25	12.10
P-18	139	21.5	11.13
P-19	158	34	13.65
P-20	152	31	13.4
P-21	153	38	16.2
P-22	147	32	14.8
P-23	154	48	20.23
P-24	168	38	13.4
P-25	157	46	18.6
P-26	151	33	14.4
P-27	161	39	15.0
P-28	138	30	15.7
P-29	160	30	14.4
P-30	168	60	21.25
P-31	148	36	16.43
P-32	154	3	13.9
P-33	162	34	12.9
P-34	171	51	17.4
P-35	160	49	19.1
P-36	145	30	14.27
P-37	146	44	20.64
P-38	168	46	16.29
P-39	139	28	15.0
P-40	151	33	14.0
P-41	151	33	14.5
P-42	153	41	17.5
P-43	161	34	13.1

Control

NO	Height (cm)	Weight (kg)	BMI (kg/M^2
C-1	172	47	15.8
C-2	167	48	17.2
C-3	151	38	13.5
C-4	153	40	17.0
C-5	164	43	15.9
C-6	163	44	16.5
C-7	147	37	17.9
C-8	156	46	18.9
C-9	163	52	19.7
C-10	169	44	15.4
C-11	165	49	17.9
C-12	166	50	18.1
C-13	158	47	18.8
C-14	151	42	18.4
C-15	163	50	18.8
C-16	160	40	15.6
C-17	162	50	19.0
C-18	163	50	18.8
C-19	164	50	18.5
C-20	148	30	13.69

Age and Sex Distribution of patients and controls

Patient

NO	Sl. No.	Age (years)	Sex
P-1	TR1	17	F
P-2	TR2	24	M
P-3	TR3	16	M
P-4	TR4	25	M
P-5	TR5	20	M
P-6	TR6	16	M
P-7	TR7	18	M
P-8	TR8	14	F
P-9	TR9	22	M
P-10	TR10	25	M
P-11	TR11	13	M
P-12	TR12	12	F
P-13	TR13	20	F
P-14	TR14	14	M
P-15	TR15	20	F
P-16	TR16	25	M
P-17	TR17	20	F
P-18	TR18	19	F
P-19	TR19	26	M
P-20	TR20	20	F
P-21	TR21	20	M
P-22	TR22	29	M
P-23	TR23	15	M

P-24	TR24	28	F
P-25	TR25	26	F
P-26	TR26	21	M
P-27	TR27	28	M
P-28	TR28	18	M
P-29	TR29	20	M
P-30	TR30	13	F
P-31	TR31	22	M
P-32	TR32	28	M
P-33	TR33	19	M
P-34	TR34	23	M
P-35	TR35	23	M
P-36	TR36	15	M
P-37	TR37	28	M
P-38	TR38	28	M
P-39	TR39	15	F
P-40	TR40	26	F
P-41	TR41	25	M
P-42	TR42	14	F
P-43	TR43	16	F
P-44	TR44	17	M
P-45	TR45	25	M

Control

NO	Sl. No.	Age (years)	Sex
C-1	TRC1	20	M
C-2	TRC2	28	M
C-3	TRC3	24	F
C-4	TRC4	27	F
C-5	TRC5	29	M
C-6	TRC6	23	M
C-7	TRC7	25	M
C-8	TRC8	20	M
C-9	TRC9	26	M
C-10	TRC10	28	M
C-11	TRC11	24	M
C-12	TRC12	24	M
C-13	TRC13		
C-14	TRC14	20	M
C-15	TRC15	26	M
C-16	TRC16	24	M
C-17	TRC17	20	M
C-18	TRC18	30	M
C-19	TRC19	25	M
C-20	TRC20	12	F

Code : 4 – 7.8

Patient

NO	FBS(MM01)	2ABF/Glucose m.m.ol	HbA_1C (%)
P-1	23.6	27.8	9.9
P-2	16.1	20.0	9.4
P-3	22.2	30.8	11.1
P-4	34.0	37.0	15.4
P-5	22.5	28.0	12.2
P-6	26.6	38.0	17.9
P-7	17.5	33.5	16.9
P-8	16.2	23.2	15.2
P-9	18.3	19.0	13.5
P-10	18.3	19.0	13.5
P-11	14.5	23.0	16.4
P-12	15.4	25.0	10.9
P-13	24.0	28.0	17.6
P-14	15.0	22.0	10.2
P-15	17.2	50.0	17.0
P-16	13.5	18.2	9.8
P-17	27.5	36.0	14.6
P-18	24.0	37.8	13.8
P-19	25.0	35.0	12.5
P-20	25.0	35.0	12.5
P-21	25.0	38.0	13.2
P-22	23.0	30.0	12.2
P-23	9.0	20.3	9.5

P-24	23.0	35.0	17.4
P-25	14.5	20.1	11.9
P-26	24.0	30.5	15.2
P-27	19.5	24.1	14.3
P-28	18.5	25.0	16.8
P-29	15.5	25.0	14.6
P-30	35.0	38.0	16.0
P-31	28.0	33.0	13.7
P-32	26.0	38.0	13.5
P-33	14.0	18.6	11.8
P-34	15.2	20.8	9.4
P-35	36.0	40.0	17.0
P-36	19.0	26.5	11.8
P-37	17.5	33.5	12.2
P-38	14.5	23.4	11.0
P-39	19.8	38.9	10.8

Control

NO	FBS(MM01)	2ABF/Glucose m.m.ol	HbA_1C (%)
C-1	4.3	6.4	5.0
C-2	5.2	6.8	4.8
C-3	4.8	6.0	5.0
C-4	5.6	5.9	5.4
C-5	5.0	6.1	5.6
C-6	4.8	5.8	5.0
C-7	4.5	6.0	5.1
C-8	5.4	6.3	3.7

C-9	4.7	5.8	5.0
C-10	4.3	5.9	5.0
C-11	5.1	6.3	5.0
C-12	4.0	5.2	5.2
C-13	4.7	5.6	5.6
C-14	4.2	5.3	5.4
C-15	4.0	5.8	4.8
C-16	3.8	5.7	5.1
C-17	5.3	6.0	4.6
C-18	4.6	5.8	5.3

Independent samples of CODE

Group 1 : COD EQ 1		Group 2 : COD EQ 2					
t-test for : CHO							
	Number of cases	Mean	Standard Deviation	Standard Error			
Group 1	45	141.2089	23.282	3.471			
Group 2	20	159.4150	37.629	8.414			
		Pooled Variance Estimate			Separate Variance Estimate		
F value	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.
2.61	.009	-2.39	63	.020	-2.00	25.69	.056

Independent samples of CODE

Group 1 : COD EQ 1		Group 2 : COD EQ 2					
t-test for : CRE							
	Number of cases	Mean	Standard Deviation	Standard Error			
Group 1	45	.9244	.207	.031			
Group 2	20	.7550	.157	.035			
		Pooled Variance Estimate			Separate Variance Estimate		
F value	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.
1.73	.195	2.26	63	.002	3.62	47.38	.001

Independent samples of CODE

Group 1 : COD EQ 1 Group 2 : COD EQ 2

t-test for : BUN

	Number of cases	Mean	Standard Deviation	Standard Error
Group 1	45	27.2711	14.088	2.100
Group 2	20	24.7250	2.849	.637

		Pooled Variance Estimate			Separate Variance Estimate		
F value	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.
24.45	.000	.80	63	.428	1.16	51.46	.251

Independent samples of CODE

Group 1 : COD EQ 1 Group 2 : COD EQ 2

t-test for : STP

	Number of cases	Mean	Standard Deviation	Standard Error
Group 1	45	7.3867	.717	.107
Group 2	20	7.8235	.635	.142

		Pooled Variance Estimate			Separate Variance Estimate		
F value	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.
1.27	.578	-2.34	63	.022	-2.46	40.94	.018

Independent samples of CODE

Group 1 : COD EQ 1 Group 2 : COD EQ 2

t-test for : AMY

	Number of cases	Mean	Standard Deviation	Standard Error
Group 1	45	150.0444	55.482	8.271
Group 2	20	171.6000	19.262	4.307

		Pooled Variance Estimate			Separate Variance Estimate		
F value	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.
8.30	.000	-1.69	63	.097	-2.31	60.75	.024

Independent samples of CODE

Group 1 : COD EQ 1 Group 2 : COD EQ 2

t-test for : IGG

	Number of cases	Mean	Standard Deviation	Standard Error
Group 1	17	1515.2647	412.805	100.120
Group 2	10	1555.1900	335.918	106.227

		Pooled Variance Estimate			Separate Variance Estimate		
F value	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.
1.51	.539	-.26	25	.798	-.27	22.23	.787

Independent samples of CODE

Group 1 : COD EQ 1		Group 2 : COD EQ 2					
t-test for : IGM							
	Number of cases	Mean	Standard Deviation	Standard Error			
Group 1	17	137.5941	74.569	18.086			
Group 2	10	117.1200	60.988	19.286			
		Pooled Variance Estimate			Separate Variance Estimate		
F value	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.
1.49	.549	.73	25	.470	.77	22.15	.447

Independent samples of CODE

Group 1 : COD EQ 1		Group 2 : COD EQ 2					
t-test for : IGA							
	Number of cases	Mean	Standard Deviation	Standard Error			
Group 1	17	313.3941	122.251	29.650			
Group 2	10	206.8900	42.659	13.490			
		Pooled Variance Estimate			Separate Variance Estimate		
F value	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.
8.21	.003	2.64	25	.014	3.27	21.66	.004

Independent samples of CODE

Group 1 : COD EQ 1 Group 2 : COD EQ 2

t-test for : C3

	Number of cases	Mean	Standard Deviation	Standard Error
Group 1	17	134.2941	46.759	11.341
Group 2	10	137.9200	30.780	9.133

		Pooled Variance Estimate			Separate Variance Estimate		
F value	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.
2.31	.205	-.22	25	.829	-.24	24.56	.810

Independent samples of CODE

Group 1 : COD EQ 1 Group 2 : COD EQ 2

t-test for : C4

	Number of cases	Mean	Standard Deviation	Standard Error
Group 1	17	41.4118	23.207	5.628
Group 2	10	28.1600	10.702	3.384

		Pooled Variance Estimate			Separate Variance Estimate		
F value	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.
4.70	.023	1.69	25	.103	2.02	24.07	.055

Independent samples of CODE

Group 1 : COD EQ 1		Group 2 : COD EQ 2					
t-test for : NA							
	Number of cases	Mean	Standard Deviation	Standard Error			
Group 1	24	135.1083	3.862	.188			
Group 2	20	137.2650	3.574	.799			
		Pooled Variance Estimate			Separate Variance Estimate		
F value	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.
1.17	.738	-1.38	42	.176	-1.39	41.50	.173

Independent samples of CODE

Group 1 : COD EQ 1		Group 2 : COD EQ 2					
t-test for : K							
	Number of cases	Mean	Standard Deviation	Standard Error			
Group 1	24	4.6125	.726	.148			
Group 2	20	4.3355	.288	.064			
		Pooled Variance Estimate			Separate Variance Estimate		
F value	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.
6.36	.000	1.60	42	.117	1.71	31.15	.096

Independent samples of CODE

Group 1 : COD EQ 1 Group 2 : COD EQ 2

t-test for : CL

	Number of cases	Mean	Standard Deviation	Standard Error
Group 1	24	95.6250	6.205	1.267
Group 2	20	111.7300	18.263	4.084

		Pooled Variance Estimate			Separate Variance Estimate		
F value	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.
8.66	.00	-4.06	42	.000	-3.77	22.66	.001

Independent samples of CODE

Group 1 : COD EQ 1 Group 2 : COD EQ 2

t-test for : CO2

	Number of cases	Mean	Standard Deviation	Standard Error
Group 1	24	24.5875	3.182	.772
Group 2	20	25.6200	1.467	.328

		Pooled Variance Estimate			Separate Variance Estimate		
F value	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.
6.65	.000	-1.15	42	.257	-1.23	30.84	.228

Independent samples of CODE

Group 1 : COD EQ 1 Group 2 : COD EQ 2

t-test for : HEIGHT

	Number of cases	Mean	Standard Deviation	Standard Error
Group 1	45	153.2667	10.532	1.570
Group 2	20	160.2500	7.070	1.581

		Pooled Variance Estimate			Separate Variance Estimate		
F value	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.
2.22	.062	-2.70	63	.009	-3.13	52.79	.003

Independent samples of CODE

Group 1 : COD EQ 1 Group 2 : COD EQ 2

t-test for : WEIGHT

	Number of cases	Mean	Standard Deviation	Standard Error
Group 1	45	35.4222	10.051	1.498
Group 2	20	40.3500	10.205	2.282

		Pooled Variance Estimate			Separate Variance Estimate		
F value	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.
1.03	.897	-1.82	63	.074	-1.81	36.02	.079

Independent samples of CODE

Group 1 : COD EQ 1 Group 2 : COD EQ 2

t-test for : BMI

	Number of cases	Mean	Standard Deviation	Standard Error
Group 1	45	14.9818	2.718	.405
Group 2	20	17.2695	1.790	.400

		Pooled Variance Estimate			Separate Variance Estimate		
F value	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.
2.31	.051	-3.44	63	.001	-.02	53.60	.000

Independent samples of CODE

Group 1 : COD EQ 1 Group 2 : COD EQ 2

t-test for : AGE

	Number of cases	Mean	Standard Deviation	Standard Error
Group 1	45	20.4444	4.827	.120
Group 2	19	23.9414	4.223	.969

		Pooled Variance Estimate			Separate Variance Estimate		
F value	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.
1.31	.548	-2.75	62	.008	-2.90	38.54	.006

Independent samples of CODE

Group 1 : COD EQ 1 Group 2 : COD EQ 2

t-test for : SEX

	Number of cases	Mean	Standard Deviation	Standard Error
Group 1	45	1.3333	.477	.071
Group 2	19	1.1579	.375	.086

		Pooled Variance Estimate			Separate Variance Estimate		
F value	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.
1.62	.268	1.43	62	.159	1.57	42.84	.123

Independent samples of CODE

Group 1 : COD EQ 1 Group 2 : COD EQ 2

t-test for : FBS

	Number of cases	Mean	Standard Deviation	Standard Error
Group 1	43	21.2465	6.204	.946
Group 2	20	4.7050	.497	.111

		Pooled Variance Estimate			Separate Variance Estimate		
F value	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.
155.95	.000	11.85	61	.000	17.36	43.15	.000

Independent samples of CODE

Group 1 : COD EQ 1 Group 2 : COD EQ 2

t-test for : P2ABF

	Number of cases	Mean	Standard Deviation	Standard Error

Group 1	43	30.2884	7.656	1.167
Group 2	20	5.7650	.432	.097

		Pooled Variance Estimate			Separate Variance Estimate		
F value	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.
314.08	.000	14.25	61	.000	20.93	42.57	.000

Independent samples of CODE

Group 1 : COD EQ 1 Group 2 : COD EQ 2

t-test for : HBA1

	Number of cases	Mean	Standard Deviation	Standard Error
Group 1	43	13.4674	2.564	.391
Group 2	20	5.1200	.304	.068

		Pooled Variance Estimate			Separate Variance Estimate		
F value	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.
71.27	.000	14.45	61	.000	21.04	44.48	.000

Annexture

PATIENTS CASE RECORD FORM

Ref. No_____ Date_____

Name of the Patient:

Father's /husband's Name:

Age: Sex: Religion:

Home District:

Rural or Urban:

Mailing Address:

Education:

Illiterate Primary SSC

HSC Graduate Postgraduate/ Masters

Occupation: Unemployed/ Service/ Doctor/ Engineer/ House wife
Teacher/ Defense Service/ Farmer/ Land Lord / Land less/ Others

Type of Work: Physical Mental Both

Physical exercise:

Monthly income: Tk...../ month

Total members of the family:

Sanitation: Latrine type Cleanness Fly proof

Water Supply

Source: Distance from house: Purity:

House: Pacca Tin Kaccha
Floor Roof Wall

Habit Tobacco Alcohol Betel
Panta rice Dried fish

Past History Measles Mumps Ch. Pox
RTI Enteritis Jaundice
Helmenthiasis

Abdomenal pain suggestive of Pancriatitis

Large, bulky loose stool

Past history of malnutrition (Puffy face, oedema, hair, ascitis, skin, gum, mouth ulcers):

Family history of Diabetes: Present/Absent

Father:

Mother:

Both parents:

Brothers and Sisters:

Cousin (maternal):

Cousin (paternal):

Uncle/Aunt (Pat):

Uncle/Aunt (Mat):

Physical examination:

Anthropometric study

Height Weight

BMI

A. Biochemical Tests:
- FBS
- HbA_1C
- Lipid profile (fasting)
- STP
- Serum Electrolyte
- Serum Amylase

B. Immunology : C3 C4
- HLA typing
- Blood Group RhD

C. Histopathology of Pancreas
- Light Microscopy: FCPD
  Chronic Pancreatitis
- Immunohistochemestry(IHC)

D. Others: Montaux Test (MT)

E. Radiology and Imaging:
- USG of Abdomen
- Plain X-Ray Abdomen
- ERCP

Consent Form

I ---------- S/O,D/O Mr/Mrs-------

---------- Address ----------

Upazilla----------District----------

Hereby by give consent to give blood for this research work. The research work was explained to me I was assured of confidentiality and any assistance in case of need. I shall not make liable anybody for any disability.

Name & Signature of the Patient

Name & signature of the collecting doctor

Date:.....

Annexture-4

বাংলাদেশ ডায়াবেটিক সমিতি
ইব্রাহিম মেমোরিয়াল ডায়াবেটিক সেন্টার
১২২, কাজী নজরুল ইসলাম এভিনিউ
শাহবাগ, ঢাকা-১০০০।

নং-বার্ডেম/ডিডি/৯০/৫৬৯ তাং- ২/৭/৯০ ইং।

" নোটিশ "

এতদ্দ্বারা সকলের অবগতির জন্য জানানো যাইতেছে যে, বার্ডেম একাডেমীর কোর্স কো-অর্ডিনেটর (সহকারী অধ্যাপক, ডাঃ মোঃ তাহমিনুর রহমান) "Aetio Pathology of Diabetic Nephropathy in Khulna Patients" শীর্ষক গবেষণায় ঢাকা বিশ্ববিদ্যালয়ের পোষ্ট গ্রাজুয়েট ফ্যাকালটীর অধীনে পি এইচ ডি গবেষণা কাজ শুরু করিয়াছেন। এ ব্যাপারে তাহাকে সকল প্রকার সহযোগিতা করার জন্য বিশেষ ভাবে বলা হইল।

অনুলিপি অবগতি ও প্রয়োজনীয় ব্যবস্থা
গ্রহণের জন্য প্রেরিত হইল :-

(ডাঃ এ, আর, খান)
মেডিকেল সুপারিনটেন্ডেন্ট (অবঃ)
ডি, ডি, সি, সি
বার্ডেম।

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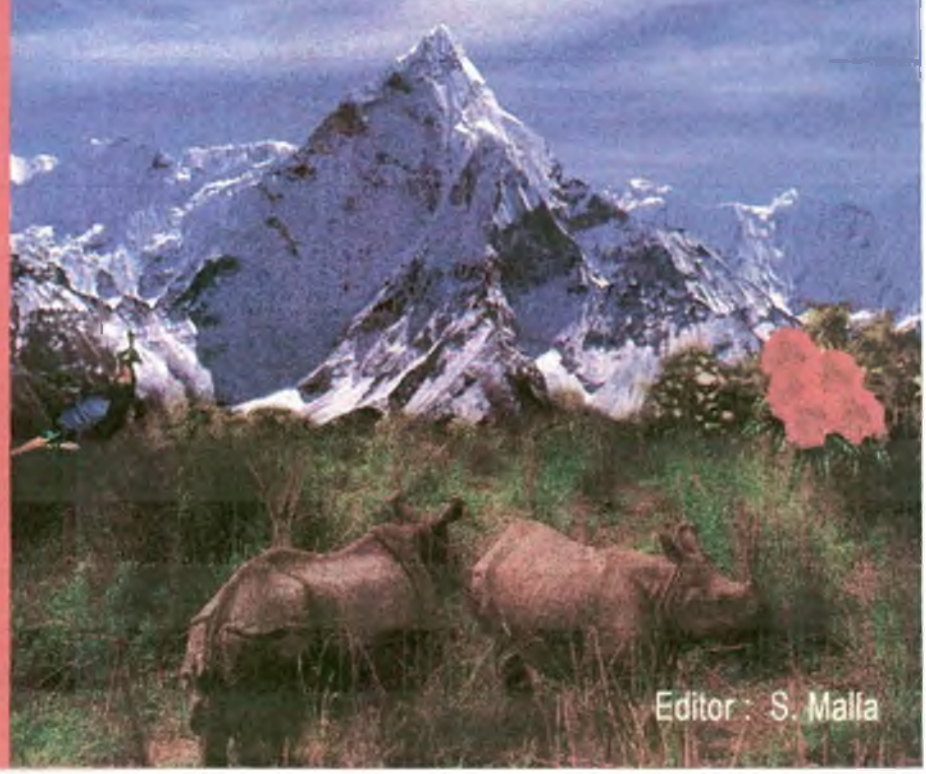
BOOK OF ABSTRACTS



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AETIOPATHOLOGY OF MALNUTRITION RELATED DIABETES MELLITUS (MRDM) IN BANGLADESHI SUBJECTS

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Summary

MRDM is insulin requiring special type of diabetes. The patients are undernourished, usually under 30 years of age and low BMI<17. They require large doses of insulin for glycaemic control, but due to some insulin reserve do not develop ketoacidosis. This type of diabetes is common in the least developing countries of the world including Bangladesh. In Bangladesh MRDM accounts for about 30% of total registered patients at BIRDEM (Diabetic Hospital). Many factors are implicatd in the etiopathology of MRDM in different parts of the world like malnutrition, infection, food habits like increased consumption of cassava, immunological destruction of pancreartic beta cells etc. But the exact etipathogenesis is unknown. With this back ground the present study was undertaken to find out some etiological factors of MRDM in Bangladesh.

Subjects

A total of 45 MRDM patients attending BIRDEM Hospital and 20 age and sex matched control were randomly selected for this study. Their detail clinical history, family history, dietary history and diabetic history were recorded in a prescribed proforma after taking verbal and written consent of the subjects. Blood samples were taken to see the glycaemic status, lipid profile, renal function tests, Amylase, electrolytes, HLA ABC typing, blood grouping and estimation of immunoglobulin and complements C3,C4. Histopathology of pancreatic tissue some selected cases were also done particularly from the patients having stone in the pancreas.

Results

Results were compiled, tabulated and statistical significance were looked for using students test and chisquare test and multivarience analysis. The results showed dyslipidemia, high triglyceride, low HDL and cholesterol levels present in MRDm patients in comparison to the control.The result was statistically significant. Immunological tests showed higher level of IgA and C4 level in MRDM patients than controls which was also statistically significant. Renal function tests showed higher urea, creatinine and lower total protein in MRDm patients than controls. Electrolyte study showed higher normal value of K^+ than controls. Genetic association was observed in MRDM patients showing increased frequency of HLA A2, CW5, CW6 in MRDM patients than control where the HLA haplotype A9 and A11, CW4 were more. Histopathological studies of pancreatic tissue from 15 patients showed marked fibrosis, glandular atrophy and dense chronic inflammatory infiltrate pointing towards an immunological mediated injury of Pancreas

Conclusion

It is evident from the present study that the etiopathology of MRDM in Bangladdesh is probably due to immunological abnormality, dyslipidemia, HLA association and associated with abnormal renal function. Further study with large number of subjects are required to substantiate it.

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Curriculum Vitae

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Educational Qualifications

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MBBS	1974 held in 1976	Dhaka Medical College, Dhaka University	Passed, Regular
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Experiences
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Medical Officer	Sylhet Medical College Hospital, Thana Health Complex,Bogra, IEDC&R,Dhaka	12.07.77 to 31.7.80	Resigned from Govt.Service on 31.7.80
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Professor & Head	Pathology, Ibrahim Medical College	24.11.04 till date	Full time, Non Practising
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	c. USM, Malaysia	3 years practical training on Histo & , Cytology , FNAC, Post Mortem as a teacher of Pathology(2001-04)	Full time
	d. Guys & St,Thomas;s Hospital, London	Training on Immunohistochemistry under Prof,Mary Dyson & Dr.Robin Poston(1998)	Fulltime

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