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Original Research Article

A study of microvascular and macrovascular complications in prediabetes

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ABSTRACT

Background: Prediabetes, a state defined by the presence of either impaired fasting glucose or impaired glucose tolerance is a condition in which blood glucose or haemoglobin A1c (HbA1c) levels are higher than normal but not high enough to be classified as diabetes.
Methods: The present study was conducted for a period of one year with effect from November 2014 to October 2015 and patients were recruited for study from OPD and wards of Department of General Medicine, ASCOMS Hospital, Sidhra. 50 Patients/subjects were selected as per specified inclusion criteria Method of collection of data is based on detailed history, clinical examination and routine investigations.
Results: In this study, out of 50 subjects, 8 case who were in the range of impaired glucose tolerance initially at the time of start of study gradually progressed to frank diabetes i.e. 15% over a study period of 1 year.
Conclusions: In this study, 50 Patients of impaired glucose tolerance or prediabetes were included in the study. Among 50 subjects, 80% were male and 20% were females. Majority were 30-60 yrs of age, average weight was 65±5 kg, and average height was 150±10cm. In risk factors, 20% of the subjects suffered from hypertension, 40% from lipid derangement, 30% suffered from obesity, 50% suffered from central obesity, 56% are smokers, and 60% have family history of diabetes. 10 subjects out of 50 i.e. 20% suffered from cardiovascular complications, no subject presented with peripheral neuropathy.

Keywords: Complications, Diabetes, Impaired glucose tolerance, Macrovascular, Microvascular, Prediabetes

INTRODUCTION

Prediabetes, a state defined by the presence of either impaired fasting glucose or impaired glucose tolerance is a condition in which blood glucose or haemoglobin A1c (HbA1c) levels are higher than normal but not high enough to be classified as diabetes.[1] Prediabetes is due to two basic defects - insulin resistance and/or beta cell failure.[2] In 2012, approximately one in three U.S. adults aged ≥20 years (an estimated 86 million Americans) had Prediabetes.[1] Each year, 11% of persons with prediabetes who do not lose weight and do not engage in moderate physical activity will progress to type 2 diabetes during the average 3 years of follow-up.[2] And the condition isn't a concern only for adults, The American Academy of Paediatrics reports that one of the every 10 males and one of every 25 females age 12 to 19 have Prediabetes. In year 1999 to 2008, the prevalence of prediabetes increased significantly, from 9% to 23%.[3]

Prediabetes or Impaired glucose tolerance (IGT) is a term which was introduced by the National Diabetes Care Group, 1979 as "an intermediate stage in the transition from normal glucose tolerance (NGT) to overt Type 2 diabetes mellitus (Type 2 DM)".[4] American diabetes association revised Type 2 DM diagnostic criteria and declared a new term called Impaired Fasting Glucose (IFG) (glucose level 100-125 mg/dl) in 1997.[5] Clinical and epidemiological studies showed that IFG and IGT are different sorts of glucose intolerance. Both IGT and IFG

are called "prediabetes" because of gradual progression to Type 2 DM.[6] The Diabetes Control and Complications Trial (DCCT), the United Kingdom Prospective Diabetes Study (UKPDS) showed hyperglycemia is a risk factor for macrovascular and especially for microvascular complications.[7-9]

IGT is considered as a prediabetic state and the risk factors for progression to diabetes include[10]

- Family history of diabetes
- Cardiovascular Disease
- Obesity
- Sedentary lifestyle
- Non-white ancestry
- Previously identified metabolic syndrome
- Hypertension
- Increased levels of triglycerides, low concentrations of high-density lipoprotein cholesterol, or both
- History of gestational diabetes
- Delivery of a baby weighing more than 9 lb (4 kg)
- Polycystic ovary syndrome
- Receiving antipsychotic therapy for schizophrenia and severe bipolar disease

There have been very few long term follow up studies on IGT on Indian subjects. The high rate of conversion from prediabetes to diabetes is expected to increase the prevalence of diabetes in the future.

Long term complications of IGT

- High glucose levels, even for short periods, can lead to serious complications. Prediabetes may be a precursor to Type2 diabetes.[11]
- People with prediabetes have a 1.5 fold risk of cardiovascular disease compared to people with normal blood sugar levels. Damage to larger blood vessels can result in heart disease, high blood pressure and stroke.[12]
- Kidney failure: There is evidence to link prediabetes to increased risk of early forms of nephropathy and chronic kidney disease (CKD), defined based on methods such as urinary albumin excretion rate (AER) and Estimated Glomerular Filtration Rate (eGFR).[13]
- Prediabetes status may be associated with an increased risk of diabetic retinopathy although the findings vary depending on the method of detection.[14]
- Neuropathies have been related to prediabetic state; the strongest supportive evidence relates to autonomic neuropathy, although the method of detection seems to be critical. Prediabetes has been found to be associated with decreased heart rate variability (HRV) a marker of parasympathetic function.[15] decreased postural changes in heart rate, increased prevalence of erectile dysfunction among men, and a worse profile in tests of sympathetic and parasympathetic functions.[16,17]

Microvascular complications in prediabetes

- Eye disease
  - Retinopathy (non proliferative and proliferative)
  - Macular edema
- Neuropathy
  - Sensory and motor (mono and polyneuropathy)
  - Autonomic
- Nephropathy

Macrovascular complications in prediabetes

- Coronary artery disease
- Peripheral vascular disease
- Cerebrovascular disease

METHODS

The present study was conducted for a period of one year with effect from November 2014 to October 2015 and patients were recruited for study from OPD and wards of Department of General Medicine, ASCOMS Hospital, Sidhra. 50 Patients/subjects were selected as per specified inclusion criteria.

Patients will be selected randomly among who have following risk factors:

- Family history of diabetes.
- Class of obesity- especially central or BMI >25.
- Dyslipidaemia.
- Ethnicity other than Caucasian.
- History of GDM.
- History of baby weighing >9 lbs.
- Sedentary life style.
- Smokers.

Inclusion criteria

- Patients having impaired glucose tolerance i.e. fasting blood sugar level: 110-125 mg/dl.
- 2hr post prandial blood sugar level 140-199 mg/dl.
- An HbA1c value of 5.7% to 6.4%.

Exclusion criteria

- Patients having IGT taking drugs which causes elevation of blood sugar like steroids, thiazide diuretics etc.
- Patients having eye disease due to other chronic inflammatory disorders e.g. hypertension
- Patients having proteinuria due to other illnesses e.g. rheumatoid arthritis, osteomyelitis, psoriatic arthritis, leprosy.

- Patients having peripheral vascular disease due to Berger's disease and other chronic non diabetic conditions.
- Patients having frank diabetes and is on drugs whose blood sugar is in range of definition of impaired glucose tolerance.
- Patients with Fever.
- Patients with Hematuria.
- Patients with acid base imbalance.
- Patients with thyroid dysfunction.
- Patients with evidence of UTI.
- Withdrawal of consent.

Method of collection of data

All the participants who fulfilled the mentioned criteria were explained the purpose of the study and written consent was obtained from them.After attaining approval from Institutional ethical committee informed consent was taken from all the subjects.Total number of 50 patients/subjects, were included on basis of following parameters:

Detailed history

Regarding the symptoms of diabetes like polyuria, polydipsia, polyphagia, weight loss and other symptoms of diabetes. History suggestive of microvascular and macrovascular complications was taken in details as follows:

- Peripheral neuropathy: Any history of tingling, numbness, burning sensation or any sensory loss.
- Autonomic neuropathy: Impotency and erectile failure, retention and incontinence of urine, impaired sweating, snoring and sleep apnoea.
- Diabetic Retinopathy: history of blurred vision, black spots, floaters and sudden vision loss.
- Diabetic Nephropathy: History of polyuria, oliguria, puffiness of face,
- Distension of abdomen and pedal edema.
- History suggestive of coronary artery disease or cerebrovascular disease.
- History suggestive of peripheral vascular disease.

Clinical examination

- Detailed examination to detect Peripheral neuropathy.
- Tests for autonomic dysfunction.
- Direct ophthalmoscopy.
- Detailed General physical examination.
- Detailed Systemic examination including respiratory, cardiovascular, neurological, peripheral vascular system and musculoskeletal system.

Routine investigations

- Hemoglobin
- TLC
- DLC
- ESR
- Blood sugar (Fasting and post prandial)
- HbA1c levels
- S. Bilirubin (Total/ direct/ indirect)
- S. Urea and creatinine
- Blood urea

Examination of urine

- Urine RM
- 24 hr urinary protein
- 24 hr urinary creatinine
- Albumin/creatinine ratio in spot urine sample
- Microalbuminuria (micral test)

Specific investigations

Eye diseases

- Fundus examination

Neuropathy

- Nerve conduction velocity (NCV)

Nephropathy

- Urine R/M
- 24 hr urinary protein
- 24 hr urinary creatinine
- Albumin /creatinine ratio in spot urine sample
- Microalbuminuruia (micral test)

Coronary artery diseases

- ECG
- Lipid profile
- Screening ECHO

Peripheral vascular disease

- Ankle brachial index (ABI)
- Colour Doppler

Cerebrovascular disease

NCCT head (if symptoms, signs or clinical examination suggestive of Cerebrovascular Disease).

RESULTS

In this study 2 patients out of 50 were aged between 20-29 years, 10 patients were of age between 30-39 years, 20 patients fell in age category 40-49 years, whereas there were 10 patients aged between 50-59 years. 6 and 2 patients were present in age category 60-69 years and 70-79 years respectively (Table 1).

Table 1: Distribution of cases according to age.

Age (Yrs)	No. of patients	Percentage
20-29	2	4.0
30-39	10	20.0
40-49	20	40.0
50-59	10	20.0
60-69	6	12.0
70-79	2	4.0

In this study 40 patients out of 50 were male and 10 patients were female. So the percentage of male and female patients in this study was 80% and 20% respectively (Table 2).

Table 2: Distribution of cases according to sex.

Sex	No. of patients	Percentage
Male	40	80
Female	10	20

In this study 5 patients out of 50 were of height between 140-149 cms, 20 patients were of height between 150-159 cms, 20 patients fell in category 160-169 cms, whereas there were 5 patients who had height between 50-59 years (Table 3).

Table 3: Distribution of cases according to Height.

Height (cm)	No. of patients	Percentage
140-149	5	10
150-159	20	40
160-169	20	40
170-179	5	10

In this study 5 patients out of 50 weighted between 40-49 kgs, 10 patients were of weight between 50-59 kgs, 15 patients fell in category of 60-69 kgs, whereas there were 15 patients weighing between 70-79 kgs. 5 patients were present in category 80-89 kgs (Table 4).

Table 4: Distribution of cases according to weight.

Weight (kg)	No. of patients	Percentage
40-49	5	10.0
50-59	10	20.0
60-69	15	30.0
70-79	15	30.0
80-89	5	10.0

In this study 8 patients out of 50 came out to be Preobese, 5 patients fell in obesity class 1, whereas there was 1 patient which fell in obesity class 2. 1 patient was classified as obesity class 3 (Table 5).

In this study out of 50 patients, 10 patients had hypertension, 15 patients were obese whereas 25 patients have central obesity. In this study 28 patients/ subjects were smoker and 30 patients had family history of diabetes. Out of 50 patients 20 patients had Dyslipidemia (Table 6).

Table 5: Distribution of cases according to BMI.

BMI	No. of patients	Percentage
Preobese	8	16
Obese class I	5	10
Obese class II	1	2
Obese class III	1	2

Table 6: Distribution of cases according to risk factors.

Risk factors	No. of patients	Percentage
Hypertension (BP>140/90mmHg)	10	20.0
Obesity	15	30.0
Central obesity	25	50.0
Smoking	28	56.0
Family H/o diabetes	30	60.0
Dyslipidemia	20	40.0

Among 10 patients out of 50 had Hypertension as risk factor whereas rest 40 was Non Hypertensive (Table 7). 15 patients out of 50 were obese whereas rest 35 was Non Obese (Table 8).

Table 7: Distribution of cases as per hypertension as risk factor.

Hypertension	No. of patients	Percentage
Hypertensive	10	20
Non Hypertensive	40	80

Table 8: Distribution of cases as per obesity as risk factor.

Obesity	No. of patients	Percentage
Obese	15	30
Non Obese	35	70

Table 9: Distribution of central obesity according to sex.

Sex	No. of patients	Percentage
Male	17	34
Female	8	16
Normal	25	50

Out of 25 centrally obese patients 17 were male patients whereas 8 were female (Table 9). 28 patients out of 50 were smoker whereas rest 22 were non smoker (Table 10). 30 patients out of 50 had family history of diabetes whereas rest 20 had no such history (Table 11). 20 patients out of 50 had dyslipidemia whereas rest 30 were normal (Table 12).

Table 10: Distribution of cases as per smoking as risk factor.

Obesity	No. of patients	Percentage
Smoker	28	56
Non Smoker	22	44
Obesity	No. of patients	Percentage

Table 11: Distribution of cases as per family history of diabetes as risk factor.

Obesity	No. of patients	Percentage
Family H/O diabetes	30	60
No family history	20	40

Table 12: Distribution of cases as per dyslipidemia as risk factor.

Obesity	No. of patients	Percentage
Dyslipidemia present	20	40
Dyslipidemia absent	30	60

From which 10 patients had increased cholesterol levels, 8 patients had increased LDL levels whereas 6 had decreased HDL levels. 12 patients/ subjects had increased triglyceride levels (Table 13).

Table 13: Dyslipidemia.

Type	No. of patients	Percentage
Increased cholesterol	10	20
Increased LDL	8	16
Decreased HDL	6	12
Increased triglyceride	12	24

Table 14: Incidence of complications in prediabetes.

Complications	No. of patients	Percentage
Progression to frank diabetes	8	15.0
Cardiovascular	10	20.0
Cerebrovascular	3	6.0
Peripheral vascular disease	4	8.0
Retinopathy	4	8.0
Nephropathy	1	2.0
Normal without complications	20	40.0

In this study out of 50 patients, 8 patients progressed to Frank Diabetes, 10 patients and 3 patients were seen to have presented with Cardiovascular and Cerebrovascular complications respectively. In this study 4 patients/ subjects had Peripheral Vascular Disease. 4 Patients and 1 patient were seen to have Retinopathy and Nephropathy respectively. Out of 50 patients 20 patients were Normal and showed no complications (Table 14).

Macrovascular complications at the time of presentation (Cardiovascular) 10 patients had presented with cardiovascular complications, out of which 1 patient had STEMI and 1 had NSTEMI. 2 patients presented with unstable angina (Table 15).

Table 15: Cardiovascular complications.

Type	No. of patients	Percentage
STEMI	01	10
Unstable angina	02	20
NSTEMI	01	10
Others	06	60

DISCUSSION

The present study was conducted for a period of one year with effect from November 2014 to October 2015 and patients were recruited for study from OPD and wards of Department of General Medicine, ASCOMS Hospital, Sidhra. 50 Patients of impaired glucose tolerance or prediabetes were included in the study. Among 50 subjects, 80% were male and 20% were females. Majority were 30-60 yrs of age, average weight was 65±5 kg, and average height was 150±10cm. In risk factors, 20% of the subjects suffered from hypertension, 40% from lipid derangement, 30% suffered from obesity, 50% suffered from central obesity, 56% are smokers, and 60% have family history of diabetes.

In this study, out of 50 subjects, 8 case who were in the range of impaired glucose tolerance initially at the time of start of study gradually progressed to frank diabetes i.e. 15% over a study period of 1 year, which is consistent with most of the western studies which shows that the rate of progression to diabetes varies from 10% to 15% per year.[18]

Among 10 subjects out of 50 i.e. 20% suffered from cardiovascular complications. Out of which 2 subjects i.e. 20% seek medical attention on complain of sudden onset of retrosternal chest pain with ghabrahat and admitted in CCU. On investigation one patient showed ST segment depressed with T wave inversion in anterior precordial leads, and the other patient showed ST segment elevation. Cardiac biomarkers were positive in both patients. 2 subjects presented with angina on rest, ECG changes and biomarkers favoured diagnosis of unstable angina. 6 subjects suffered from angina, in which ECG, cardiac biomarkers were found to be negative but exercise stress test was positive. The results are consistent with Tominaga study.[19] Tominaga et al, found that risk of death from cardiovascular disease was significantly increased in those with IGT.[19] Glucose tolerance and cardiovascular mortality comparison of fasting and 2-hour diagnostic criteria have demonstrated that IGT is

associated with an increased risk of cardiovascular mortality as shown by DECODE study group.[20]

In our study, cerebrovascular complications in the form of ischemic strokes and TIA were reported in 3 subjects i.e. 6%.While diabetes is a known risk factor for vascular disease and stroke, more data support the idea that the effects of abnormal blood glucose can have adverse health consequences, even before frank diabetes develops, as stated by Fonville et al.[21]

Jia Q et al, comprised of 2186 consecutive first-ever acute ischemic stroke patients with baseline HbA1c values.[22] After excluding patients who died from non-stroke recurrence and patients lost to follow up, 1817 and 1540 were eligible for 3-month and 1-year analyses, respectively. Multivariate Cox regression was performed to evaluate the associations between HbA1c and 3-month and 1-year stroke recurrence a higher "normal" HbA1c level reflecting pre-stroke glycaemia status independently predicts stroke recurrence within one year after non-cardioembolic acute ischemic stroke onset. Peripheral vascular disease was reported in 4 subjects i.e. 8%. The results are in with support with some of well-known European studies which states that a body of evidence is accumulating that suggests that diabetes associated macrovascular diseases develops earlier than microvascular disease, when plasma glucose levels are in prediabetic range. Same observation was noted in the DECODE Study.[20] Because these abnormalities occur well before the onset of diabetes (as currently defined), Authors will refer to this form of macrovascular disease as dysglycaemic macroangiopathy. Microvascular complications in the form of retinopathy detected on fundus examination were reported in 8%.

In this study nephropathy detected by microalbuminuria was seen in 4% subjects.

In this study no subject presented with peripheral neuropathy.

CONCLUSION

This study was conducted for a period of one year with effect from November 2014 to October 2015 and patients were recruited for study from OPD and wards of Department of General Medicine, ASCOMS Hospital, Sidhra. 50 Patients of impaired glucose tolerance or prediabetes were included in the study. Among 50 subjects, 80% were male and 20% were females. Majority were 30-60 yrs of age, average weight was 65±5 kg, and average height was 150±10cm. In risk factors, 20% of the subjects suffered from hypertension, 40% from lipid derangement, 30% suffered from obesity, 50% suffered from central obesity, 56% are smokers, and 60% have family history of diabetes.

Annual progression to frank diabetes is 15% per year. Majority of them (prediabetics) suffered from cardiovascular complications i.e. 20%. Major events reported were acute myocardial infarction including both STEMI and NSTEMI, unstable and stable angina. Incidence of cerebrovascular complications is 6%. No patient presented with haemorrhagic stroke in this study. Incidence of peripheral vascular disease is 8%. Incidence of retinopathy is 8%. Incidence of nephropathy in the form of microalbuminuria is 4%. There was no case of peripheral neuropathy reported in this study. Incidence of complications is more in subjects having multiple risk factors like Hypertension, Obesity, Central obesity, Smoking, Family H/o diabetes and dyslipidaemia.

Pre diabetes has no signs or symptoms so it is important to be aware of the risk factors. Without lifestyle changes, including healthy eating, exercise and losing weight, approximately one in three people with pre-diabetes will eventually develop type 2 diabetes. The reasons for treating prediabetes include prevention of progression to diabetes, mitigation of some of the potential consequences of progression to diabetes as well as prevention of the potential consequences of prediabetes itself. Majority of the studies in this field of research have focused on diabetes incidence among prediabetic individuals and support the concept that lifestyle change should be the cornerstone for diabetes prevention.

Prediabetes increases mortality, morbidity and healthcare costs so it is accepted as an important public health problem. Thus, alleviating the progression of IGT and/or IFG to type 2 DM is a reasonable way to combat with diabetes epidemic and to lessen healthcare costs. Pre diabetes, type 2 diabetes and heart disease can be prevented by making lifestyle changes. In most cases, if enough lifestyle changes are made, type 2 diabetes can be prevented. Once diagnosed with pre-diabetes, lifestyle changes are most important. A repeat oral glucose tolerance test in 12 months, unless patient develops symptoms of diabetes is advised

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