"STUDY OF ORAL GLUCOSE TOLERANCE TEST IN FIRST DEGREE RELATIVES OF KNOWN TYPE2 DIABETIC PATIENTS" – A CROSS SECTIONAL HOSPITAL BASED STUDY.

DISSERTATION BY

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In partial fulfillment of the requirements for the award of the degree of

M.D

In

GENERAL MEDICINE

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DECLARATION

I hereby declare that this thesis entitled **"STUDY OF ORAL GLUCOSE TOLERANCE TEST IN FIRST DEGREE RELATIVES OF KNOWN TYPE 2 DIABETIC PATIENTS" – A CROSS SECTIONAL HOSPITAL BASED STUDY"** is a bonafide and genuine research work carried out by me under the guidance of **DR M.S.Biradar Professor & Principal, Dept. of General Medicine** as a part of my post-graduate study in partial fulfillment of the regulations of B.L.D.E University Bijapur, Karnataka,for the award of degree of M.D. (General Medicine) examination to be held in October 2013. This has not formed the basis for the award of degree or diploma to me previously from any University.

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Dr. Sheetal Reddy Desai

ABSTRACT

Title :

"Study of oral glucose tolerance test in first degree relatives of known type2 diabetic patients" – A cross sectional hospital based study.

AUTHORS : Dr Sheetal Reddy Desai, Dr M.S.Biradar.

ABSTRACT :

Background & Objectives

This study was conducted to know the prevalence of pre-diabetes and diabetes amongst the first-degree relatives of type2 DM. DM is characterized by asymptomatic phase between actual onset of hyperglycemia and clinical diagnosis, which has been estimated to last atleast 4-7 years. So screening for early detection of pre-diabetes is recommended to prevent/delay onset of Type2 DM by lifestyle modification, diet and drugs. Although micro vascular complications do not occur at onset of disease, due to delay in diagnosis they are commonly present at the time of diagnosis. Aim of the study was also to detect microvascular complications at the time of diagnosis of DM.

Methods

246 first degree relatives of Type 2 DM patients were screened with 2 hour OGTT for detection of IFG, IGT & Type 2 DM. Detailed clinical examination and relevant investigations were carried out. Newly detected Type 2 DM subjects were examined for microvascular complications.

Results

110 subjects out of 246 have glucose dysregulation. 19 (7.7 %) have isolated IFG, 37 (15 %) have isolated IGT, 39 (15.9 %) have both IFG & IGT and 15 (6.1 %) were diagnosed to have Type 2 DM-(newly detected). Amongst the newly detected Type 2 DM subjects, two of them have diabetic retinopathy & nephropathy, one of the two also has diabetic neuropathy (symmetric sensory polyneuropathy). Hypertension was the most common associated co-morbidity. The association between glucose dysregulation and obesity was significant.

Conclusion

It was noted that prevalence of IFG, IGT and DM are significantly high amongst the first-degree relatives. In the present study, it was noted that the number of complications were minimal at the time of diagnosis of diabetes. Hypertension was the most common associated co-morbidity. The association between glucose dysregulation and obesity was significant. The results of this study should help in understanding the importance of early recognition of pre-diabetes and diabetes in first-degree relatives of known cases of type2 diabetes mellitus & prevent/delay onset of diabetes by lifestyle modification & diet.

Key words :

Family History, oral glucose tolerance test, diabetes, pre-diabetes, obesity, metabolic syndrome, Body mass index, Hypertension.

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LIST OF ABBREVIATIONS

BMI : Body Mass Index

DM : Diabetes Mellitus

DPP : Diabetes Prevention Programme

ESRD : End Stage Renal Disease

FPG : Fasting Plasma Glucose

GDM : Gestational Diabetes Mellitus

HbA_1C : Glycosylated hemoglobin

HDL : High Density Lipoprotein

HNF : Hepatocyte Nuclear Transcription Factor

IDF : International Diabetes Federation

IFG : Impaired Fasting Glucose

IGT : Impaired Glucose Tolerance

IHD : Ischemic Heart Disease

MS : Metabolic Syndrome

NGT : Normal Glucose Tolerance

NIDDM : Non-Insulin Dependent Diabetes Mellitus

OGTT : Oral Glucose Tolerance Test

PA : Per Abdomen

PGBS : Post Glucose Blood Sugar

PVD : Peripheral Vascular Disease

RCT : Randomised Control Trial

RS : Respiratory System

STOP NIDDM : Study to Prevent Non-Insulin Dependent Diabetes Mellitus

T_1DM : Type-1 Diabetes Mellitus

T_2DM : Type-2 Diabetes Mellitus

TG : Triglyceride

TIA : Transient Ischemic Attack

UKPDS : United Kingdom Prospective Diabetes Study

WHO : World Health Organisation

INTRODUCTION

Diabetes is the third most common cause for morbidity and mortality, following cardiovascular diseases and malignancies. According to International Diabetes Federation, the prevalence of diabetes is expected to increase from 5.9% (2003) to 8.1%, by 2025. That is, by 20 25, India will have 90,97,99,000 diabetic patients.[1] The recently concluded First International Congress on pre-diabetes and the Metabolic Syndrome was of the opinion that more than 50% of people with diabetes will come from Asia over the next decade. Such is the magnitude of diabetes.[2]

Familial aggregation of diabetes is considered as a risk factor for the development of type2 Diabetes Mellitus (type2 DM hereafter referred as DM).[3] As family members (first degree relatives) not only share the genetic/hereditary factors involved in the etiopathogenesis of DM, but also the socio-environmental and other risk factors (obesity, hyperlipidemia, hypertension) they constitute a high risk group.

Type2 DM precedes the clinical diagnosis by four to seven years. It is known that diabetic complications depend on both duration as well as glycemic control. Thus, early diagnosis of type2 DM is important so that diabetes related morbidity and mortality could be reduced. It will be possible to identify these high-risk subjects by screening.

Oral Glucose Tolerance Test (OGTT) will be an ideal way to screen this high-risk group. It has been noted that the development of DM or its complications can be postponed or prevented by exercise, diet, and good glycemic control. In this part of the state, no study has been undertaken to evaluate the prevalence of glucose

intolerance or type2 DM in first-degree relatives of known diabetic patients. Hence, the need for the study, to highlight the glucose tolerance test to find out the prevalence of glucose intolerance and DM.

AIMS AND OBJECTIVES

1. To find out the incidence of IFG, IGT and Type 2 diabetes in first-degree relatives of known type 2 DM patients.
2. To detect the microvascular complications in newly detected Type 2 Diabetic first degree relatives of known Type 2 DM patients.

REVIEW OF LITERATURE

Definition :

Diabetes Mellitus is a group of metabolic diseases characterized by hyperglycemia, resulting from defects in insulin secretion, insulin action or both.[4] It is a chronic illness that requires continued medical care to prevent acute complications, and to reduce the risk of long-term complications.

Clinical descriptions of polyuric states resembling DM have been described from 15th century B.C. Ancient Indian Physicians described clinical features suggestive of DM (400BC).

During 16th to 18th century, diabetes was diagnosed as a separate entity. Following table shows the important landmarks in the history of DM.[5]

Date	Researcher	Observation
17th century	Thomas Willis	Diabetic urine contains sugar
18th century	Matthew Dobson	Diabetic serum contains sugar
1797	John Rolo	Coined the term Mellitus (which means honey in Greek)
1810-20	William Prout	Diabetic coma described
1815	Michel Chevreul	Excess sugar in DM is glucose
1857	Wilhelm Petters	Acetone in diabetic urine
1869	Paul Langerhans	Pancreatic islets identified
1874	Adolf Kussmaul	Acidotic breathing in diabetic coma
1889	Minkowski and Von Mering	Pancreatectomy causes DM in dog

Date	Researcher	Observation
1907	Jean de Meyer	Hypothetical glucose lowering hormone, named insulin
1922	Banting, Best Collip, Macleod	Isolation and first clinical use of insulin
1923	JR.Murlin	Discovered and named glucagon
1955	F. Sanger	Sequencing of insulin
1971	Roth et al	Discovered insulin receptor
1977	Ulrich et al	Insulin gene cloned

1978	Purified "single-peak" pork insulin introduced (Lilly Company)
1978	Open-loop insulin delivery system clinically introduced (Pickup and coworkers)
1981	Insulin-receptor kinase activity described (Kahn and coworkers)
1982	Recombinant human insulin becomes available (Lilly Company)
1989	First islet transplants (Lacy and coworkers)
1990s (early)	Insulin pen delivery devices become popular
1996	Short-acting insulin analogue introduced—insulin lispro (Humalog)
2000	"Edmonton Protocol" improved results of islet transplantation
2001	Long-acting insulin analogue introduced—insulin glargine (Lantus, Aventis Company)

Etiologic Classification of Diabetes Mellitus :[6]

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

A. Immune-mediated

B. Idiopathic

II. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance).

III. Other specific types of diabetes :

A. Genetic defects of β-cell function characterized by mutations in:

1. Hepatocyte nuclear transcription factor (HNF) 4α (MODY 1)
2. Glucokinase (MODY 2)
3. HNF-lα (MODY3)
4. Insulin promoter factor (IPF) 1 (MODY 4)
5. HNF-lβ(MODY5)
6. NeuroDl (MODY6)
7. Mitochondrial DNA
8. Subunits of ATP-sensitive potassium channel
9. Proinsulin or insulin

B. Genetic defects in insulin action

1. Type A insulin resistance
2. Leprechaunism
3. Rabson-Mendenhall - Syndrome
4. Lipodystrophy syndromes

C. Diseases of the exocrine pancreas - pancreatitis, pancreatectomy, neoplasia, cystic fibrosis, hemochromatosis, fibrocalculous pancreatopathy, mutations in carboxyl ester lipase

D. Endocrinopathies - acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma

E. Drug - or chemical-induced – Vacor (a rodenticide), pentamidine, nicotinic acid, glucocorticoids, diazoxide, β-adrenergic agonists, thiazides, hydantoins, asparaginase,

α-interferon, protease inhibitors, antipsychotics (atypical & others), epinephrine

F. Infections - congenital rubella, cytomegalovirus, coxsackie virus

G. Uncommon forms of immune-mediated diabetes –

"stiff-man" syndrome, anti-insulin receptor antibodies

H. Other genetic syndromes sometimes associated with diabetes - Down's syndrome, Klinefelter's syndrome, Turner's syndrome, Wolfram's syndrome, Friedreich's ataxia, Huntington's chorea, Laurence-Moon-Biedl syndrome, myotonic dystrophy, porphyria,

Prader-Willi syndrome.

IV. Gestational diabetes mellitus (GDM)

Abbreviation : MODY – Maturity onset diabetes of the young.

Source : American Diabetes Association, 2011.

Though diabetes is classified into 4 major groups, prevalence of type2 DM exceeds 90% of all diabetes. Genetic predisposition, urbanisation, lack of exercise, obesity, malnutrition during childhood, are the main contributory factors for development of type2 DM.

Type2 DM does not have specific or characteristic clinical manifestations. It is often detected by blood glucose testing done for some other reasons, such as pre-operative setting, myocardial infarction, stroke, etc. As type2 DM can present directly with complications and thereby increase the morbidity and mortality, it is important to detect the disease earlier.

The metabolic dysregulation associated with DM causes secondarypathophysiological changes in multiple organ systems, that impose a tremendous burden on the individuals with DM and the health care system**.**

Epidemiology :

Both DM and pre-diabetes are rising worldwide. They are expected to rise further because of sedentary lifestyle, increasing obesity, and increased life expectancy. Age related increase in

DM is as follows :

- 1.9% in people <20 years.
- 8.6% in people > 20 years.
- 20.1% in people > 65 years.[6]

Changes in human behaviour and lifestyle over the last century have resulted in a dramatic increase in the incidence of DM worldwide. There is convincing evidence to

support the partial genetic determination. The life-time risk of development of DM, of first degree relative of a patient with type2 DM has been estimated at about 35%.

The relative risk of DM in a first-degree relative of a known case of type2 DM compared to general population is in between three to four fold.[7]

Therefore in this study, we are screening patients with a genetic background for DM (i.e. family history), in order to detect them early, so that intervention with respect to environmental factors (i.e. life-style modification) could help delay/prevent DM in them.

Epidemiology in India :

India today leads the world with its largest number of diabetic subjects in any given country.[8]

Following table shows the results of studies that show a rising prevalence of DM in India.[9]

Year	Author	Place	Prevalence %	
			Urban	Rural
1971	Tripathi et al	Cuttack	1.2	
1972	Ahuja et al	New Delhi	2.3	
1979	Gupta et al	Multicenter	3.0	1.3
1984	Murthy et al	Tenali	4.7	
1986	Patel	Bhadron	3.8	
1988	Ramchandran et al	Kudremukh	5.0	
1989	Kodali et al	Gangavathi	2.2	
1989	Rao et al	Eluru	1.6	
1991	Ahuja et al	New Delhi	6.7	
1992	Ramchandran et al	Chennai	8.2	2.4
1997	Ramchandran et al	Chennai	11.6	
2000	Mohan et al	Chennai	12.0	
2000	Kutty et al	Thiruvanthpuram	12.4	
2001	Misra et al	New Delhi	11.2	
2001	Ramchandran et al	Six Urban Centres (DESI-study)	12.1	
2002	Mohan et al	Chennai	12.1	
2004	Shoukat et al		5.6%	

India has already become the diabetic capital of world with over three crores affected. patients, which is just the tip of the iceberg. In India, studies have shown a rising prevalence of type2 DM, which is more in urban than rural areas. Prevalence of IGT is also high.

Considering the high rate of conversion of IGT to diabetes, this would imply a further increase in number of diabetics in future.

According to the survey conducted by WHO, in 2000, in India, using OGTT, the prevalence of DM rose from 2.6 to 34.6% in different age groups. [10]

Following table shows the prevalence of type2 DM and IGT in 2003 and the expected rise by 2025.[1]

No. of people with D.M. in 1000's in the age group of 20-79 years as per www.idf.org for the year 2003 and 2025, dated 26.07.05

For Year	Population	Prevalence	Rural	Urban	DM (male)	DM (female)	20-39 yrs	40-59 yrs	60-79 yrs	Total
2003	6,03677	5.9%	13290.5	22213	17969	17533	7147.9	18,234	10116	35503
2025	90,9799	8.1%	18553.8	54922.1	37275	36200	11827	37,427	20,230	73475.9

No. of people with IGT in 1000's in the Age group of 20-79 yrs as per www.idf.org for the year 2003 and 2025, dated 26.07.05

For year	Population	Prevalence	IGT (Male)	IGT (Female)	20-39 yrs	40-59 yrs	60-79 yrs	Total
2003	6,03,677	14.2%	44069	41561	42484	30100	13046	85630
2025	9,09,799	14.5%	68123	63865	55892	50190	25906	131989

NATURAL HISTORY OF DM :

Type2 DM is characterized by :

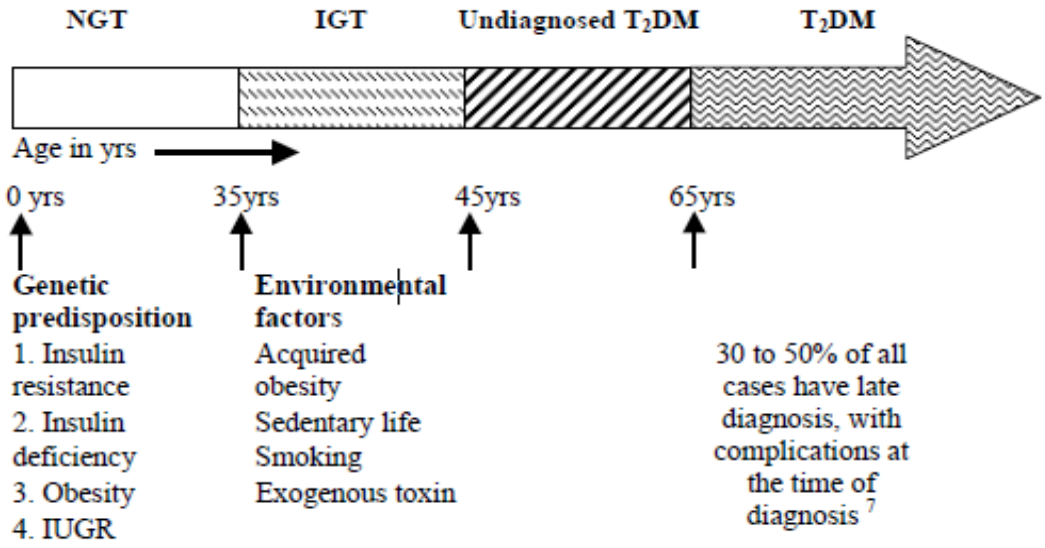
1. Impaired insulin secretion.

2. Insulin resistance and

3. Excessive Hepatic glucose production.

In the early stage, glucose tolerance remains normal, despite insulin resistance because pancreatic beta cells compensate by increasing insulin secretion. As insulin resistance increases, and compensatory hyperinsulinemia progresses, pancreatic cells fail to sustain this state, and produce Impaired Glucose Tolerance (IGT). Further decline in insulin secretion and an increase in hepatic glucose production lead to overt fasting hyperglycemia and ultimately to frank DM.[6]

FIGURE NO. 1



In the CUPS (Chennai Urban Population Study) following were the prevalence rates of complications at the time of diagnosis of DM.[8]

Complications	Prevalence (%)
Coronary Heart Disease	21.4%
Neuropathy	17.5%
Peripheral Vascular Disease	6.3%
Retinopathy	19.0%
Microalbuminuria	26.3%

Diagnosis :

Clinical Features :

- Most of the patients are asymptomatic.
- Often the patient :

- typically presents with polydipsia polyphagia, polyuria, or weight loss.
- may present with acute metabolic complications.
- may present with chronic complications – neuropathy, retinopathy, nephropathy, coronary heart disease, peripheral vascular disease

Criteria for the diagnosis of DM : American Diabetes Association 2011

1) Symptoms of DM plus random blood glucose concentration ≥200mg/dl (random is defined as any time of day without regard to time, since last meal). The classical symptoms of DM include polyuria, polydipsia and unexplained weight loss.

or

2) Fasting Plasma Glucose ≥ 126mg/dl or

(fasting is defined as no caloric intake for at least eight hours).

or

3) Two hours plasma glucose ≥ 200mg/dl during an Oral Glucose Tolerance Test The test should be performed using a glucose load containing the equivalent of 75gm anhydrous glucose dissolved in water.

or

4) A1C > 6.5 %

The test should be performed in laboratory certified according to A1C standards of the Diabetes Control & Complications Trial

Note : In the absence of unequivocal hyperglycemia, these criteria should be confirmed by repeat testing on a different day.

The OGTT is not recommended for routine clinical use but may be required in the evaluation of patients with IFG, IGT or when diabetes is still suspected despite a normal FPG as with a postpartum evaluation of women with Gestational Diabetes Mellitus (GDM).

Glucose tolerance is classified into three categories based on :[3,6]

A. FPG : (Fasting Plasma Glucose)

1. FPG < 100mg/dl - is considered normal.
2. FPG ≥ 100mg/dl but <126mg/dl is Impaired Fasting Glucose – (IFG)
3. FPG ≥ 126mg/dl - warrants diagnosis of DM.

B. IGT: (Impaired Glucose Tolerance)

1. Two hours post Glucose < 140mg/dl – considered normal.
2. Two hours post glucose ≥ 140mg /dl but <200mg/dl is IGT.
3. Two hours post Glucose ≥ 200mg/dl - warrants diagnosis of DM.

Individuals with IFG/IGT are at substantial risk of development of type2 DM (40% risk over next five years) and cardiovascular diseases.[13 &14]

In the study conducted by Hu. G. et al. it was observed that patients with obesity and / IGTprogress to type2 DM. In this study, 4369 people aged between 45 and 64 years, without history of known diabetes, were followed. During a mean follow up of 9.4 yrs they found 120 cases of type2 DM.[11]

The recently concluded First International Conference on Pre-diabetes and the Metabolic syndrome opined that people with pre-diabetes and metabolic syndrome have high risk for diabetes mellitus and cardiovascular diseases.[2]

Diabetes Prevention Programme (DPP)[12], Finnish diabetes prevention study, Da Qing IGT and Diabetes study, STOP NIDDM trial and TRIPOD study observed that patients with IGTprogressed to diabetes mellitus unless there was intervention with life style modification or drugs.[13]

Both IFG and IGT are associated with a substantially increased risk of developing diabetes. The highest risk is in people with combined IGT and IFG. Nearly 60% of people who develop diabetes mellitus have either IGT or IFG five yrs or so before.[14]

In the study by Henkel E. et al. a total of 358 subjects with normal glucose tolerance at the time of enrolment into the study, were followed up for 2.9 ± 0.47 yrs. Of the 358, 284 subjects remained within normal glucose level range, while 64 developed IGT and ten developed type2 DM. On analysis, subjects who converted to IGT or diabetes showed significant insulin resistance and also impaired insulin secretion. These facts suggest that fasting and two hours post challenge glucose are the most important predictors of subsequent glucose intolerance.[15]

COMPLICATIONS :[6]

Some studies have shown diabetic retinopathy is common in patients with newly diagnosed diabetes mellitus.[16] It is seen in 39% of men and 35% of women, with marked retinopathy present in 8% men and 4% women at the time of diagnosis of diabetes mellitus in UKPDS.[17]

The prevalence of overt nephropathy is about 3% in newly diagnosed diabetes mellitus.[18] Type 2 diabetes with microalbuminuria have median risk ratio of 8.5 for developing nephropathy . Diabetes constitutes 44.5% of end stage renal disease.

Symptomatic peripheral neuropathy is found in up to 1.5% of newly diagnosed diabetes, where as by clinical signs it is found in 2.3% of newly diagnosed diabetes.[19] The degree of neuropathy is associated with degree of hyperglycemia.

MECHANISMS OF COMPLICATIONS :[6]

Chronic hyperglycemia leads to non-enzymatic glycosylation resulting from interaction of glucose with amino groups from proteins. These are called advanced glycosylation end products. (AGE.) AGE'S cross-link with protein and thus accelerate atherosclerosis, promoting glomerular dysfunction and inducing endothelial dysfunction.

A second theory proposes that hyperglycemia increases glucose metabolism via the sorbitol pathway. Increased sorbitol concentration increases reactive oxygen species.

A third hypothesis proposes that hyperglycemia activates protein kinase C which alters the endothelial cell protein collagen and contractile proteins. Another theory proposes that hyperglycemia increases fructose–6-phosphatase, which in turn increases plasminogen activator inhibitor-1 and growth factor.

All these together increase growth factors (vascular endothelial growth factor, transforming growth factor B, platelet derived growth factor, epidermal growth factor, insulin-like growth factor, basic fibroblast growth factor). These growth factors appear to play an important role in DM related complications. DM is the leading cause for end stage renal disease The United Kingdom Prospective Study (UKPDS), which studied more than 5000 individuals for more than ten years, noted that chronic hyperglycemia plays a causative role in the pathogenesis of diabetic microvascular complications.

A similar study in a small trial of lean Japanese individuals in type2 DM demonstrated the effectiveness of improved glycemic control in reducing chronic diabetic microvascular complications.[6]

The UKPDS demonstrated that each percentage point reduction in Glycosylated hemoglobin (HbA1C or A1C) was associated with a 35% reduction in micro-vascular complications.

The DCCT trial (Diabetic Control and Complication trial), demonstrated that the improvement of glycemic control, reduced :

- Retinopathy - by 47%.
- Microalbuminuria – by 39%
- Nephropathy – by 54%
- Neuropathy – by 60%

The results of DCCT predicted that individuals in the intensive diabetes management group would gain 7.7 additional years of vision, 5.8 years free from End Stage Renal Disease. This translates into an additional 5.1 year of life expectancy for individuals in intensive diabetes management group.[6]

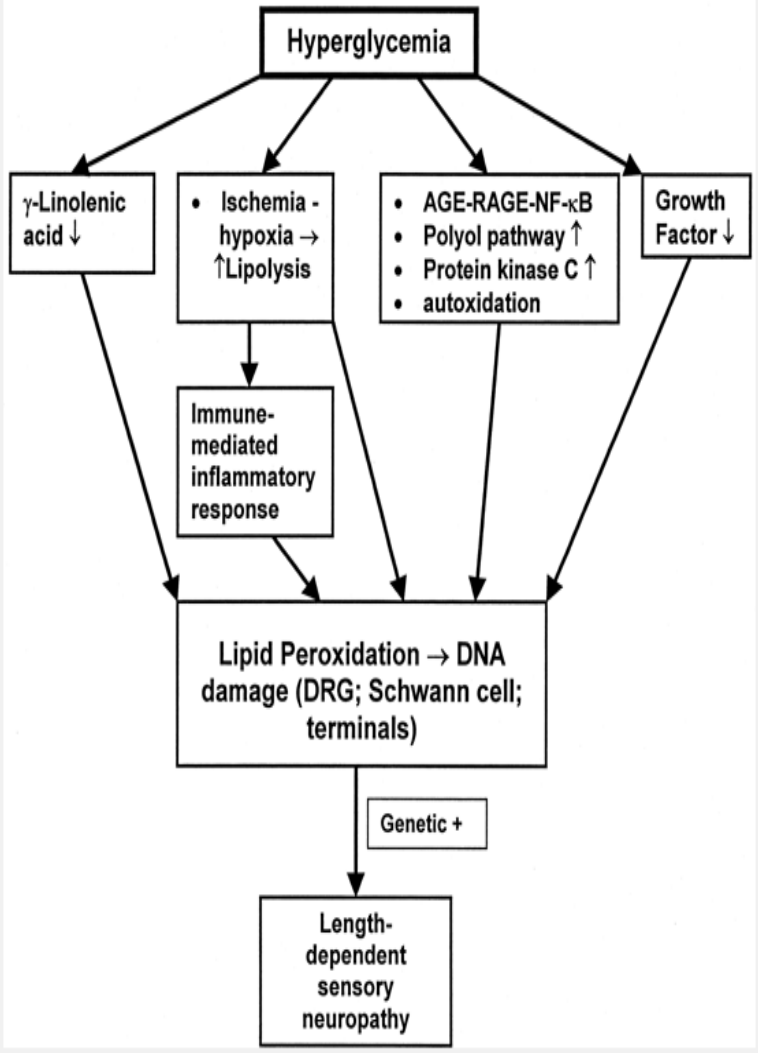


Figure 50.1. Suggested pathogenesis of diabetic neuropathy.

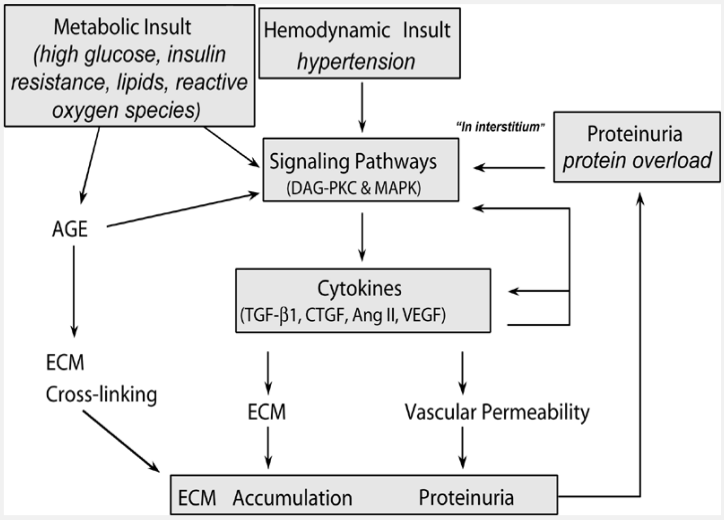


Figure 51.2. Schematic representation of the interaction, at the cellular and intracellular levels, of three insults operating in diabetic nephropathy. AGE, advanced glycation end-product; ECM, extracellular matrix; TGF-β1, transforming growth factor-1β; Ang II, angiotensin II; CTGF, connective tissue growth factor; VEGF, vascular endothelial growth factor; MAPK, mitogen-activated protein kinases; PKC, protein kinase C; DAG, diacylglycerol.

Prevention of DM and its complications :

As type2 DM is preceeded by a period of glucose intolerance of four to seven years, a number of life style modifications and pharmacological measures prevent / delay the onset of type2 DM. The following few studies show the importance of life style modification or pharmacological intervention in preventing type2 DM.

In the Diabetes Prevention Program, 3,234 patients with IGT and a BMI greater than 24 kg/m2 were randomly assigned to one of the following groups: placebo, metformin, or intensive lifestyle modification. The lifestyle modification group was offered a 16-lesson curriculum aimed at achieving a weight loss goal of more than seven percent of their initial body weight through a low-calorie, low-fat diet and moderate-intensity exercise for 150 minutes per week. After an average follow-up of 2.8 years, there was a 58 percent relative risk reduction in the progression to diabetes in the lifestyle intervention group compared with the placebo group. The relative risk

reduction was 31 percent in the metformin group compared with the placebo group. In this study, lifestyle intervention was effective in men and women, and in all ethnic groups. It was most beneficial in patientsolder than 60 years; in this group, it reduced the incidence of diabetes by about 71 percent.

In the Finnish Diabetes Prevention Study, 522 obese patients with a mean BMI of 31 kg/m2 and IGT were randomly assigned to a control group or an intervention group. Patients in the intervention group were instructed to lose five percent of their body weight, limit fat intake to less than 30 percent of daily calories, limit saturated fat intake to less than ten percent of daily calories, increase fiber intake to at least 15 g per 1,000 calories, and exercise moderately for at least 150 minutes a week. After 3.2 years of follow-up, there was a 58 percent relative risk reduction in the incidence of diabetes in the intervention group compared with the control group. There was also a significant positive correlation between the ability to achieve lifestyle modifications and preventing progression to diabetes.

In the Da Qing IGT and Diabetes Study in China, 577 patients with IGT were randomly assigned to a control group or to one of three treatment groups:

diet alone, exercise alone, or diet plus exercise. Over six years of follow-up, the relative risk reduction in progression to diabetes was 31 percent in the diet group, 46 percent in the exercise group, and 42 percent in the combined group.

Although not as effective as lifestyle interventions, drug therapy with metformin and acarbose has been shown to prevent the progression of IGT to diabetes. Success also has been achieved with troglitazone, although U.S Food and Drug Administration has withdrawn this drug from the market because of liver toxicity.

In the Diabetes Prevention Program, treatment with metformin was associated with 31 percent relative reduction in the progression of diabetes in patients with IGT. Metformin was more effective in younger patients with a higher BMI and higher fasting plasma glucose levels, and was least effective in patients older than 60 years.

In the study to Prevent Non-Insulin Dependent Diabetes Mellitus (STOPNIDDM), patients with IGT who were treated with acarbose showed 25 percent relative reduction in progression to diabetes. This risk reduction did not persist when acarbose therapy was discontinued at the end of the study. The incidence of diabetes increased in the group that originally had been treated with acarbose, indicating that this drug therapy must be continued to maintain preventive effects.

Lifestyle interventions can be difficult to implement because it is impractical for the usual family practice systems to provide intensive dietary and exercise interventions similar to those used in clinical trials. However, lifestyle interventions are highly effective and superior to drug therapy, and should be the first choice in treating patients with IGT or IFG.

Although pharmacologic agents have been shown to be successful in preventing or delaying the onset of diabetes, whether these agents can prevent complications of diabetes or protect against cardiovascular disease remains unknown. Routine use of pharmacologic agents as a substitute for lifestyle modification should be discouraged until more studies have been conducted and the cost-effectiveness of

drug therapy has been assessed. A healthier lifestyle can modify other risk factors for cardiovascular disease such as obesity, hypertension, and dyslipidemia. Drug therapy can be considered when aggressive lifestyle interventions are unsuccessful.

Summary of Major Diabetes Prevention Trials

Study	Study population	Mean BMI (kg per m^2)	Type of Intervention	Relative risk reduction (%)
Diabetes Prevention Program	3,234 patients with IGT	34	Lifestyle modification	58
			Metformin, 850 mg twice daily	31
Finnish Diabetes Prevention Study	522 patients with IGT	31	Lifestyle modification	58
Da Qing IGT and Diabetes Study	577 patients with IGT	25.8	Diet	31
			Exercise	46
			Diet plus exercise	42
STOP-NIDDM trial	1,429 patients with IGT	31	Acarbose 100 mg three times daily	24
TRIPOD study	236 Hispanic women with a history of gestational diabetes	30	Troglitazone 400 mg daily	55

Recommended Lifestyle Changes

- **Daily calories**

Fat: <25 to 30 percent

Saturated fat: <10 percent

Carbohydrates: 50 to 60 percent

Protein: 15 to 20 percent

- Daily fiber intake: >15 g for every 1,000 calories consumed.

Foods: salad, vegetables, fruits, whole grains, fish high in omega-3 fatty acids, legumes, lean meat, minimal intake of refined sugars.

- Exercise: moderate-intensity physical activity, such as brisk walking or biking, for 150 minutes per week.
- Weight loss goal: Five to seven percent of body weight.
- Counselling by professionals, on weight reduction and exercise, with regular follow-up and reinforcement.

Screening for diabetes :

Purpose of screening is to identify asymptomatic individuals who are likely to have DM.

Type2 DM is often not diagnosed until complications appearor classical symptoms develop.

Approximately 1/3rd of all people with DM may be undiagnosed. As type2 diabetes is associated with serious, life threatening complications, individuals at high risk should be screened for DM / Pre-diabetes.

Criteria for screening in asymptomatic, undiagnosed adults are :[20]

1. Testing for DM should be considered in all individuals at age 45 years and above, particularly in those with a BMI ≥25 kg/m2 and if normal, should be repeated at three years interval. (American Association of Clinical Endocrinologists recommends that screening should begin at an early age i.e. 30 years).

2. Testing should be considered at a younger age / be carried out more frequently in individuals who are overweight (BMI ≥ 25kg/m2) and have additional risk factors as follows

- Are habitually physically inactive.
- Have a first-degree relative with DM.
- Are members of a high-risk ethnic population.
- Have delivered a baby weighing > 9lb/have been diagnosed with GDM.
- Are hypertensive ≥140/90mm Hg.
- Have a High Density Lipoprotein (HDL) cholesterol level < 35 mg/dl and / a Triglyceride (TG) level of > 250mg/dl.
- Have Polycystic Ovarian Syndrome.
- On previous testing had IGT/IFG.
- Have other clinical conditions associated with insulin resistance (Acanthosis Nigricans).
- Have history of vascular disease.

Screening with FPG test and two hours OGTT (with 75 grams glucose load) is appropriate.

Two hours OGTT identifies people with IGT and thus more people who are at increased risk for the development of DM and cardio vascular diseases.

OGTT :

- For diagnosis of DM, any one of the following three criteria is required :
- FPG $\geq$ 126mg/dl.
- Elevated two-hour plasma glucose during OGTT $\geq$ 200mg/dl.
- Random plasma glucose $\geq$ 200mg in a symptomatic individual.

Patient will be on a stable diet, weight, level of exercise and without any stress, or recent hospitalization. The subject is to fast over night (usually 8-14 hours) and should take nothing by mouth except water. No medication/caffeine/tobacco are to be taken until the completion of test. Two samples are drawn : time zero and two hours samples. Time zero is when the subject begins to drink the sugar beverage. Adults receive 75gm of glucose. The beverage should be consumed in five minutes or less, the maximum glucose concentration in the beverage is 25gm/100ml. Pre-diabetes is diagnosed when the FPG is between 100 to 125 mg/dl (i.e., IFG), and / or the two hours plasma glucose during OGTT is between 140 mg/dl to 199mg/dl (IGT) in the absence of hyperglycemia as defined above.

Individuals with pre-diabetes are at high risk of progressing to frank type2 DM, unless the patient loses weight, exercises and /or alters diet. There are data showing that OGTT is more sensitive than measuring fasting plasma glucose alone for the diagnosis of diabetes / pre-diabetes. OGTT is also used in screening of diabetes during pregnancy.[21]

Fasting blood sugar is the lowest glucose level during the day, post glucose blood sugar (PGBS) shows the magnitude of glucose elevation (peak) after glucose load, lasting one to three hours. HbA1C- indicates mean glycemic level during the last three monthssummarizing both fasting and PGBS.

Although IGT is clearly associated with presence of underlying insulin resistance, IFG may or may not be associated with insulin resistance. It is instead more likely to be associated with declining β-cell function. There are no prospective Randomised Control Trials (RCT) suggesting that pharmacological therapy of IFG yields treatment benefits either with regard to prevention or adverse coronary outcomes or the prevention of progression of type2 DM.

Nonetheless it seems clear that pharmacologic modification may present a successful approach to this particular health problem because, pharmacological intervention with regard to IGT has been demonstrated to be successful with regard to prevention of type2 DM.

Studies, such as DPP, TRIPOD studies and STOP-NIDDM have demonstrated efficacy of metformin, thiazolidinediones and Acarbose respectively.[13]

Finnish Diabetes Prevention study, Da Quing IGT and diabetes study demonstrated that lifestyle modification diet, exercise reduce the relative risk of development of type2 DM.[13]

It is observed that mean Body Mass Index (BMI) and percentage of obesity will be significantly high in families with positive family history of DM i.e. familyhistory of DM clustered with increased Waist Hip Ratio (WHR) and Body Mass Index (BMI). Thus family history of DM may increase the risk of hypertension and hyperlipidemia indirectly through its connection with BMI.[22]

It was observed in studies that, family history of DM increased in parallel with IGT, suggesting genetic factors in the pathogenesis of type2 DM. This is significantly noted in younger patients and less obese patients than older and obese patients.[23,24]

Bo-S et al, concluded that parental DM leads to an earlier onset of DM and higher LDL cholesterol values in children, and the presence of DM in relatives, other than parents constituted a small risk of earlier manifestation of type2 DM.[25]

DECODA (Diabetes Epidemiology Collaborative analysis of Diagnostic criteria in Asia) Study revealed that two hours PGBS remained an independent predictor of cardiovascular morbidity after adjusting for other risks. Similarly in a study in Sweden, in patients with acute myocardial infarction, 31% had asymptomatic DM and 35% had IGT when tested for glucose tolerance.

Metabolic Syndrome :

The concept of metabolic syndrome has been in existence for at least 80 yrs. In 1947, Vague drew attention to upper body adiposity (android or male type obesity) as the obesity phenotype that was commonly associated with metabolic abnormality, in turn associated with type2 DM and CVD.

In recent years, number of expert groups like WHO, European Group for the study of Insulin Resistance (EGIR) and the National Cholesterol Education Programme – third Adult Treatment Panel (NCEP – ATP III) have attempted to define metabolic syndrome. From a clinical perspective, ATP III definition is probably most useful.

The metabolic syndrome is a collection of frequently associated cardiovascular risk factors that tend to aggregate in selected patient populations and that, together increase cardiovascular mortality and total mortality. Following table cites the current criteria for diagnosis of metabolic syndrome according to NCEP guidelines.[6]

Risk Defining level

Abdominal obesity

- Men (waist circumference) >102cm
- Women (waist circumference) >88cm

Tri Glyceride levels >150 mg/dl

HDL cholesterol levels

- Men <40mg/dl
- Women <50mg/dl

Blood Pressure $\geq$ 130/$\geq$ 85mm of Hg

Fasting plasma glucose > 110 mg/dl

A diagnosis of Metabolic Syndrome (MS) is made by presence of three or more abnormalities. Although each abnormality may be associated with IR, no requirement exists for an experimental demonstration of IR or a measurement of insulin mediated glucose disposal.

Although it is currently under examination, IFG ($\geq$ 110mg/dl) is one of the five diagnostic criteria used for determining the patient of MS. In contrast, some authors have suggested that patients with otherwise normal FBS may demonstrate IGT at the point of two-hour challenge test during an OGTT. Although a recent consensus development conference of American College of Endocrinology recommended two hours PGBS $\geq$ 140 mg/dl as a potential alternative to the 110mg/dl of risk, this addition has not been recommended because OGTT is believed to be too difficult for practitioners and potentially impractical in routine, clinical setting. However the physician can wish to offer such testing where possible to clarify patient status with the MS, and to ascertain potential impairment of carbohydrate metabolism or even overt DM.

Metabolic syndrome is highly effective in predicting excess of cardiovascular risk. MS may also be an outstanding risk predictor of future diabetes. In the Framingham offspring study a recent analysis suggested that diagnosis of MS predicted a five fold, eight years future risk of DM in males and six-fold increase in future risk of DM in females.[26]

Hyperinsulinemia and insulin resistance are pervasive features of obesity, increasing with weight gain and diminishing with weight loss. Insulin resistance is more strongly linked to intra abdominal fat than to fat in other depots. There are many mechanisms which link insulin resistance and obesity. As many as 80% of patients with type2 DM are obese.[6]

In the study by Ramchandran et al, the risk of both IGT and DM were noted for BMI > 22kg/m^2.

It is noted that the MS has high and increasing prevalence in Indians.

As observed by C Snehalatha et al., BMI is an independent risk variable with IGT. Obesity is considered to be a risk factor for conversion of pre-diabetes to DM. V Mohan et al observed the mean BMI in their study population to be 22.6 kg/m^2 which is much lower compared to western populations. They also noted that South Indians have higher risk of DM even with low BMI.[15] Sargeant L.A et al noted that 38% of the excess risk of DM in people with family history of DM could be avoided if their BMI did not exceed 30kg/m^2. Individuals with family history of DM are at increased risk of metabolic consequences of obesity and form an easily identifiable group who may benefit from targeted intervention to prevent the development of obesity through increased physical activity.

Familial risk factors :

Subjects with family history had two to three times higher risk of developing glucose intolerance. The role of hereditability has long shown that subjects with family history of diabetes develop diabetes earlier compared to subjects without family history. [24]

South Indians showed complex nature of genetic pathology in type2 DM.Certain mutations of candidate genes related to insulin secretion and insulin action such as Calpain 10, Vitamin D, Insulin receptor substrate-1, UCP2, UCP3,Apolipoprotein D gene are associated with the disorder. However the nature of the major gene (s) responsible for the disease remain elusive.[9]

Few studies have made an attempt to look at the cumulative effect of these factors, particularly with family history of diabetes, which confers potentially high risk for developing glucose intolerance.[24]

Torben Hansen concluded that type2 DM is polygenic, each genetic defect contributing a small amount to the overall risk.[7]

Matsuda A, Kuzuya T, in 1984, observed that the frequency of positive family history of DM in parents was higher in patients with the onset of DM earlier than 40 years of age. The frequency of positive family history of DM was about 20%. [27]

Hagura et al in 1994 noted that the prevalence of DM in parents and siblings of T2DM was higher (43-49%) than in those of type1 DM (16.33%)[13] patients. It was particularly high in parents of young onset type2 DM patients.[23]

Mitchell BD et al, in 1995 showed that post OGTT, prevalence of DM amongst children with diabetic mother was 61.4% whereas it was 64.3% with diabetic father.[28]

Ramchandran et al in 1996, recorded that 53.91% of known case of type2 DM had family history of DM.[3]

Klein BE et al in 1996 demonstrated that at least one parent had diabetes in 18.6% to 38.6% of patients with type2 DM when it was enquired. [29]

Ramchandran et al again in 2000 showed that the family history of DM was present in 24.7% of patients with obesity, which itself is a risk factor for development of T2DM.[22]

Bo S et al noted that prevalence of DM in mother, father and other relatives was 25.5, 6.5 and 21.2% respectively.[25]

Sergeant LA, Wereham NJ, Khaw KT in their Epic Norfolk study concluded that crude prevalence in individuals without a family history and BMI of 22.5-24.9 kg/m2 was 2.2% compared to 33.3% in those with a family history and BMI over 35 kg/m2. Individuals with a family history of diabetes are at increased risk for the metabolic consequences of obesity.[30]

Vijay V et al in 1997, when studied the prevalence of IGT and DM in off-spring of parents with diabetic nephropathy and without diabetic nephropathy, found that DM was detected in 7.1% and 9.7% respectively in each group and IGT was detected in 25% in both groups. The relatively high plasma glucose values in the patients of normal insulin secretion in both groups of off-springs of diabetic parents suggests the presence of insulin resistance.[31]

METHODOLOGY

Source of data :

First-degree relatives of known type2 DM patients attending to Shri B. M. Patil Medical College hospital & research centre over a period of one & half year from Nov 2010 to Dec 2012.

Sample Size :

With average proportion rate of 28% [9], 95% confidence interval & 20% margin of error, the worked out sample size will be 246 using formula

$$n = \frac{(1.96)^2 \times p \times (1- p)}{L^2}$$

P = Proportion rate of IFG + IGT + DM

L = margin of error 20 %

The sample size will be 246 subjects.

Inclusion criteria :

Brothers/sisters/sons/daughters with age of $\geq$30 & $\leq$ 60 years [10]of

known T2DM patients.

Exclusion criteria :

1. Adopted sons/daughters of known type2 DM patients.

2. Known diabetic who is a first degree relative of type2 DM.

3. Subjects taking diabetogenic drugs/ on starvation.

Definitions and diagnostic criteria

Diabetes and Impaired glucose tolerance will be diagnosed based on criteria laid by the ADA guidelines 2011.

i.e.

Diabetes if fasting plasma glucose (FPG) $\geq$ 126 mg/dl or 2 hr post-plasma glucose value $\geq$ 200 mg/dl.

Impaired Fasting Glucose (IFG) if Fasting Plasma Glucose is 100 – 125 mg/dl and

Impaired glucose tolerance (IGT) if 2 hr post plasma glucose value is 140–199 mg/dl.

In the absence of unequivocal hyperglycemia, diagnosis will be confirmed by repeat testing.

Measurements of study variable :

1. Sex
2. Age
3. Weight / BMI
4. Relation of subject to the patient
5. Hypertension (> 140/90 mm Hg).
6. Hyperlipidemia (HDL < 35 mg/dl or triglyceride > 250 mg/dl, or both
7. Habitual Physical inactivity.

Method of collection of data :

First-degree relatives of known cases of type2 DM patients will be counselled

and explained the procedure, its importance, study design, benefit / harm if any involved in the study. Subjects will be explained that their privacy and confidentiality will be maintained unless it is required otherwise by the law. Subjects will be told that, they will not be given any compensation for participating in the study. Written consent will be obtained.

History of other risk factors will be taken.

Weight :

Body weight of the subject will be measured , to the nearest 0.1kg, using standard portable weighing machine. (scale will be zeroed before each session). Subjects will be in light clothes & without footwear.

Height :

Height will be measured using standard calibrated measuring tape.

Body Mass Index :

BMI was calculated by using formula

$$BMI = \frac{\text{Weight in kg}}{\text{Height in m}^2}$$

Physical inactivity

Physical activity level will be graded as light, moderate and heavy based on a physical activity questionnaire, which includes job-related and leisure time activities and specific questions on exercise.

For habitual physical inactivity, the WHO [11] criteria will be adopted, which is as follows:

Light work : (75% of time spent sitting and 25% of time spent working)

Moderate work : (40% of time spent sitting and 60% of time spent working)

Heavy work : (25% of time spent sitting and 75% of time spent working)

Blood pressure (BP) measurement :

Using mercury sphygmomanometer, by auscultatory method twice supine BP will be measured, using appropriate sized cuff.

Pulse :

Radial pulse will be counted for one full minute. All peripheral pulses will be examined.

Examination of foot :

Foot will be examined for calluses, nail changes, ulcers and pressure points.

Systemic examination : Detailed systemic examination will be done & relevant tests will be done with reference to diabetic complications.

Fundus examination : Fundus will be examined in newly detected type 2 diabetic subjects for diabetic & hypertensive changes.

Investigations

OGTT :

Subject will be asked to fast for minimum of eight hours and asked not to do vigorous exercise, drink tea, coffee or smoke. First venous sample will be drawn and subject will be given 300ml of water with 75gm of glucose orally to drink over five minutes. He/she will be asked, not to eat/drink/smoke for next two hours. After two hours, second venous sample will be drawn and subject will be asked to do his routine work.

Fasting lipid profile will be obtained for all subjects.

Relevant investigations will be done in newly detected Type 2 Diabetic subjects depending upon the complications noted in each subject.

STATISTICAL ANALYSIS PLAN

1) Mean $\pm$ SD
2) Percentages
3) Statistical tests – X^2 test, Z test, etc

RESULTS

In this study, 246 first-degree relatives of known cases of type2 DM were screened for IFG, IGT or Type 2 DM by doing 2 hour OGTT. During the same, it was worked up with regard to BMI, microvascular complications (by fundoscopy, Serum Creatinine, Urine microalbuminuria,etc), associated conditions like hypertension and the relation between glucose dysregulation and overweight/obesity.

TABLE 1 : Sex distribution

Gender	Number	Percentage
Male	144	58.5
Female	102	41.5

Study group consisted of 144 male and 102 female subjects.

TABLE 2 : Distribution of subjects by age

Age (yrs)	Number	Percentage
30-40	89	36.2
41-50	73	29.7
51-60	84	34.1

Subjects were distributed throughout the age spectrum from 30 years onwards. There were 89 subjects in 30 – 40 years age group, 73 subjects in 41-50 years age group & 84 subjects in 51-60 years age group.

TABLE 3 : Relation of TYPE 2 DM Patients with subject

Relation	Number
Father	129
Mother	101
Brothers/Sisters	19
Son/Daughters	--
Both Parents	15
More than one family member	31

There were 129 subjects who had a diabetic father , 101 subjects had diabetic mother, 19 subjects had either diabetic brother or sister. In 15 subject's, both mother & father were diabetic.

TABLE 4 : Response to glucose tolerance test

Glucose Tolerance	Male	Female	%age
NGT	84	52	55.3
IFG only	11	8	7.7
IGT only	19	18	15.0
IFG+IGT (Both)	21	18	15.9
Type 2DM	9	6	6.1
Total	144	102	100

Out of 246 subjects, 136 had normal glucose tolerance, while 110 had glucose intolerance. In the present study prevalence of both i.e. IFG and IGT (n=39; 15.9%) was more than that of diabetes (n=15;6.1%), IFG (n=19;7.7%) or IGT (n=37;15.0%). In this study 60 male and 50 female subjects had glucose dysregulation.

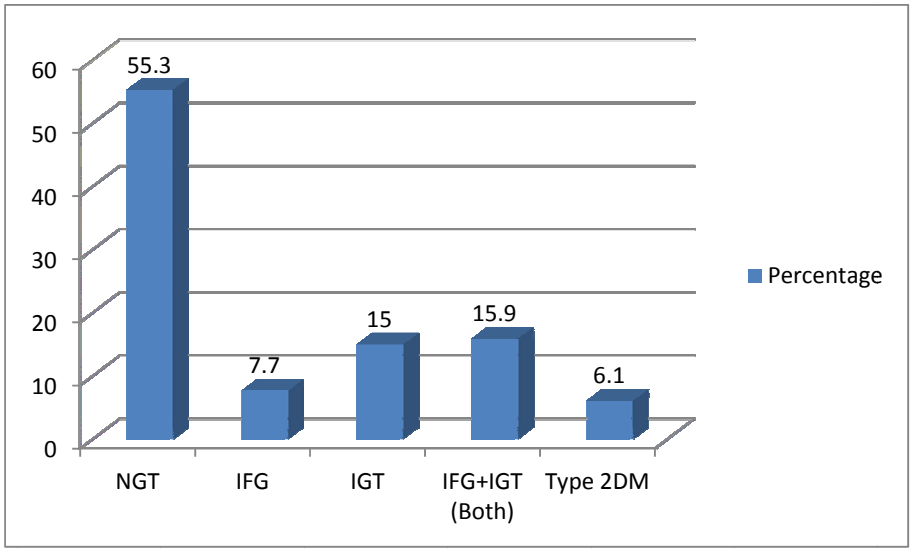


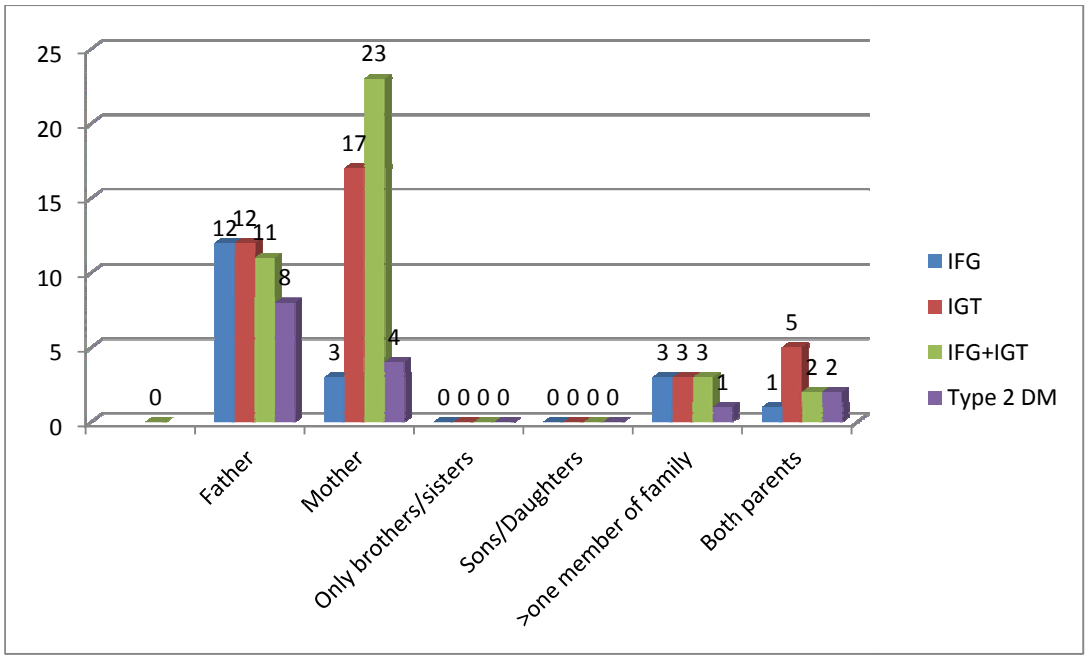
TABLE NO. 5 : Glucose dysregulation with relation to age group

Age	NGT	IFG only	IGT only	IFG+IGT (Both)	Type 2 DM	Total	%age
30-40	63	5	15	4	2	89	36.2
41-50	39	5	9	15	5	73	29.7
51-60	34	9	13	20	8	84	34.1

In the present study glucose dysregulation was observed in 50 subjects who were in 51-60 years age group , 34 subjects in 41-50 years age group & 26 subjects in 30-40 years age group.

TABLE **NO 6 : Distribution of subjects with glucose dysregulation with respect to their relation with patient.**

Relation	IFG only	IGT only	IFG+IGT (Both)	Type 2 DM	Total	%age
Father	12	12	11	8	43	39.1
Mother	3	17	23	4	47	42.7
Only brothers/sisters	--	--	--	--	--	0
Sons/Daughters	--	--	--	--	--	0
>one member of family	3	3	3	1	10	9.1
Both parents	1	5	2	2	10	9.1



In this study, out of 110 subjects with glucose dysregulation, n=47 (42.7%) had diabetic mother whereas n=43(39.1%) had diabetic father. Both parents were diabetic in n=10 (9.1%) subjects who had glucose dysregulation. More than one member of the family were diabetic in n=10 (9.1%) subjects who had glucose dysregulation.

In this it was observed excess maternal transmission compared to the paternal transmission.

Relation with subject	Number of subjects whose relative was Type 2 Diabetic	First degree relatives with glucose dysregulation
Father	129	43
Mother	101	47

Z=2.04, p=0.04 ;

Significant difference is there, more subjects (n=47) have glucose dysregulation out of 101 subjects whose mother have/had Type 2 DM ; compared to subjects (n=43) with glucose dysregulation out of 129 subjects whose father have/had Type 2 DM.

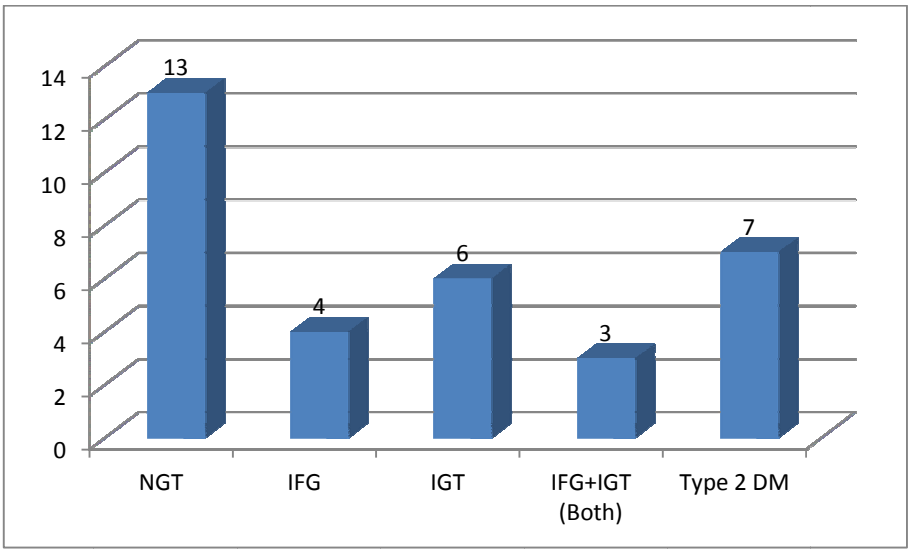
TABLE 7 : Clinical manifestations in subjects with glucose dysregulation

Clinical features	IFG only	IGT only	IFG+IGT (Both)	Type 2 DM	Total
Osmotic symptoms	0	0	1	1	2
Weight loss	0	0	0	0	0
Delayed wound healing	0	0	0	0	0
Fatigue	0	0	0	1	1
Visual	0	0	0	1	1
Other	0	0	0	0	0

In the present study out of 110 subjects with glucose dysregulation only 4 were symptomatic of which three had DM. Other subjects were asymptomatic.

TABLE 8 : Glucose dysregulation associated with hypertension

Glucose tolerance	Number
NGT (136)	13
IFG only (19)	4
IGT only (37)	6
IFG+IGT (Both 39)	3
Type 2 DM (15)	7



In this study, 33 subjects have hypertension. Out of 110 subjects who had glucose dysregulation, 20 have hypertension whereas13 out of 136 subjects with normal glucose tolerance have hypertension. One of the subject who has diabetes had Grade I hypertensive changes in the fundus.

TABLE NO 9: Glucose dysregulation and complications

Complications	Type 2 DM
Retinopathy	2
Nephropathy	2
Neuropathy	1

In this study complications at the time of diagnosis of Type 2 DM were :

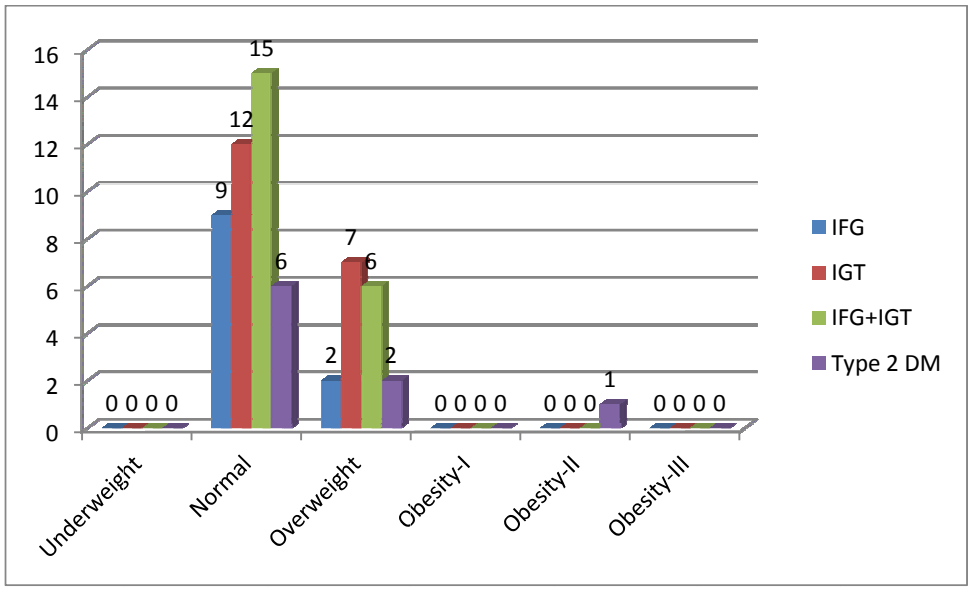
Two subjects who were diagnosed to have diabetes had diabetic retinopathy. One had mild NPDR- Non Proliferative Diabetic Retinopathy & another had moderate NPDR. The same two subjects also had diabetic nephropathy & one of them had diabetic neuropathy – Symmetric sensory polyneuropathy.

BMI was classified according to WHO as follows

Nutritional status	BMI in kg/m^2
Undernourished	<18.5
Normal	18.5-24.9
Over weight	25 to 29.9
Obesity – I	30 to 34.9
Obesity – II	35 to 39.9
Extreme obesity	≥40

TABLE NO. 10 : Relation between BMI (WHO criteria) and glucose dysregulation in MALE SUBJECTS

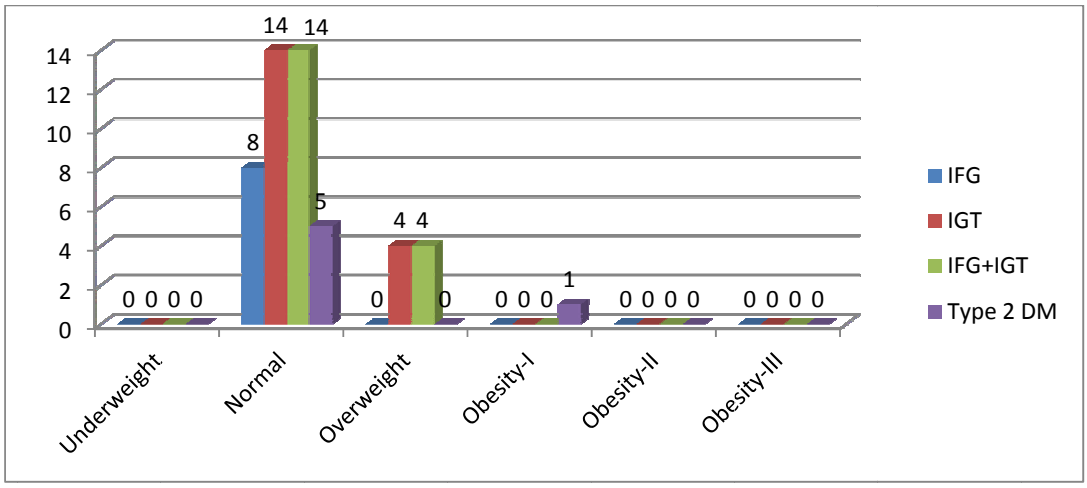
Nutrition	BMI in kg/m^2	IFG only	IGT only	IFG+IGT (Both)	Type 2 DM	Total
Underweight	<18.5	0	0	0	0	0
Normal	18.5-24.9	9	12	15	6	42
Overweight	25-29.9	2	7	6	2	17
Obesity-I	30-34.9	0	0	0	0	0
Obesity-II	35-39.9	0	0	0	1	1
Obesity-III	>40	0	0	0	0	0



In this study it was observed that when WHO criteria for classifying BMI was used, out of 60 male subjects with glucose dysregulation, 42 had BMI <25kg/m2. There were only 17 subjects with overweight and 1 had class II obesity.

TABLE 11 : Relation between BMI (WHO criteria) and glucose dysregulation in FEMALE SUBJECTS

Nutrition	BMI in kg/m^2	IFG only	IGT only	IFG+IGT (Both)	Type 2 DM	Total
Underweight	<18.5	0	0	0	0	0
Normal	18.5-24.9	8	14	14	5	41
Overweight	25-29.9	0	4	4	0	8
Obesity-I	30-34.9	0	0	0	1	1
Obesity-II	35-39.9	0	0	0	0	0
Obesity-III	>40	0	0	0	0	0



Similarly, when WHO criteria for BMI classification were used, 41out of 50 female subjects had BMI <25kg/m2, 8 female subjects were overweight & one had class I obesity.

TABLE NO. 12 : Table showing BMI (WHO CRITERIA) and its relation to glucose dysregulation in MALES AND FEMALES together

Nutrition	**BMI in kg/m^2**	**IFG only**	**IGT only**	**IFG+IGT (Both)**	**Type 2 DM**	**Total**
Underweight	<18.5	0	0	0	0	0
Normal	18.5-24.9	17	26	29	11	83
Overweight	25-29.9	2	11	10	2	25
Obesity-I	30-34.9	0	0	0	1	1
Obesity-II	35-39.9	0	0	0	1	1
Obesity-III	>40	0	0	0	0	0

In the present study using WHO criteria, in the male and female combined group 83out of 110 subjects with glucose dysregulation had BMI<25kg/m2, 25 subjects with glucose dysregulation were overweight, Two subjects with glucose dysregulation had Obesity.

In subjects with glucose dysregulation without obesity, 95 out of 108 (88 %) had pre-diabetes and only 13 (12 %) had diabetes. Among 4 obese persons two had normal glucose tolerance & two have diabetes.

TABLE NO. 13 : Relation between Hypertension, BMI and glucose dysregulation

Glucose dysregulation	Hypertension	BMI in kg/m^2		
		Normal	Overweight	Obese
IFG only	4	17	2	0
IGT only	6	26	11	0
IFG+IGT both	3	29	10	0
Type 2 DM	7	11	2	2

DISCUSSION

The present study was conducted on first-degree relatives of known cases of type2 DM to know the prevalence of impaired fasting glucose, impaired glucose tolerance, both or Type 2 diabetes mellitus. Though diabetes is classified into 4 major groups, prevalence of type2 DM exceeds 90% of all diabetes. As type2 DM can present directly with complications and thereby increase the morbidity and mortality, it is important to detect the disease earlier.

The relative risk of DM in a first-degree relative of a known case of type2 DM compared to general population is in between three to four fold. Therefore in this study, we screened subjects with genetic background for Type 2DM (i.e. family history), in order to detect them early, so that intervention with respect to environmental factors (i.e. life-style modification) & diet could help delay/prevent DM in them. Subjects with family history had two to three times higher risk of developing glucose intolerance. The role of hereditability has long shown that subjects with family history of diabetes develop diabetes earlier compared to subjects without family history.

To detect diabetes at an earlier age, oral glucose tolerance test is an ideal screening method. In this study, all the eligible candidates were subjected to

oral glucose tolerance test.

It was noted that the prevalence of diabetes was 6.1%. The present prevalence is less compared with studies conducted by Ramankutti et al., Ramchandran et al, Mohan et

al.9 CUPS-14 study which screened 1399 subjects with family hi story of diabetes, found that prevalence of diabetes to be 12%.

The prevalence of isolated IFG noted was 7.7 % in this study. Prevalence of IFG was found to be 5.3% of subjects in a study by Gupta A et al.[33] Jermendy G. et al. noted 13.1% prevalence of IFG in his study.[34] The prevalence of isolated IGT in the present study was 15.0 %. Similarly prevalence of IGT in the study, by C Snehalatha et al. in house to house survey, (Post OGTT) was found to be between 13.1 to 15.7%.[32] According to International Diabetes Federation (i.d.f.), the present prevalence of IGT in India is 14.2% [1],which co-relates with the present study. Similar conclusion was reached by A Ramchandran.[9] CUPS-14 study,[24] which conducted a similar type of study, noted prevalence of IGT to be around 5.9%.

The Diabetes Prevention Programme study (DPP) based on oral glucose tolerance test noted the prevalence of IFG and IGT together to be 27%, which is high compared to this study.

In the present study glucose dysregulation was observed in 50 subjects who were in 51-60 years age group , 34 subjects in 41-50 years age group & 26 subjects in 30-40 years age group. This is similar to the observation made by V. Mohan et al. In his study, prevalence of diabetes increased with age i.e, at age < 30 yr it was 0.6% where as at 60 to 70 yrs it was 34.2%.[24] Contrary to this observation, Bo S et al noted the prevalence of DM to be high amongst younger subjects with strong family history.[25]

In this study, out of 110 subjects with glucose dysregulation, n=47 (42.7%) had diabetic mother whereas n=43(39.1%) had diabetic father. This excess maternal

transmission was not observed in studies done by Ramchandran et al.,[22] Bo S et al[25] and Mitchell B.D. et al.[28] These authors observed that there was no significant difference amongst children with diabetes who had either diabetic father or mother. Familial aggregation of type2 DM was noted by Vishwathan et al. in a questionnaire based study, where they failed to replicate the evidence for excessive maternal transmission.[3]

In the present study it was noted that high prevalence of hypertension existed amongst subjects with pre-diabetes and diabetes. Similar opinion was observed by A Ramchandran et al,[28] V. Mohan et. al[24] and Gupta A et al.[33]

In this study, prevalence of pre-diabetes & Type 2 DM is more common in overweight & obese individuals compared to persons with normal BMI. In present study microvascular complications were detected at the time of diagnosis of Type 2 DM.

The results of present study highlight identification of pre-diabetes and diabetes at an earlier age. It also helps in detecting early complications of diabetes.

CONCLUSIONS

1. Screening of first degree relatives of known cases of type2 diabetes mellitus will help in diagnosing pre-diabetes and diabetes.

2. The overall prevalence of pre-diabetes and undiagnosed diabetes is very high in first-degree relatives of known case of type2 diabetes mellitus.

3.Prediabetes can be diagnosed much earlier by screening & onset of Type 2 DM can be prevented or delayed by diet & lifestyle modification.

4. Microvascular complications might be present at the time of diagnosis of Type 2 DM. Progression can be prevented or delayed by strict glycemic control & regular checkup.

5. Prevalence of pre-diabetes & Type 2 DM is more common in overweight & obese individuals compared to persons with normal BMI.

6. Hypertension is a very common associated condition in pre-diabetes and Type 2 DM.

SUMMARY

In this study, 246 first-degree relatives of known cases of type2 DM were screened for IFG, IGT or Type 2 DM by doing 2 hour OGTT. Study group consisted of 144 male and 102 female subjects.

Out of 246 subjects, 136 had normal glucose tolerance, while 110 had glucose intolerance. 60 male and 50 female subjects had glucose dysregulation. Prevalence of both IFG and IGT n=39 (15.9 %) was more than that of diabetes n=15 (6.1 %), isolated IFG n=7 (7.7 %) or IGT n=37 (15.0 %).

In the present study glucose dysregulation was observed in 50 subjects who were in 51-60 years age group , 34 subjects in 41-50 years age group & 26 subjects in 30-40 years age group. It was more common in old age group. Out of 110 subjects with glucose dysregulation, n=47 (42.7%) had diabetic mother whereas n=43(39.1%) had diabetic father. It was observed excess maternal transmission compared to the paternal transmission.

In this study, 33 subjects have hypertension. Out of 110 subjects who had glucose dysregulation, 20 have hypertension whereas13 out of 136 subjects with normal glucose tolerance have hypertension

In this study complications at the time of diagnosis of Type 2 DM were :

Two subjects who were diagnosed to have diabetes had diabetic retinopathy. The same two subjects also had diabetic nephropathy & one of them had diabetic neuropathy – Symmetric sensory polyneuropathy.

In the present study using WHO criteria, in the male and female combined group ; 83out of 110 subjects with glucose dysregulation had BMI<25kg/m2, 25 subjects with

glucose dysregulation were overweight, Two subjects with glucose dysregulation had Obesity. There was significant correlation between overweight/obesity & glucose dysregulation.

The results of present study highlight identification of pre-diabetes and diabetes at an earlier age. It also helps in detecting early complications of diabetes

PROFORMA

"STUDY OF ORAL GLUCOSE TOLERANCE TEST IN FIRST DEGREE RELATIVES OF KNOWN TYPE2 DIABETIC PATIENTS" – A CROSS SECTIONAL HOSPITAL BASED STUDY

Name:	**IP. No:**
Age:	**Address:**
Sex:	**Date of Admission:**
Occupation:	**Date of Discharge:**
Religion:	**Status at Discharge:**

PRESENTING COMPLAINTS :

HISTORY OF PRESENTING ILLNESS :

PAST HISTORY :

PERSONAL HISTORY :

FAMILY HISTORY: TYPE2 DIABETES MELLITUS:

FATHER:YES/NO MOTHER:YES/NO

BROTHERS:YES/NO SISTERS :YES/NO

SONS : YES/NO DAUGHTERS : YES/NO

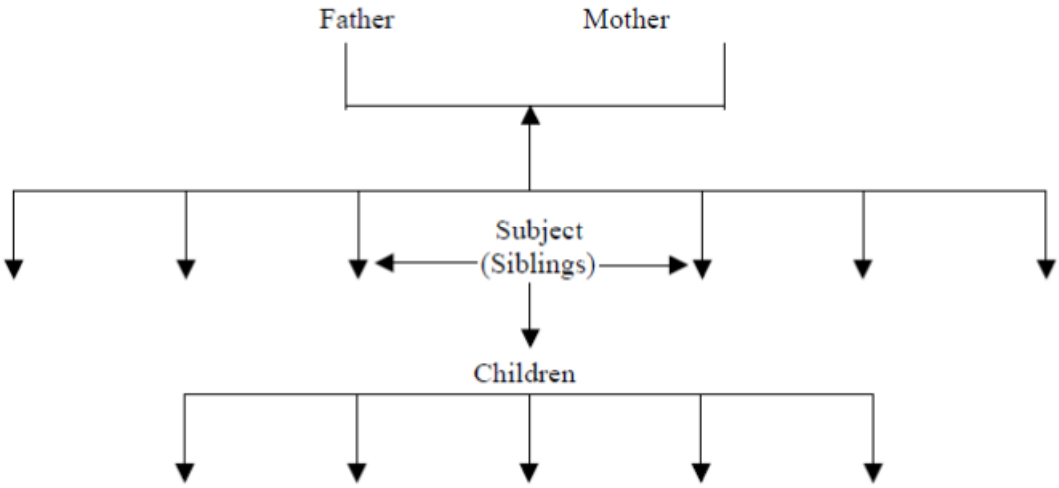


FIGURE NO. 2 : FAMILY HISTORY

GENERAL PHYSICAL EXAMINATION:

Pallor:

Icterus:

Cyanosis:

Clubbing:

Pedal edema:

Lymphadenopathy:

height: _____meters

weight _____kg

bmi_____kg/m^2

sclera : clear/muddy/yellow

xanthelesma: present/absent.

skin:

neck : thyroid gland - normal/enlarged:

VITALS

Pulse rate :

Blood pressure :

Temperature :

Respiratory rate :

GASTROINTESTINAL SYSTEM

Inspection :

Palpation :

spleen: palpable/not palpable

liver: palpable/not palpable

Percussion :

Auscultation :

CARDIOVASCULAR SYSTEM **:**

inspection

palpation

percussion

auscultation

RESPIRATORY SYSTEM :

inspection

palpation

percussion

auscultation

CENTRAL NERVOUS SYSTEM :

higher mental functions

cranial nerves

motor system

sensory system

cerebellar signs

HIGH RISK FACTORS FOR DIABETES MELLITUS ADA 2004 GUIDELINES

1. Family history of diabetes
2. Overweight (BMI $\geq$ 25 kg/m^2)
3. Age > 45 years
4. Previously identified impaired fasting glucose (IFG) or impaired glucose tolerance (IGT)
5. Hypertension (> 140/90 mm Hg).
6. Hyperlipidemia (HDL < 35 mg/dl or triglyceride > 250 mg/dl, or both)
7. History of GDM or delivery of a baby over 9lb or 4.1 kg
8. Habitual physical inactivity.
9. Race or ethnicity with high risk of diabetes.

PROVISIONAL DIAGNOSIS :

INVESTIGATIONS

	2 Hour OGTT Fasting lipid profile Other relevant investigations	

DIAGNOSIS:

IMPRESSION:

CONCLUSION:

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