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The epidemiology of cystic fibrosis related diabetes (CFRD) in cystic fibrosis patients attending the adult cystic fibrosis clinic at the Charlotte Maxeke Johannesburg Academic Hospital

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2012-01-27
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THE EPIDEMIOLOGY OF CYSTIC FIBROSIS RELATED DIABETES (CFRD) IN CYSTIC FIBROSIS PATIENTS ATTENDING THE ADULT CYSTIC FIBROSIS CLINIC AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfillment of the requirements for the degree of Master of Medicine in the branch of Internal Medicine

Johannesburg, 2011

I, Marc Romain, declare that this thesis is my own work. It is being submitted for the degree of Master of Medicine in the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

……

15th day of March 2011
Final submission

In appreciation to my wife Heidi and children, Batya Sarah and Ashira Ora, for your constant love and support

ABSTRACT

Background
Cystic fibrosis (CF) is one of the most common fatal autosomal recessive inherited conditions in the Caucasian population. Survival of patients with cystic fibrosis has increased due to optimal medical therapy and as a consequence, later complications such as cystic fibrosis related diabetes (CFRD) may develop.

Materials and methods
A retrospective patient file review was conducted on all the patient files in the Adult Cystic Fibrosis Unit, Ward 496, Charlotte Maxeke Johannesburg Academic Hospital. The aim of the review was to determine the prevalence of Cystic fibrosis related diabetes (CFRD) and to determine the characteristics of patients with CFRD in terms of age, gender, genotype, lung function, body mass index (BMI), $HBA1_c$, use of corticosteroids and pancreatic function.

Patients were classified as normal glucose tolerance, impaired glucose tolerance or CFRD based on the results of oral glucose tolerance testing. For statistical analysis, patients with impaired glucose tolerance and CFRD were analyzed together under the group abnormal glucose homeostasis.

50 patient files were reviewed.

Results
12 patients (24%) had normal glucose tolerance, 10 (20%) had impaired glucose tolerance, 23 (46%) had CFRD without fasting hyperglycaemia and 3 patients (6%) had CFRD with fasting hyperglycaemia. 2 patients (4%) did not have OGTT done and therefore could not be categorised. The prevalence of CFRD was 54 % (including all patients with CFRD without fasting hyperglycaemia and patients with CFRD with fasting hyperglycaemia). 75 % of patients had abnormal glucose homeostasis. Statistical analysis failed to demonstrate any significant difference in the characteristics of patients with and without CFRD. This may be related to the small sample size. $HBA1_c$ values were higher in patients with abnormal glucose homeostasis compared to patients with normal glucose tolerance.

Conclusions
The prevalence of CFRD in the adult cystic fibrosis population at Charlotte Maxeke Johannesburg Academic Hospital correlates with the prevalence of CFRD in other cystic fibrosis centres. There were no statistically significant differences in the characteristics of patients with and without CFRD.

ACKNOWLEDGEMENTS

1. Thank you to Professor Mervyn Mer for assisting me with the choice of an appropriate research topic for my MMed, for supervising the process and for guiding me through the research report.

2. Thank you to Doctor Alison Bentley for all the succinct and practical lectures delivered which guided me through the research process and for all the assistance during my research.

3. Thank you to Elena Libhaber for teaching me the necessary tools for the statistical analysis of my MMed and for assisting in the final analysis.

4. Thank you to Doctor Cathy Baird from the adult cystic fibrosis clinic at Charlotte Maxeke Johannesburg Academic Hospital for providing me with access to the patient files. The patient record review was made easier by the excellent note keeping in the clinic.

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1.0 INTRODUCTION

This research report involved a retrospective patient file review on all the patient files in the adult cystic fibrosis (CF) unit, Ward 496, Charlotte Maxeke Johannesburg Academic Hospital. The research report fulfils part of the requirements for the degree of Master of Medicine in the branch of Internal Medicine.

The patient population under review included all the patients attending the cystic fibrosis clinic from 2004 till November 2009. The aim of the research report is to determine the prevalence of CFRD in this population of CF patients and to determine the characteristics of the patients with CFRD in terms of age, gender, genotype, lung function, body mass index (BMI), $HBA1_c$, use of corticosteroids and pancreatic function. There is currently no data available in South Africa regarding these statistics.

The research report will begin with a literature review focusing on cystic fibrosis and specifically cystic fibrosis related diabetes (CFRD). The epidemiology, pathogenesis, complications, diagnosis and management of CFRD will be discussed. The methods used in the research report including details of the statistical analyses will be mentioned. The results of the retrospective review will be presented and compared with data from other cystic fibrosis centres.

1.1 Literature review

Cystic fibrosis is one of the most common fatal autosomal recessive inherited conditions in the Caucasian population with an incidence of 1 per 2500 live births. The genetic defect involves the long arm of Chromosome 7 and results in abnormal

synthesis of the cystic fibrosis transmembrane regulator (CFTR). This protein is responsible for regulation of water and electrolyte composition of bodily fluids and defects in the CFTR result in abnormal viscous secretions leading to mucus plugs which precipitate pulmonary, pancreatic, gastrointestinal and genitourinary complications. A patient with CF may present with chronic airway infections with resultant bronchiectasis, exocrine pancreatic insufficiency, intestinal dysfunction, urogenital dysfunction and abnormal sweat gland function. The degree of clinical dysfunction depends primarily on which mutations are present in a patient with cystic fibrosis.

There are over 1500 known mutations, which are divided into five classes based on phenotypic severity of the cystic fibrosis. Classes I – III are associated with more severe clinical symptoms due to major abnormalities in the CFTR channel. Classes IV – V lead to milder forms of disease (Rowe, Miller & Sorscher 2005).
The most common mutation is the ΔF508 mutation (loss of a phenylalanine residue at position 508). It is a class II mutation and is identified in 70% of CF patients (Preumont, Hermans & Buysschaert 2008). Patients are classified as homozygous if both alleles have the ΔF508 mutation and heterozygous if only one ΔF508 mutation is present.

Survival rates among cystic fibrosis patients have improved due to optimal medical management and the current life expectancy is around 37.4 years according to the CF Foundation Registry (Marshall et al. 2009). As a consequence of improved survival, later complications may develop such as cystic fibrosis related diabetes (CFRD) and cystic fibrosis related bone disease.

1.2 Cystic fibrosis related diabetes

The American Diabetes Association classifies diabetes into four categories namely, Category I (Type 1), Category II (Type 2), Category III (Other specific types) and Category IV (Gestational diabetes). CFRD is classified in the category of 'Other specific types [of diabetes]' (Category III) under the sub-heading 'C. Diseases of the exocrine pancreas'.

Other types of diabetes included under this heading refer to diabetes due to pancreatitis, trauma, neoplasia and haemochromatosis.

CFRD shares features of both type 1 and type 2 diabetes.

1.2.1 Epidemiology

CFRD has an average age of onset of 18 – 21 years (Lanng et al. 1994a) with less than 10% of cases of occurring before the age of 10 and more than 40% of cases occurring in patients older than 30 years (Lanng et al. 1994a, Lanng et al. 1995).

The prevalence of CFRD among European patients with cystic fibrosis approximates 12 % in children and 30 % in adults with an average age dependent increase of 4-9% (Lanng et al. 1995, Adler et al. 2007). In Denmark, annual oral glucose tolerance screening is performed on all CF patients and the prevalence of CFRD is 50 % of the CF population older than 30 years of age (Lanng et al. 1994a). A recent study of the Dutch CF population showed the prevalence of CFRD to be 40% overall and this figure rose to 52% in patients older than 40 years (van den Berg, Kouwenberg & Heijerman 2009).

A study performed in 1999 in Italy followed CF patients over a 10 year period and showed that 42.8% of patients developed diabetes over the 10 year period (Cucinotta et al. 1999).

The CF patient group receiving treatment at the University of Minnesota in America had a prevalence of CFRD of 2% of children, 19% of adolescents and 40-50% of adult (Moran et al. 2009).

The risk for developing CFRD is increased with increasing age, presence of exocrine pancreatic insufficiency, ΔF508 homozygous genotype, lower BMI and female gender (Marshall et al. 2005, Bismuth et al. 2008, Blackman et al. 2009, van den Berg, Kouwenberg & Heijerman 2009). It is unclear whether the use of corticosteroids is associated with an increased incidence of CFRD (Marshall et al. 2005).

1.2.2 Pathogenesis

Glucose metabolism is influenced by many factors in patients with Cystic Fibrosis including malnutrition, elevated energy expenditure, acute and chronic infections, glucagon deficiency, malabsorption, abnormal transit time of glucose in the GUT, liver disease and increased work of breathing (Marshall et al. 2005).

Insulin is secreted by the beta (β) cells of the pancreatic Islets of Langerhans in response to a glucose load in normal healthy individuals. The release of insulin occurs in two phases namely first-phase and second-phase insulin release.

First phase insulin release results in a rapid increase in plasma insulin after ingestion of a glucose load. The first phase insulin release prevents postprandial hyperglycaemia. Second-phase insulin release follows first-phase insulin release and results in slower, sustained release of insulin.

In CFRD patients, there is defective pancreatic β cell function due to progressive destruction and fibrosis of the β cells as well as amyloid deposition and fatty infiltration of the pancreas. This results in defective first- phase insulin release resulting in a delayed peak in insulin secretion which results in postprandial hyperglycaemia. In this way, CFRD shares features of Type 1 diabetes but patients with CFRD are not prone to ketoacidosis (Mohan et al. 2009).

Type 2 diabetes is characterized by insulin resistance. The role of insulin resistance in the pathogenesis of CFRD remains unclear. Insulin sensitivity in a patient with CF may vary at any given point in time and is affected by the individual's age, nutritional status, degree of underlying pulmonary disease and the presence and severity of underlying chronic infections (Lombardo et al. 2003). A patient may therefore have normal, decreased or increased insulin sensitivity.

Patients may therefore experience fluctuations in their degree of glucose intolerance depending on their overall health, nutritional status and concurrent medication usage (including corticosteroids) (Zirbes, Milla 2009).

1.2.3 Complications

CFRD is associated with increased morbidity and results in a six-fold increase in mortality (Mohan et al. 2009). Patients with CFRD are reported to have a median survival of 35.6 years compared to non-CFRD patients who have a median survival of 47.0 years. Female patients with CFRD have higher mortality rates than male patients who appear to have the same mortality as patients without CFRD (Milla, Billings & Moran 2005).

Microvascular complications of diabetes namely retinopathy, nephropathy, gastropathy and neuropathy occur in patients with CFRD. The risk of macrovascular complications does not appear to be increased (Schwarzenberg et al. 2007).

Patients with CFRD have been reported to have a lower forced expiratory volume in one second (FEV_1), a more rapid decline in pulmonary function and have more frequent pulmonary exacerbations than patients without CFRD. These findings may either indicate that patients with more severe cystic fibrosis may develop CFRD or it may indicate that CFRD itself, contributes to disease progression and is not only a marker of advanced disease (Lanng et al. 1994b).

CFRD is also associated with greater nutritional compromise that results in stunted growth and further deterioration in lung function (Lanng et al. 1994b). Insulin is an anabolic hormone and the relative insulin deficiency may in part explain the nutritional compromise (Marshall et al. 2005). The above factors, namely lower

FEV_1 and greater nutritional compromise, raise an important question. Are sicker patients more likely to develop CFRD or does the presence of CFRD make patients with CF sicker? (Marshall et al. 2005).

Initiation of insulin therapy results in weight gain and an improvement in pulmonary function suggesting that insulin deficiency is a direct cause of the declining health status (Lanng et al. 1994b). A further study showed that the rate of decline in pulmonary function was directly proportional to the degree of glucose intolerance and an inverse relationship was demonstrated between the rate of decline in pulmonary function and the level of insulin secretion at baseline (Milla, Warwick & Moran 2000). This study further supports the fact that insulin deficiency leads to the deterioration in health status.

1.2.4 Diagnosis and Screening

CFRD should be considered in all CF patients with symptoms of diabetes like polyuria and polydipsia, poor weight gain, poor growth velocity and unexplained chronic decline in pulmonary function. The decline in pulmonary function and weight may predate the diagnosis of CFRD by about 6 years.

Oral glucose tolerance testing (OGTT) is the recommended screening method for the detection CFRD (UK Cystic Fibrosis Trust Working Group 2004). According to the UK CF trust working group, a screening OGTT is suggested for CF patients older

than 12 years old. The American CF consensus guidelines suggest routine OGTT for CF patients older than 10 years (Yankaskas et al. 2004).

Three days prior to an OGTT the patient should consume at least 150g/day of carbohydrate and then fast overnight prior to the test. The OGTT is then performed by giving an oral glucose load of 1.75g/kg (Maximum 75g) mixed with 300mls of water to the patient to be ingested within 5 minutes. Blood samples are collected before the ingestion of the glucose and 2 hours after ingestion. The OGTT should be performed during periods of clinical stability as acute illness and stress may affect glucose metabolism.

Four categories of glucose tolerance are recognized based on the OGTT (Table 1.1):

- Normal glucose tolerance (NGT)
- Impaired glucose tolerance (IGT)
- CFRD without fasting hyperglycaemia
- CFRD with fasting hyperglycaemia

(Moran et al. 1999)

The criteria for the diagnosis of CFRD include:

- 2 hour plasma glucose (PG) > 11mmol/l during a 75g OGTT
- Fasting plasma glucose (FPG) > 7mmol/l on two or more occasions
- FPG > 7mmol plus casual glucose level of > 11.1mmol/l
- Casual glucose levels > 11.1 on two or more occasions with symptoms

Table 1.1: Categories of glucose tolerance in patients with CF based on response to oral glucose tolerance testing

Condition	**Fasting plasma glucose** (mmol/l)	**2 hour plasma glucose** (mmol/l)
Normal glucose tolerance (NGT)	<7	<7.8
Impaired glucose tolerance (IGT)*	<7	7.8 – 11.1
CFRD without fasting hyperglycaemia*	<7	> 11.1
CFRD with fasting hyperglycaemia*	>7	OGTT not indicated

*Abnormal glucose homeostasis

From the table it can be seen that patients with fasting plasma glucose levels > 7 mmol/l on two or more occasions are classified as having CFRD with fasting hyperglycaemia. A fasting plasma glucose level that is < 7 mmol/l will miss patients with CFRD without fasting hyperglycaemia and therefore an OGTT should be performed on all patients (Moran et al. 1999).

It is also possible to classify patients based on the oral glucose tolerance test into two groups, namely normal glucose tolerance and abnormal glucose homeostasis. The latter group includes patients with impaired glucose tolerance, CFRD without fasting hyperglycaemia and CFRD with fasting hyperglycaemia (Preumont, Hermans & Buysschaert 2008).

Oral glucose tolerance testing, while being the preferred method for screening, has a few drawbacks. The OGTT creates artificial glucose conditions in the patients and the current guidelines for interpretation of the test are based on other patients with diabetes, not specifically patients with CFRD. The cut-off points for diabetes according to the OGTT are based on data relating to prevention of cardiovascular complications. Patients with CFRD often show a decline in overall health before any abnormality will be seen on the OGTT and perhaps lower values should be used in the diagnosis of CFRD. As discussed earlier, glucose homeostasis in the patient with CF is affected by many factors and this may play a role in the interpretation of the test. For this reason, the test should be performed during periods of clinical stability.

Due to the problems associated with the OGTT, continuous glucose monitoring (CGM) is another tool that has now been used to assess CFRD. The test offers a broader view of glucose control under real life situations as opposed to the artificial conditions created by the OGTT. Earlier abnormalities in glucose tolerance may be detected using CGM. The test is costly and time consuming and is only being used in research studies (Franzese et al. 2008).

Haemoglobin $A1_c$ ($HBA1_c$) is used to determine the long term glycaemic control in patients with diabetes. $HBA1_c$ should not be used as a screening test for CFRD as the values are usually normal in patients with CFRD. There are numerous reasons for this. In the early phases of CFRD, intermittent hyperglycaemia is present and this may not be intense or prolonged enough to raise the $HBA1_c$. Another theory is that red cell survival may be shortened in patients with CF due to the effects of chronic inflammation thus leading to spuriously low $HBA1_c$ levels (Lanng et al. 1995).

No matter how CFRD has been diagnosed, correct management is vital to limit the significant complications associated with the condition.

1.2.5 Management

Insulin remains the mainstay of treatment for patients with CFRD based on the pathophysiology of the disease. Patients with CFRD with fasting hyperglycaemia will definitely require insulin. Patients with CFRD without fasting hyperglycaemia and patients with impaired glucose tolerance may require insulin especially during times of stress and illness as well as when taking medications like corticosteroids as their glucose homeostasis will change during these times.

Oral agents like sulphonylureas and glyburide have been used for patients with CFRD without fasting hyperglycaemia in an attempt to improve insulin sensitivity. There is no evidence to suggest that they are of any benefit as the primary problem in CFRD is insulin deficiency. There is a concern about toxicity with oral agents as sulphonylureas bind to CFTR and glyburide is eliminated in the bile and toxic levels may increase in patients with Cystic Fibrosis (Moran et al. 1999).

The patient with CFRD should be managed in a specialist unit as there are some important differences and considerations compared to other patients with type 1 and type 2 diabetes. The dose of insulin will need to be adjusted during stress, illness and when taking corticosteroids. Many patients with CF have increased sputum production during the morning and as a result may not eat breakfast. The dose of insulin may therefore need to be decreased in the morning (Alexander, Bridges 2010). Some CF patients receive nasogastric feeds at night to supplement their diet and insulin requirements may increase at night.

Diet modification is very different when compared to other patients with diabetes. Patients with CF are catabolic due to chronic inflammation and will require an increased amount of calories. High glycaemic index foods and beverages should be avoided (Alexander, Bridges 2010).

2.0 METHODS

2.1 Study sample

This study involved a retrospective patient file review on all the patient files in the Adult Cystic Fibrosis Unit, Ward 496, Charlotte Maxeke Johannesburg Academic Hospital. This included all files currently available from the inception of the clinic in 2004 till November 2009. The total number of files reviewed was 50. The file review was conducted from September to November 2009.

The retrospective patient file review was performed after obtaining ethical clearance from the Human Research Ethics Committee at the University of the Witwatersrand (Reference R14/49, clearance certificate M090905). Written permission to perform the study was also obtained from the acting Chief Executive Officer (CEO) of Charlotte Maxeke Johannesburg Academic Hospital, Dr S.B. Mfenyana.

2.2 Study information

The following information was obtained from the patient files:

- Age at most recent visit (in years)
- Sex
- Genotype based on evidence available at the time of record review

  Patients were classified into three groups:

  - Homozygous for ΔF508 mutation if two ΔF508 mutations were present
  - Heterozygous for ΔF508 mutation if only one ΔF508 mutation was present
  - Other if two other mutations were present
- Body mass index (BMI) as at most recent visit in kg/m^2

- Lung function based on the most recent forced expiratory volume in 1 second (FEV_1) in liters per second and percentage of calculated value.
- Degree of exocrine pancreatic insufficiency was assessed by the amount of pancreatic enzyme replacement required in the (Creon)
- Corticosteroid usage was determined. If corticosteroids had been used at any point during the patient's time at the CF clinic (2004 to 2009), the duration, cumulative dose and maximum single dose of corticosteroid used were documented. All corticosteroids used were converted to the equivalent dose of prednisone. The total duration of corticosteroid usage over the years that the patient attended the CF clinic as well as the maximum single course dosages were used in the data analysis.
- Evidence of CFRD based on the most recent OGTT
- $HbA1_c$ based on the most recent blood tests performed at the CF clinic.

2.3 Statistical analysis

The information collected from the files was placed onto a data sheet and later formulated into an Excel spreadsheet to facilitate data analysis. The data was analyzed using basic statistics on Excel as well as Statistica (Version 8.0, Statsoft, USA) for continuous variables. For categorical variables the statistical program SAS (Version 9.2, SAS Institute Inc., USA) was used.

The 50 patients were analysed together to obtain baseline characteristics of the group as well as to determine the prevalence of CFRD. The data was then divided into 4 groups for further analysis based on glucose tolerance as normal glucose tolerance,

impaired glucose tolerance, CFRD without fasting hyperglycaemia and CFRD with fasting hyperglycaemia.

For subsequent analysis, the patients with CFRD including CFRD without fasting hyperglycaemia and CFRD with fasting hyperglycaemia were analysed together.

Final analysis was performed comparing patients with normal glucose tolerance to patients with abnormal glucose homeostasis. This latter group included patients with impaired glucose tolerance, CFRD without fasting hyperglycaemia and CFRD with fasting hyperglycaemia.

Prevalence was expressed as a percentage.

The continuous variables (age, BMI, lung function, creon dosage, duration of corticosteroid use, maximal single course of corticosteroid use, $HBA1_c$) were expressed as median and range, as all data was non-normally distributed. Comparison between two groups of patients (normal glucose tolerance and abnormal glucose homeostasis) was performed using the Mann-Whitney test as data was non-normally distributed. When three groups were compared (normal glucose tolerance, impaired glucose tolerance and CFRD) continuous variables were compared using the Kruskal Wallis test.

The categorical variables (sex, genotype, creon required and corticosteroid required) were expressed as frequency, percentage or proportion. The two groups of patients (normal glucose tolerance and abnormal glucose tolerance) were compared using the Fisher exact test.

When three groups were compared (normal glucose tolerance, impaired glucose tolerance and CFRD) categorical variables were also compared using the Fisher exact test.

Significance was set at a p value of < 0.05.

3.0 RESULTS

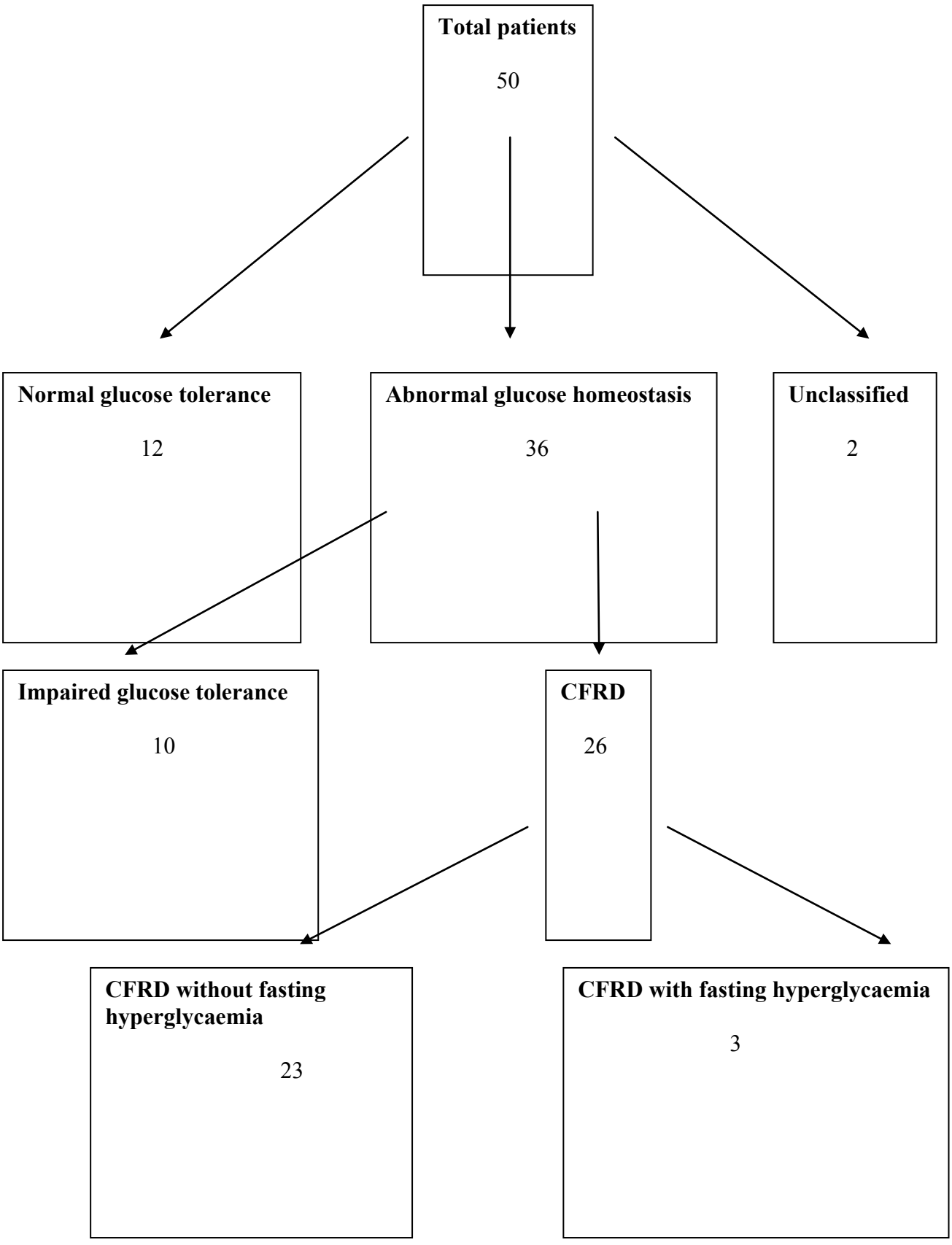
3.1 Overall results (Table 3.1)

Fifty patient files were reviewed. There were 24 male and 26 female patients.
The median age of patients attending the clinic was 24.7 years (Range 17.1 – 51.0 years).
A total of 32 patients (64%) were homozygous for Δ F508 mutation, 14 patients (28%) were heterozygous and 4 patients (8%) had two other mutations excluding ΔF508.
On the basis of an oral glucose tolerance test, 12 patients (24%) had normal glucose tolerance, 10 (20%) had impaired glucose tolerance, 23 (46%) had CFRD without fasting hyperglycaemia and 3 patients (6%) had CFRD with fasting hyperglycaemia. 2 patients (4%) did not have OGTT done and therefore could not be categorized. These 2 patients did not have pancreatic insufficiency (Figure 3.1).

The median BMI was 19.9 kg/m^2 (Range 15.6 to 28.0 kg/m^2) which is in the normal range for BMI.

Pulmonary function testing revealed a median FEV_1 of 2.2 litres per second (Range 0.6 to 4.0 litres/s) and a median percentage predicted FEV_1 of 59.6 % (Range 14.0 to 106.0 %). This is lower than the expected 80 % for normal subjects.

Figure 3.1: Number of patients within each group based on OGTT



Forty eight patients (96%) had pancreatic insufficiency and 2 patients (4%) had no pancreatic insufficiency. Of the 48 patients who had pancreatic insufficiency, 46 required lipase enzyme replacement (96%). The median amount of Creon required per day was 275 000 lipase units (Range 30 000 to 1 000 000 lipase units)

Thirty two patients (64 %) had never required intravenous or oral corticosteroid treatment during their time at the clinic (2004 to 2009) and 18 patients (36%) had. The median total corticosteroid dose received by these 18 patients during their time in the clinic was 607.5 mg (Range 20-1995mg).

The maximum single course dosage of corticosteroids was 385mg (Range 20-700mg). The median total duration of corticosteroid usage was 18.5 days (Range: 1- 158 days). 47 patients had an $HBA1_c$ performed with a median of 5.8 % (Range 5.0 to 12.9%)

Two patients did not have OGTT and therefore could not be classified into any of the above groups. These patients did not have pancreatic insufficiency and have never required corticosteroids. These patients were not included in subsequent statistical analysis.

Table 3.1: Characteristics of the CF population according to OGTT

	Normal glucose tolerance	**Impaired glucose tolerance**	**CFRD without fasting hyperglycaemia**	**CFRD with fasting hyperglycaemia**
Number	12	10	23	3
Sex: [n,(percent)]				
Male	5 (42)	6 (60)	11 (48)	0 (0)
Female	7 (58)	4 (40)	12 (52)	3 (100)
Genotype: [n,(percent)]				
Homozygous	6 (50)	7 (70)	14 (61)	3 (100)
Heterozygous	4 (33)	3 (30)	7 (30)	0 (0)
Other	2 (17)	0 (0)	2 (9)	0 (0)
Age (Years)*	26.1(20-37)	23.8(17.5-26.6)	25.8(19.1-51.1)	30.3(21.7-32.1)
BMI (kg/m^2)*	20.7(16.5-24.0)	20.1(17.5-27.8)	19.6(15.6-23.8)	23.7(18.3-26.4)
$HBA1_c$ (%)*	5.6 (5.1-6)	5.9 (5-7)	6.0 (5.3-12.6)	8.6 (5.2-12.9)
FEV_1 (litres/s)*	2.4(0.79-4)	2.1(0.77-3.8)	1.6(0.56-3.7)	2.1(1.67-2.8)
FEV_1 percentage predicted (%)*	71.5(26.0-92.0)	52.5(19.0-106.0)	55.0(14.0-93.0)	66.0(58.0-93.0)
Exocrine pancreatic insufficiency (n)	12	10	23	3
Creon required [n, (percent)]	12 (100)	10 (100)	22 (96)	2 (67)
Creon dose (lipase units)*	337500 (30000-1000000)	175000 (40000-750000)	250000 (30000-625000)	462500 (300000-625000)
Corticosteroid treatment [n,(percent)]	2 (17)	3 (33)	11 (48)	2 (67)
Cumulative CS dose (mg)*	880 (590–1170)	720 (550-1180)	625 (20 – 1995)	342.5 (300 – 385)
Maximum single CS course (mg)*	420 (420 – 420)	420 (250-420)	350 (20 – 700)	255 (210 – 300)
Total duration of CS use (days)*	17.5 (13.0 – 22.0)	24.0 (15.0 – 44.0)	22.0 (1.0-158.0)	12.0 (10.0 –14.0)

*Note: All continuous variables are reported as median and range

Key:
BMI = Body mass index
$HBA1_c$ = Haemoglobin A1c
FEV_1 = Forced expiratory volume in 1 second
CS = Corticosteroid

3.2 Results by group

3.2.1 Normal Glucose tolerance compared to abnormal glucose homeostasis

(Table 3.2)

Twelve patients had normal glucose tolerance, 36 patients had abnormal glucose homeostasis including 10 patients with impaired glucose tolerance and 26 patients with CFRD (23 had CFRD without fasting hyperglycaemia and 3 had CFRD with fasting hyperglycaemia)

The continuous variables in each group (age, BMI, FEV_1, percentage predicted FEV_1, creon dose, corticosteroid use, $HBA1_c$) were compared using the Mann Whitney test. All continuous variables except $HBA1_c$ failed to show any significance with p values > 0.05. The $HBA1_c$ value was higher in patients with abnormal glucose homeostasis compared with values in patients with normal glucose tolerance ($p = 0.05$)

The categorical variables in each group (genotype, sex, creon required and corticosteroid required) were compared using the Fisher Exact test. There was no statistical significance between the variables in the two groups.

Table 3.2: Characteristics of patients with normal glucose tolerance vs abnormal glucose homeostasis

	Normal glucose tolerance (n=12)	**Abnormal glucose homeostasis** (n=36)	**p value**
Sex: [n,(percent)] Male Female	 5 (42) 7 (58)	 17 (47) 19 (53)	0.74
Genotype: [n,(percent)] Homozygous Heterozygous Other	 6 (50) 4 (33) 2 (17)	 24 (67) 10 (28) 2 (5)	0.34
Age (Years)*	26.1(20.0-37.0)	24.6(17.5-51.1)	0.51
BMI (kg/m^2)*	20.7(16.5-24.0)	19.7(15.6-27.8)	0.68
$HBA1_c$ (%)*	5.6 (5.1-6.0)	5.8(5.0-12.9)	0.05
FEV_1 (litres/s)*	2.4(0.8-4.0)	2.0(0.56-3.8)	0.12
FEV_1 percentage predicted (%)*	71.5(26.0-92.0)	55(14.0-106.0)	0.10
Creon required [n,percent)]	12 (100)	34 (94)	1.00
Creon dose (lipase units)*	337500 (30000-1000000)	250000 (30000-750000)	0.51
Corticosteroid treatment ([n,(percent)]	2 (17)	16 (44)	0.17
Cumulative CS dose (mg)*	880 (590–1170)	592.5 (20 – 1995)	0.72
Maximum single CS course (mg)*	420 (420 – 420)	325 (20 - 700)	0.35
Total duration of CS use (days)*	17.5 (13.0 – 22.0)	18.5 (1.0 – 158.0)	0.78

*Note: All continuous variables are reported as median and range

Key:
BMI = Body mass index
$HBA1_c$ = Haemoglobin A1c
FEV_1 = Forced expiratory volume in 1 second
CS = Corticosteroid

3.2.2 Impaired glucose tolerance compared to CFRD (Table 3.3)

Twelve patients had normal glucose tolerance, 10 patients had impaired glucose tolerance and 26 patients had CFRD (23 had CFRD without fasting hyperglycaemia and 3 had CFRD with fasting hyperglycaemia).

The continuous variables in each group (age, BMI, FEV_1, percentage predicted FEV_1, creon dose, corticosteroid use, $HBA1_c$) were compared using the Kruskal Wallis test but failed to show any significance with p values all > 0.05. The $HBA1_c$ comparison approached significance though with higher values in patients with impaired glucose tolerance and CFRD (p=0.08 and 0.07).

The categorical variables in each group (genotype, sex, creon required and corticosteroid required) were compared using the Fisher Exact test. There was no statistical significance between the three groups.

Table 3.3: Characteristics of patients with normal glucose tolerance, impaired glucose tolerance and CFRD

	Normal glucose tolerance (n=12)	**Impaired glucose tolerance** (n=10)	**CFRD** (n=26)	**p value**
Sex: [n,(percent)]				
Male	5 (42)	6 (60)	11 (42)	0.69
Female	7 (58)	4 (40)	15 (58)	
Genotype: [n,(percent)]				
Homozygous	6 (50)	7 (70)	17 (65)	0.77
Heterozygous	4 (33)	3 (30)	7 (27)	
Other	2 (17)	0 (0)	2 (8)	
Age (Years)*	26.1(20.0-37.0)	23.8(17.5-26.6)	26.4(19.1-51.1)	0.21
BMI (kg/m^2)*	20.7(16.5-24.0)	20.1(17.47-27.8)	19.6(15.6-26.4)	0.54
$HBA1_c$ (%)*	5.6 (5.1-6.0)	5.9(5.0-7.0)	6.1(5.2-12.9)	0.08
FEV_1 (litres/s)*	2.4(0.8-4)	2.1(0.8-3.8)	1.8(0.6-3.7)	0.17
FEV_1 percentage predicted (%)*	71.5(26-92)	52.5(19.0-106.0)	56.5(14.0-93.0)	0.24
Creon required [n,percent)]	12 (100)	10 (100)	24 (96)	1.00
Creon dose (lipase units)*	337500 (30000-1000000)	175000 (40000-750000)	275000 (30000-625000)	0.64
Corticosteroid treatment [n,(percent)]	2 (17)	3 (33)	13 (50)	0.14
Cumulative CS dose (mg)*	880 (590–1170)	720 (550-1180)	560 (20 – 1995)	0.81
Maximum single CS course (mg)*	420 (420 – 420)	420 (250-420)	300 (20 – 700)	0.5
Total duration of CS use (days)*	17.5 (13.0 – 22)	24 (15.0 – 44.0)	14.0 (1.0-158.0)	0.65

*Note: All continuous variables are reported as median and range

Key:
BMI = Body mass index
$HBA1_c$ = Haemoglobin A1c
FEV_1 = Forced expiratory volume in 1 second
CS = Corticosteroid

4.0 DISCUSSION

The prevalence of CFRD in the population of Cystic fibrosis patients in the Adult Cystic Fibrosis Unit, Ward 496, Charlotte Maxeke Johannesburg Academic Hospital was 54 % (including all patients with CFRD without fasting hyperglycaemia and patients with CFRD with fasting hyperglycaemia). 75 % of patients have abnormal glucose homeostasis (This includes patients with impaired glucose tolerance, CFRD without fasting hyperglycaemia and CFRD with fasting hyperglycaemia).

The risk for developing CFRD is increased with increasing age, presence of exocrine pancreatic insufficiency, lower BMI, ΔF508 homozygous genotype and female gender (Marshall et al. 2005, Bismuth et al. 2008, Blackman et al. 2009, van den Berg, Kouwenberg & Heijerman 2009) It is unclear whether the use of corticosteroids is associated with an increased incidence of CFRD (Blackman et al. 2009).

These potential risk factors were analysed in the cohort of patients attending the CF clinic at Charlotte Maxeke Johannesburg Academic Hospital. 64 % of patients in the clinic are homozygous for the ΔF508 mutation. This figure is lower that the 70 % quoted in the literature (Preumont, Hermans & Buysschaert 2008). The median age of patients attending the clinic was 24.7 years (Range 17.1 – 51.0 years). There was no statistically significant difference in age between the groups of patients. As the cohort of patients increase in age, there may be a difference between patients with and patients without CFRD. The age at onset as well as the prevalence for different age groups was not assessed.

All the patients included in the final analysis (48) had pancreatic insufficiency and this was therefore not an independent risk factor for CFRD in this cohort.

The median BMI of patients in this cohort was 19.9 kg/m^2 (Range 15.6 to 28.0 kg/ m^2). This is within the normal range for BMI and indicates the overall good nutritional status of this cohort of patients. There was no statistically significant difference in BMI between the two groups.

In this cohort, there were 24 males and 26 female patients. The female gender was not associated with a higher incidence of CFRD.

In keeping with other studies, corticosteroid usage was also not associated with a higher incidence of CFRD. Only a small number of patients (36%) had used corticosteroids during their time in the clinic (2004 – 2009) and these corticosteroids were prescribed for a short period (Median 18.5 days).

Pulmonary function in terms of FEV_1 was also analysed to assess whether patients with CFRD had worse pulmonary function when compared to patients without CFRD. The patients with CFRD did not demonstrate worse pulmonary function compared to patients without CFRD. This may be as a result of early screening and diagnosis of CFRD as well as aggressive treatment protocols followed within the unit in terms of limiting invasive respiratory tract infections.

$HBA1_C$ values were compared to ascertain if values were higher in patients with CFRD even though $HBA1_C$ is not used as part of screening for the disease. $HBA1_c$ values were higher in patients with abnormal glucose homeostasis compared to patients with normal glucose tolerance ($p=0.05$). $HBA1_c$ is a marker of long term glycaemic control. The median value of 5.8 % in patients with abnormal glucose homeostasis is still well below the value of 6.5 % - 7.5% accepted as an indicator of tight glycaemic control (National Institute for Health and Clinical Excellence (NICE), 2008). This indicates that patients with abnormal glucose homeostasis are being

managed effectively and are compliant on treatment and as a result, are achieving tight glycaemic control. This value may also indicate that the patients in this cohort are diagnosed early. The overall value of $HBA1_c$ in patients with abnormal glucose homeostasis still remains questionable as patients with cystic fibrosis have chronic inflammation and the life span of the red blood cells will be shortened resulting in lower levels of $HBA1_c$ (Lanng et al. 1995).

The cohort of patients at the CF clinic at Charlotte Maxeke Johannesburg Academic Hospital only includes about 50 patients and therefore only 50 patient files were reviewed. The data was of a high quality and good records were available on all patients. Two patients however did not have OGTT done and could not be classified into any groups and were not included in the comparative analysis.

The small sample size is a limitation of this study. On statistical analysis certain measures like FEV_1 and age may approach significance if larger numbers were available. The patients with impaired glucose tolerance and CFRD (including CFRD without fasting hyperglycaemia and CFRD with fasting hyperglycaemia) were included together in a group called abnormal glucose homeostasis to increase the statistical power. When compared to data regarding prevalence and risk factors for CFRD from CF centres in America and the United Kingdom and Europe this sample size is exceedingly small in comparison. Marshall et al collected data from 8247 CF patients in the Intermountain CF centre in Utah (Marshall et al. 2005).

Adler et al was able to review data from 50 CF clinics in the United Kingdom, which included 8029 patients (Adler et al. 2007). The observed prevalence in this research report was in line with the prevalence of CFRD in these large CF centres.

The significance of their observations with regard to other risk factors may be more significant than the observations in this study based on the larger cohort of patients.

5.0 CONCLUSIONS

Cystic fibrosis is a common autosomal recessive condition. With improved medical care, the survival of patients with CF into adulthood has increased. This has resulted in patients with CF developing complications like cystic fibrosis related diabetes.

A retrospective patient file review was performed on the files in the adult Cystic Fibrosis Unit, Ward 496, Charlotte Maxeke Johannesburg Academic Hospital to determine the prevalence of CFRD in this population. The characteristics of these patients were also noted and analysed to ascertain if any risk factors could be found for the development of CFRD.

The prevalence of CFRD in the population of cystic fibrosis patients in the Adult Cystic Fibrosis Unit, Ward 496, Charlotte Maxeke Johannesburg Academic Hospital was 54 % (including all patients with CFRD without fasting hyperglycaemia and patients with CFRD with fasting hyperglycaemia). 75 % of patients have abnormal glucose homeostasis (This includes patients with impaired glucose tolerance, CFRD without fasting hyperglycaemia and CFRD with fasting hyperglycaemia). The above figures correlate well with data from other centers in the world.

Possibly related to the small sample size, analyses failed to demonstrate any statistically significant difference in the characteristics of patients with and without CFRD. The characteristics analysed included, age, sex, genotype, pulmonary function, corticosteroid use and $HBA1_c$. Of note, the $HBA1_c$ values were higher in patients with abnormal glucose homeostasis compared to patients with normal glucose tolerance.

This is the first study to look at these factors in the South African CF population and only a small cohort of patients has been studied. In the future, collaboration with other cystic fibrosis centres may provide a larger cohort of patients to analyse. This may provide better insight into the prevalence of CFRD in the overall South African CF population as well as insight into the risk factors leading to the development of CFRD.

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ADDENDUM

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Marc Romain

CLEARANCE CERTIFICATE	**M090905**
PROJECT	The Epidemiology of Cystic Fibrosis Related Diabetes (CFRD) in Cystic Fibrosis Patients Attending the Adult Cystic Fibrosis Clinic at CM Johannesburg Academic Hospital
INVESTIGATORS	Dr Marc Romain.
DEPARTMENT	Department of Internal Medicine
DATE CONSIDERED	2009/10/02
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 2009/10/02 **CHAIRPERSON** .....
pp (Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Prof M Mer

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...