A Dissertation on

MICROVASCULAR COMPLICATIONS AND METABOLIC SYNDROME IN NEWLY DIAGNOSED TYPE 2 DIABETICS OF LOW SOCIO-ECONOMIC GROUP

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CERTIFICATE

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DECLARATION

I solemnly declare that this dissertation entitled **"MICROVASCULAR COMPLICATIONS AND METABOLIC SYNDROME IN NEWLY DIAGNOSED TYPE 2 DIABETICS OF LOW SOCIO-ECONOMIC GROUP"** was done by me at Madras Medical College and Government General Hospital during the academic years 2006 – 2009 under the guidance and supervision of **Prof. A.R.Malathy,M.D**. This dissertation is submitted to the Tamil Nadu Dr. M.G.R. Medical University, towards the partial fulfillment of requirement for the award of M.D. Degree in General Medicine (Branch – I).

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INTRODUCTION

Type 2 diabetes mellitus is associated with metabolic syndrome and specific microvascular complications namely diabetic retinopathy, diabetic nephropathy and diabetic neuropathy. Many studies had proven that persistent hyperglycemia and associated metabolic syndrome features like hypertension, dyslipidemia and obesity contribute to the development of microvascular complications. All these metabolic derangements exist for many years in the asymptomatic phase of type 2 diabetes and they predispose to development of complications even before clinical diagnosis.

India is claimed to be the diabetes capital of the world and it has a large low socio-economic group population affected by this disease. Chronic complications of diabetes cause a substantial burden for both the patient and the health care system. The level of awareness about the symptoms, complications of diabetes and the necessity for early and sustained care for the disease is lacking in low socio-economic group population. This target group tends to present late to the health care system and hence expected to have high prevalence of micro vascular complications compared to the general population with diabetes.

Metabolic syndrome is considered to be a precursor of type 2 diabetes. Metabolic syndrome usually is associated with high socio-economic group and western population, who consume high calories and follow sedentary lifestyle.

Hence it is thought to be a syndrome of plenty rather than poverty. Prevalence of metabolic syndrome in low socio-economic group has not been well studied.

There are very few studies in India about the prevalence of microvascular complications and metabolic syndrome in low socio-economic group population particularly in early stages of type 2 diabetes. There is lacuna of knowledge about the disease characteristics in this target group. This study aims to address this issue.

AIMS AND OBJECTIVES

1. To study the prevalence of micro vascular complications in newly diagnosed type 2 diabetes mellitus patients of low socio-economic group.
2. To assess the prevalence of metabolic syndrome in newly diagnosed type 2 diabetes mellitus patients of low socio-economic group.
3. To know the average duration of early presentation of diabetes in subsequent generations (generation gap of onset of diabetes) in subjects belonging to low socio-economic group.

REVIEW OF LITERATURE

DIABETES MELLITUS

DEFINITION[1]

Diabetes mellitus is characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both.

DIAGNOSTIC CRITERIA[1]

1. Fasting plasma glucose ≥ 126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 hours*.

(or)

2. 2 hour post load glucose ≥ 200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 grams anhydrous glucose dissolved in water*.

(or)

3. Symptoms of diabetes plus casual plasma glucose concentration ≥ 200 mg/dl (11.1 mmol/l). Casual is defined as any time of day without regard to time since last meal. The classic symptom of diabetes include polyuria, polydipsia and unexplained weight loss.

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

EPIDEMIOLOGY

Overall the prevalence of diabetes is expected to increase worldwide by 122% (from 135 million to 300 million people) from 1995 to 2025; 90% of these people will have type 2 diabetes. The developing world will suffer the most, with a predicted 170% increase in cases that will mainly affect the 45 to 64 years age group; by contrast the diabetic population in developed countries will increase by only 40% and particularly among those aged > 65 years[2].

Indian scenario

According to the most recent estimates India has the largest number of diabetic patients in the world, estimated to be 40.9 million in the year 2007 and expected to increase to 69.9 million by the year 2025[3]. Type 2 diabetes in Asian Indians differ from the western population in that the disease onset is at younger age, obesity is less common, and genetic factors appear to be more common[4]. Both thrifty genotype and thrifty phenotype hypotheses hold good for the Indian population. Thrifty genotype hypothesis is applicable to the Indian population as a whole while thrifty phenotype could be applicable for low-socio economic group population.

Thrifty Genotype v/s thrifty phenotype

Thrifty Genotype hypothesis

Because food supply was neither predictable nor consistent throughout most of the history of Homo sapiens, it is likely that ancestral hunter-gatherers experienced alternating cycles of feast and famine[5]. It is postulated that evolutionary pressures in the late Paleolithic era favored the selection of 'thrifty genes' for efficient intake and utilization of fuel stores[6] thereby promoting storage of fuel for periods of impending famine. It appears that these thrifty genes have not changed appreciably for the past 10,000 years and certainly not with the explosion in the prevalence of type 2 diabetes during the past 40 to 100 years[7].

Thrifty phenotype hypothesis

Retrospective studies have shown that low birth weight is associated with insulin resistance and type 2 diabetes in adult life (especially in subjects who become obese), perhaps indicating that poor fetal nutrition may influence long-term metabolic responses[8]. Maternal protein restriction has been shown to be associated with many metabolic defects in adult offspring, including insulin resistance[9].

Type 2 Diabetes in Low Socio – economic group

Possible causes are:

1. Thrifty phenotype, poverty, lack of education and awareness about diabetes and inner-city deprivation emerge as significant risk factors.
2. Dramatic increases in the consumption of low-cost fat and simple carbohydrate calories have resulted in steep increases in incidence of overweight and obesity even among the poorest individuals.
3. Increase in life expectancy even among low socio-economic group is also important, as diabetes prevalence rises with age.

PATHOGENESIS OF TYPE 2 DIABETES

Genetics v/s Environmental Factors

Diabetes is viewed as a multi-factorial disorder with genetic factors conferring an increased susceptibility upon which environmental factors must act in order for hyperglycemia to develop. It is estimated that between 25 and 75% of the occurrence of type 2 DM can be attributed to genetic factors[10]. Type 2 DM is a polygenic disorder. The interaction between genetic and environmental factors varies between populations and between persons. Recent rise in the incidence of diabetes to pandemic proportions must be largely attributed to the environmental factors mainly diabetogenic life-style factors. As

modern lifestyles spread, the most genetically vulnerable individuals develop diabetes first followed progressively by the capture of those with lower inherited susceptibility; those with the most protective genetic make-up mainly remain unaffected. Thus communities and ethnic groups with different underlying genetic susceptibilities will develop different prevalence rates of diabetes in response to a similar degree of life-style change.

Insulin Resistance v/s Beta cell failure

Most patients with type 2 dm exhibit two apparently different defects:

(a) Insulin Resistance- an impairment in the ability of muscle, fat and liver to respond to insulin action

(b) Failure of beta cell to compensate for this insulin resistance by appropriately increasing insulin secretion[11].

The ability of beta cells to adapt to insulin resistance by increasing insulin secretion depends on various genetic factors that determine the total beta cell mass, rates of replication and apoptosis of the cells, and the activity of the key biochemical components of these cells[12-14]. In addition, environmental factors can probably aggravate the genetic predisposition to beta cell failure. Even though the beta cell failure occurs, there is substantial secretary capacity maintained by remaining beta cells. Thus the plasma insulin concentration is high enough to prevent the massive increases in triglyceride break down and

ketone-body formation in type 2 diabetes. This feature differentiates Type 2 from Type 1 diabetes.

Natural history of type 2 diabetes

Insulin resistance is a consistent finding in type 2 diabetes[15-17] Prospective studies have shown that insulin resistance predates the onset of type 2 diabetes by 10 to 20 years and is the best clinical predictor of subsequent development of type 2 diabetes[18,19]. Type 2 diabetes is characterized by an asymptomatic phase between the actual onset of diabetic hyperglycemia and clinical diagnosis. This phase has been estimated to last at least 4-7 years. Consequently 30% of type 2 diabetes patients remain undiagnosed[20]. Initially insulin resistance is compensated for by the adaptive capacity of the beta cells to increase insulin concentrations, thus preventing any serious disturbance in glucose homeostasis. Ultimately insulin secretion reaches a plateau, during which blood glucose levels rise initially into the subclinical stage of pre-diabetes. Pre-diabetes includes Impaired Glucose Tolerance (IGT) and Impaired Fasting Glucose (IFG). This process usually takes several years and IGT is considered as an intermediate stage in the evolution of Type 2 diabetes[21]. However, the development of frank diabetes mellitus appears to require an additional defect in insulin secretion[22]. This defect in insulin secretion called beta cell failure coincides with the progression from IGT to frank diabetes[23-27].

Clinical features

Type 2 diabetes has a gradual and insidious onset. Usual age of onset is over 40 years of age but increasingly the disease is becoming more common in younger adults and even in children. The diagnosis is made incidentally during hospital visits in almost one-third of cases and almost one-half do not complain of obvious diabetic symptoms.

Symptoms of diabetes

Classical symptoms of diabetes are polyuria, polydypsia, and weight loss. Other important symptoms of diabetes that help in diagnosis include fatigue, weakness, blurring of vision, repeated skin infections, non-healing wound, balanophosthitis, vulvovaginitis, pruritis vulvae, urinary tract infections, gingivitis, periarthritis shoulder, and neuropathic symptoms described below.

Treatment of type 2 dm

Assessment of glycemic control is best done by measuring biochemical parameters. Indexes such as body weight, frequency of polyuria, polydipsia, number of hypoglycemic reactions, fatigue and sense of well-being are important clinical parameters but can be misleading about the overall level of control. Patients with very poor control often can be identified easily by their symptoms; however patients whose fasting glucose levels are 140 to 180 mg/dl

and postprandial glucose levels are 180 to 240 mg/dl can feel quite well and present a false clinical picture of satisfactory diabetes control.

Clinical goals as defined by ADA

In the most recent standards of glycemic control, the ADA recommends a HbA1c of less than 7%, a pre-prandial plasma glucose level of 90 to 130 mg/dl and a postprandial plasma glucose level of less than 180 mg/dl[28].

Treatment options

Diet, lifestyle modifications, oral anti-diabetic drugs and insulin are the important modalities available. Choices of medications are individualized based on the duration of the disease, severity of metabolic derangements, motivation level of the patient with regards to the glycemic goals, awareness about the symptoms and hypoglycemic reactions. Majority of patients respond to treatment with oral anti-diabetic agents initially but over a period of time the response decreases. Almost 60 % of type 2 diabetes patients need insulin testament after 7- 10 years of diabetes detection, because oral hypoglycemic agents become ineffective[33,34].

Prognosis

Life expectancy is reduced by approximately 5-10 years in middle-aged people as compared to the general population[29-32]. Life expectancy is reduced

even more in women, in those with microvascular complications or cardiovascular risk factors and in those with a long duration of diabetes or whom the disease presented at a younger age and in those with poor blood glucose or blood pressure control[29].

MICROVASCULAR COMPLICATIONS IN DIABETES

Various systemic factors such as hyperglycemia, hypertension, dyslipedemia, over-activity of the sympathetic nervous system and vascular inflammation affect the tissues that are prone to diabetic micro vascular complications. All these changes begin to develop at least 9 to 12 years before clinical diagnosis.

On a cellular level, striking similarities exist between many mechanisms thought to be responsible for microvascular complications. Cellular mechanisms responsible are (a) formation of advanced glycation end-products due to increased intracellular glucose concentrations, (b) oxidative stress resulting from activation of polyol pathway and inhibition of pentose phosphate pathway (c) activation of Protein Kinase C.

The microvasclar complications of diabetes are diabetic neuropathy, diabetic retinopathy and diabetic nephropathy.

DIABETIC NEUROPATHY

(a) Chronic distal sensorymotor polyneuropathy (DSPN):

The most common form of Diabetic neuropathy is chronic distal sensorymotor polyneuropathy (DSPN) which is often insidious in onset and asymptomatic. It may be detected by chance during routine clinical examination and may present even with complications like painless foot ulcer. Acute sensory (painful) neuropathy is a distinctive variant of DSPN[35-37].

(b) Acute sensory (painful) neuropathy: Many of the symptoms of acute sensory and chronic sensorimotor neuropathy are similar but there are clear differences in the mode of onset, accompanying signs and prognosis. The differences between acute sensory and chronic sensorymotor neuropathy[37,40,41] is given below:

	Acute sensory	**Chronic sensorimotor**
Mode of onset	Relatively rapid	Gradual, insidious
Symptoms	Severe burning pain, aching: weight loss usual	Burning pain parasthesiae, numbness; weight loss unusual
Symptom severity	+ + +	0 to + +
Signs	Mild sensory in some: motor unusual	Stocking and glove sensory loss: absent ankle reflexes
Other diabetic complications	Unusual	Increased prevalence

Electrophysiological investigations	May be normal or minor abnormalities	Abnormalities unusual in motor and sensory nerves
Natural history	Complete recovery within 12 months	Symptoms may persist intermittently for years: at risk of foot ulceration

Contrary to the belief that acute painful neuropathy is always a small fiber neuropathy, a recent review based on sural nerve biopsies concluded that painful neuropathy is not restricted to selective involvement of small or large fibers[38-40]. It may be related to neural ischemia precipitated by sudden flux in blood glucose levels.

Apart from the above differentiation, based on the type of fibers involved neuropathy can be classified as described below into small and large fiber neuropathy.

(i) S**mall fibre neuropathy**

Symptoms: (a) positive symptoms[42] such as burning pain, pins and needles sensation, aching pain, paraesthesia, dysaesthesia – becoming worsened at night-time and when the patient is stressed or tired (b) negative symptoms include numbness.

Diagnosis: by 1 gm Semmes-Weinstein monofilament and pricking sensation using the Waardenberg wheel, thermal perception testing, quantitative autonomic function tests. Electro physiologically it is silent.

(ii) Large fibre neuropathy

Symptoms: impaired vibration sensation (often the first objective evidence) and position sense, depressed deep tendon reflexes and delta type deep-seated gnawimg , dull or even crushing or cramp-like pain, sensory ataxia, wasting of small muscles of feet.

Diagnosis: Bedside examination for ankle jerk and with 128 Hz tuning fork is important. Biothesiometry for measuring vibration perception, 10 gm monofilament testing for pressure sensation, thermal perception threshold testing are used. Nerve conduction studies are done mainly to rule out other causes of neuropathy or to identify neuropathies super imposed on DSPN.

Treatment of diabetic neuropathy

Glycemic control is of foremost importance. Maintaining stable blood glucose levels without fluctuations is particularly important in managing acute painful neuropathy. Symptomatic treatment for painful neuropathy includes tricyclic antidepressants, selective serotonin reuptake inhibitors, velnafaxine, topical capsaicin. Second line drugs include carbamazepine, gabapentin and lamotrigine. In patients with neuropathy utmost care should be taken to prevent progression to ulcer foot.

DIABETIC RETINOPATHY

Diabetic retinopathy is a highly specific vascular complication of both type 1 and type 2 diabetes and the duration of diabetes is significant risk factor for the development of retinopathy[43]. Hyperglycemia[33,44,45], hypertension[45], diabetic nephropathy[46], dyslipidemia[47], and pregnancy[48-50], present a significant risk for the development and progression of diabetic retinopathy. Broadly diabetic retinopathy is classified into nonproliferative and proliferative types.

Signs: Earliest sign is microaneurysm. Others include dot and blot hemorrhages, hard exudates, venous dilatation, venous beading or loop formation, Intra retinal microvascular abnormalities (IRMA), proliferative changes in retinal vessels, macular edema.

Diagnosis: Direct ophthalmoscopy with dilated pupil can be used to pickup signs. However for more precise screening fundus photography is done and compared with colour EDTRS standard photographs. Fundus fluorescein angiography is done to differentiate microaneurysm from dot hemorrhages and to study vascular abnormalities in the retina.

Treatment: Focal or panretinal (scatter) photocoagulation is done depending on the stage of the disease. Periodical follow up is very essential to know the progression of disease through various stages and to plan early treatment.

DIABETIC NEPHROPATHY

In the case of type 1 diabetics, nephropathy develops usually 5 years after diagnosis. Because of the indefinite start of the disease the natural history of diabetic nephropathy in type 2 diabetics is less well characterized. Characteristic features of diabetic nephropathy include albuminuria, unremarkable urinary sediment and majority having retinopathy preceding onset of nephropathy. Microalbuminuria is the earliest marker for diabetic nephropathy; however not all patients with microalbuminuria progress to overt proteinuria and renal failure. It is also an independent risk factor for cardio vascular disease.

Risk factors: Hyperglycemia, hypertension, dyslipedemia, genetical factors, ethnicity.

Diagnosis of microalbumiuria: Albumin/creatinine ratio, 24 hours urine albumin, albumin excretion rate are used. Persistent microalbumiuria on two of atleast three occasions within a 3 to 6 months period is considered as diabetic nephropathy.

Treatment: Apart from strict glycemic control normalizing or even sub-normalizing blood pressure is essential[51,52]. Angiotensin converting enzyme inhibitors and Angiotensin receptor blockers are first choice drugs in controlling hypertension and delaying progression of renal disease.

Epidemiology of microvascular complications in undiagnosed and newly diagnosed type 2 diabetes:

Prevalence of undiagnosed diabetes is about 30% of all cases of diabetes [53]. In secondary analysis of US National Health and Nutrition Examination Survey (NHANES) of undiagnosed diabetes patients, 24.9% were found to have nephropathy and 21.5% were found to have peripheral neuropathy[54]. 20% of persons of undiagnosed diabetes in the US population had retinopathy[55]. In Hoorn screening study conducted in Netherlands on newly diagnosed diabetic patients visiting general practice, 1.9% were found to have diabetic retinopathy, 48.3% were found to have impaired foot sensitivity, and 26.7% were found to have microalbuminuria[56].

Indian Scenario

In the Chennai Urban Rural Epidemiological Study (CURES) conducted in Chennai with a subgroup consisting of newly diagnosed diabetics from general population, 5.1% of subjects had retinopathy[57], 23.8% had microalbumiuria[58] and 3.6% had macroalbuminuria[58].

METABOLIC SYNDROME

Metabolic syndrome is characterized by clustering of metabolic abnormalities which included insulin resistance, glucose intolerance, huperinsulinaemia, dyslipidaemia and hypertension. This cluster occurring in the same individual appears to confer a substantial additional cardiovascular risk, over and above the sum of the risk associated with each abnormality[59-61].

Historical background

In the Banting lecture of 1988 Gerarld Reaven introduced the term 'syndrome X' for describing Metabolic Syndrome[62]. In 1989 it was described by Kaplan as the 'Deadly Quartet' [63] and then as the 'Insulin Resistance Syndrome' [64,65]. In 1936, Himsworth described two distinct forms of diabetes, insulin 'sensitive' and 'insensitive', and initiated the concept of insulin resistance as fundamental etiological factor in the development of type 2 diabetes[66]. Twenty years later, Vague observed that central distribution of adiposity was a risk factor for diabetes and atherosclerosis, accounting for the higher prevalence of these conditions in males[66]. In 1966 Welborn et al demonstrated that patients with essential hypertension had elevated insulin levels, highlighting the link between dysfunctional insulin action and risk of cardiovascular disease. In 1970s, Reaven's group showed that type 2 diabetes is

characterized by a reduction in insulin's ability to stimulate whole-body glucose uptake (insulin resistance) [63].

Epidemiology

Metabolic syndrome is believed to be driving the twin global epidemics of type 2 diabetes and cardiovascular disease. Prevalence of metabolic syndrome increases with age. Using the NCEP –ATP III guidelines, the estimated prevalence of metabolic syndrome in the United States is currently greater than 20% among all adults older than 20 years of age, and greater than 40% among the population older than 50 years. It is estimated that around a quarter of the world's adult population have metabolic syndrome[69] and they are twice as likely to die from and three times as likely to have a heart attack or stroke compared with people without the syndrome[59].

Role of various components of Metabolic Syndrome:

Among the components of metabolic syndrome insulin resistance and central obesity are considered important risk factors. Genetics, physical inactivity, ageing, proinflammatory state and hormonal changes may also have a causal effect, but the role of these may vary depending on ethnic group[70,71].

1. **Insulin resistance and atherogenic lipid profile –** Strongly associated with irregularities in both glucose and lipid metabolism, insulin resistance is the underlying feature of both metabolic syndrome and type 2 diabetes. Insulin

resistance causes decreased activity of lipoprotein lipase, and enhanced paracrine actions of cytokines in the adipose cells of abdomen result in increased delivery of free fatty acids to the liver via the portal circulation. This causes an increased production of VLDL and apolipoprotein B which in turn results in increased exchange of cholesteryl esters from HDL/LDL to VLDL along with triglyceride from VLDL TO HDL/LDL[72-75]. This accumulated triglyceride in LDL and HDL cause an increase in small dense LDL levels which in turn causes damage to vascular endothelial cells via generation of oxygen free radicals.

2. Central obesity and physical inactivity- Obesity contributes to hypertension, high serum cholesterol, low HDL-c and hyperglycaemia, and is independently associated with higher CVD risk[76-78]. The mechanism by which excessive body fat causes insulin resistance and impairs glucose metabolism is not clearly defined but fat stores (particularly visceral adipose tissue) are an important cause of increased FFA and TGL in the skeletal muscle, which impairs insulin secretion, raising blood glucose levels and the likelihood of developing diabetes. Excess adipose tissue (particularly the visceral fat tissue in the abdomen) also releases inflammatory cytokines that increase insulin resistance in the body's skeletal muscles. Furthermore, central obesity is also associated with a decreased production of adiponectin, which is the adipose-

specific, collagen-like molecule found to have antidiabetic, anti-atherosclerotic and anti-inflammatory functions[79].

Lack of physical activity may be pro-atherogenic independent of the associated weight gain. Aerobic exercise causes significant improvement in endothelial function[80].

3. **Hypertension and insulin resistance –**Whether hyperinsulinemia is a cause, a consequence or an epiphenomenon in hypertension remains controversial. But elevation in serum insulin concentrations in patients with essential hypertension had been demonstrated by various cross-sectional epidemiological studies[81-83].

Role of Metabolic syndrome in Type 2 diabetes and its complications

People with metabolic syndrome have a fivefold greater risk of developing type 2 diabetes[84]. Type 2 diabetes in reality is a descriptive term and a manifestation of a much broader underlying disorder[85] namely metabolic syndrome. Reaven demonstrated that subjects with IGT or established diabetes had similar degrees of insulin resistance[62]. Insulin resistance has more of an impact on macrovascular function while hyperglycemia is more closely associated with microvascular abnormalities, although there is a clear overlap.

Role of Metabolic syndrome in cardiovascular disease (CVD)

The risk of coronary artery disease is greatly increased not only in type 2 diabetes but also in IGT. Cardiovascular disease (CVD) is responsible for up to 80 percent of deaths in diabetics[86,87]. An increase in TGL, in addition to high LDL levels, significantly increases the risk for CVD while low HDL is considered to be a particularly key risk factor for CVD in both non-diabetic and diabetic individuals, as confirmed in epidemiological studies[88] and in the Lipid Research Clinics Prevalence Study[89], which found low HDL to be an independent contributor to CVD in both men and women and a stronger risk factor for CVD in people with diabetes compared with non diabetic individuals[90]. Significantly, low HDL and high TGL are frequently found with insulin resistance, with or without type 2 diabetes[91].

Treatment of Metabolic syndrome (IDF Recommendations)

Once a diagnosis of the metabolic syndrome is made, the future management of the condition should be aggressive and uncompromising in its aim to reduce the risk of CVD and type 2 diabetes. Patients should undergo a full cardiovascular risk assessment (including smoking status) in conjunction with the following:

- **Primary intervention**

The primary management for the metabolic syndrome is healthy lifestyle promotion. This includes moderate calorie restriction (to achieve a 5–10 per cent loss of body weight in the first year), moderate increase in physical activity, change in dietary composition. Studies have shown the marked clinical benefits associated with a small weight loss in terms of preventing (or at least delaying by several years) the conversion to type 2 diabetes among high-risk individuals with glucose intolerance who were, generally, obese[92,93].

• **Secondary intervention**

In people for whom lifestyle change is not enough and who are considered to be at high risk for CVD, drug therapy may be required to treat the metabolic syndrome. While there is a definite need for a treatment that can modulate the underlying mechanisms of the metabolic syndrome as a whole and thereby reduce the impact of all the risk factors and the long term metabolic and cardiovascular consequences, these mechanisms are currently unknown and specific pharmacological agents are therefore not yet available. Therefore it is currently necessary to treat the individual components of the syndrome, so that a reduction in the individual risk associated with each one will reduce the overall impact on CVD and diabetes risk.

IDF recommended treatment of the individual components of the

Metabolic syndrome:

(a) Atherogenic dyslipidaemia

Primary aims for therapy: Lower TGL (as well as lowering Apo B and non-HDL cholesterol), raise HDL-c levels, and reduce LDL-c levels (elevated levels represent a high risk in the metabolic syndrome)

Options: Fibrates or statins are mainly used. Fibrates in combination with statins can be used but may be complicated by side effects

(b) Elevated blood pressure

Categorical hypertension (BP ≥ 140 / ≥ 90 mm Hg) should be treated according to the JNC 7 recommendations. In patients with established diabetes, antihypertensive therapy should be introduced at BP ≥ 130 / ≥ 80 mm Hg[94].

(c) Insulin resistance and hyperglycaemia

There is growing interest in the possibility that drugs such as metformin and thiozolidinediones that reduce insulin resistance will delay the onset of type 2 diabetes and will reduce CVD risk when metabolic syndrome is present[95-97]. Similarly, other studies have shown that both acarbose and orlistat can be used to delay the development of type 2 diabetes in patients with IGT[98,99]. In addition, emerging therapies such as incretin mimetics, dipeptidyl peptidase IV inhibitors, protein tyrosine phosphatase 1B inhibitors, and the endocannabinoid receptor blocking agents offer potential as future therapies for the metabolic syndrome.

MATERIALS AND METHODS

Setting

Outpatient sections of the Department of Diabetology and the Institute of Internal medicine, Madras Medical College and Government General Hospital, Chennai – 3.

Collaborating Departments

The Institute of Internal Medicine and the Department of Diabetology, Madras Medical College and Government General Hospital, Chennai – 3.

Study Design

Single centre, cross-sectional and analytical study.

Period of Study

The work was carried out from March,2008 to September,2008, continuously over a period of seven months.

Ethical Committee Approval

Ethical committee approval obtained from the Institutional Ethical committee.

Inclusion Criteria

Newly diagnosed type 2 diabetic adult patients greater than 20 years of age belonging to low socio-economic group (as per modified Kuppuswamy scale[100]) who gave voluntary consent were included.

Exclusion Criteria

- Type 1 diabetes
- Pregnancy
- Patients on steroid therapy
- Patients on Angiotensin Converting Enzyme(ACE) inhibitors
- Patients on Angiotensin Receptor Blockers(ARB)
- Patients with urinary tract infections, fever, severely ill patients
- Alcoholics
- Smokers

Sample Size

103 newly diagnosed type 2 diabetic patients.

Consent

An informed consent was obtained from participants.

Selection of study subjects

Newly diagnosed type 2 diabetics were recruited randomly from the outpatient sections of the Department of Diabetology and Institute of Internal Medicine, Madras Medical College and Government General Hospital. All patients recruited belong to the low socio-economic group as per the Modified Kuppuswamy Scale criteria[100]. Initially 148 subjects were recruited, of which 45 were excluded (Impaired Glucose Tolerance-17, Impaired Fasting Glucose-8, patients on ACE inhibitors and ARB therapy - 4, chronic steroid therapy – 2, urinary tract infection - 5, alcoholics - 3, smokers -6)

Details of study subjects

Their ages ranged from 25 to 72 years. All study subjects were interviewed during their first visit of the study and their medical history was obtained using a proforma. Details of the history included age, education, occupation, monthly income, family history of diabetes (if family history is present in consequent generations, then the difference in age of diagnosis – "Generation gap" of diagnosis of DM), symptoms of diabetes and its complications, and reason for attending the out-patient department. Laboratory data collected include fasting plasma glucose, 2 hours post 75 grams plasma glucose(OGTT), fasting lipid profile – (total cholesterol, HDL,TGL), urine protein-creatinine ratio (if elevated, then urine culture and sensitivity and 24 hours urine protein were done). Anthropometric measurements including height, weight, waist

circumference and blood pressure measurements were recorded. Assessments of microvascular complications and presence of metabolic syndrome were done.

METHODOLOGY

Anthropometric measurements

Height was measured with a tape to the nearest one centimeter. Subjects were requested to stand upright without shoes with their back against the wall, heels together and eyes directed forward.

Weight was measured with weighing machine using spring balance that was kept on firm horizontal surface. The scale was checked every day and calibration was done with known weights. Care was taken that the subjects wear light clothing and weight was recorded to the nearest 0.5 kg.

Waist circumference was measured using a non-stretchable plastic measure tape. The participants were asked to stand erect in a relaxed position with both feet together and one layer of clothing was accepted. At the end of expiration waist circumference was measured at the midpoint of lowermost border of twelfth rib and uppermost point of the iliac crest.

Body Mass Index (BMI) was calculated using the formula:

$$BMI = \text{weight (Kg)} / \text{height } (m^2).$$

Blood pressure (BP) measurement

It was done by using the sphygmomanometer (Diamond Deluxe sphygmomanometer). BP was recorded after making the patient to rest in the sitting position for ten minutes. Average of two readings taken five minutes apart was taken into consideration.

Biochemical Tests

After a period of 8 to 12 hours fasting venous blood was drawn in the morning hours from the subjects visiting the out patient sections. Plasma glucose was measured by enzymatic (glucose oxidase – peroxidase) calorimetric method using semi auto- analyzer – ERBA CHEM -7. Lipid profile was measured by fully automated clinical chemistry analyzer - ERBA XL - 300. Total cholesterol and triglycerides were measured enzymatically. High density lipoprotein cholesterol was measured by immunoinhibition method. Urine protein measured by sulphosalicylic acid method. Urine creatinine was measured by picrate method.

Diabetic Neuropathy

(a) Symptomatic Neuropathy:

1. Positive symptoms (as compiled by consensus committee that examined end points for painful neuropathy[101]) – Painful sensations like burning,

prickling, tingling, squeezing, constricting, hurting, freezing, throbbing, allodynia, hyperalgesia were considered.

2. Negative symptoms – hypoesthesia, total loss of sensation.

(b) Quantitative Sensory Testing

Diabetic neuropathy was tested objectively by Bio-thesiometry. It was used for measuring vibration perception threshold (VPT). Patients having VPT of < 10 were considered as normal, 11 – 15 were considered as having mild, 16 – 20 as having moderate, > 20 as having severe neuropathy.

Diabetic Retinopathy

Patients were evaluated for retinopathy at the Department of Diabetology, Government General Hospital and Government Ophthalmology Hospital, Egmore by direct ophthalmoscopy examination of dilated pupil.

Presence of at least one micro aneurysm was taken as the minimum criteria for diagnosing diabetic retinopathy. Also other features such as venous changes (dilatations, beading, looping), hard exudates, dot or blot hemorrhages, intra-retinal microvascular abnormalities, proliferative changes in retinal vessels were considered for diagnosis.

Diabetic Nephropathy

Presence of microproteinuria (protein creatinine ratio ≥ 0.2 or 24 hours urine protein ≥ 150 mg) or macroproteinuria (protein creatinine ratio ≥ 3.0 or 24 hours urine protein ≥ 500 mg) in the absence of other obvious renal diseases. Patients with fever, cardiac failure, renal failure, urinary tract infection (by urine culture and sensitivity) were excluded for the diagnosis of micro/macro albumunuria.

DEFINITIONS

(a) Diabetes Mellitus

According to the American Diabetes Association (ADA) criteria[1] a fasting plasma glucose concentration of ≥ 126 mg/dl and a 2 hour post glucose plasma glucose concentration of ≥ 200 mg/dl.

(b) Metabolic Syndrome

As per the International Diabetes Federation (IDF) criteria[102],

Central obesity as defined by waist circumference **-for south Asians** (for males ≥ 90 cm, for females ≥ 80 cm. If BMI >30 Kg/m^2 then central obesity can be assumed and waist circumference need not be measured).

Plus any two of the following four criteria:

1. Raised triglyceride level ≥ 150 mg/dl or specific treatment for this lipid abnormality.
2. Reduced HDL cholesterol of < 40 mg/dl in males, < 50 mg/dl in females or specific treatment for this lipid abnormality.
3. Raised blood pressure – systolic BP ≥ 130 mm Hg, diastolic BP ≥ 85 mm Hg or specific treatment for previously diagnosed hypertension.
4. Raised fasting plasma glucose ≥ 100 mg/dl or previously diagnosed type 2 diabetes.

(c) Socio-economic status scale

Kuppuswamy's socioeconomic status scale is an important tool in hospital and community based research in India. It takes into account the education, occupation and total income of all the earning members of the family (family income per month) as the criteria for stratifying the socio-economic status. Initially it was proposed in 1976 [103] and later modified in 1998[104] and subsequently revised in 2007 [100] after adjusting for the current inflation with a new base year of 2001.

In this study, subjects with total score ≤ 10 are considered as belonging to low socio-economic group. The latest modification of Kuppuswamy's scale which was followed in this study is given below:

Kuppuswamy's Socioeconomic Status Scale:

(i) Education	**Score**
1. Profession or Honors	7
2. Graduate or post graduate	6
3. Intermediate or post high school diploma	5
4. High school certificate	4
5. Middle school certificate	3
6. Primary school certificate	2
7. Illiterate	1

(ii) Occupation	**Score**
1. Profession	10
2. Semi-Profession	6
3. Clerical, Shop-owner, Farmer	5
4. Skilled worker	4
5. Semi-skilled worker	3
6. Unskilled worker	2
7. Unemployed	1

(iii) Family income per month (Rupees)	**Score**
1. Above 19575	12
2. 9788-19574	10
3. 7323- 9787	6
4. 4894- 7322	4
5. 2936-4893	3
6. 980-2935	2
7. Below 979	1

Total Score	Socioeconomic class
26-29	Upper
16-25	Upper Middle
11-15	Middle, Lower middle
5-10	Lower, Upper lower
<5	Lower

(c) Family History

Family history of diabetes was considered as positive if at least one among the parents or the siblings or the off springs had diabetes. If family history is present in subsequent generations, then the difference in age of diagnosis – i.e, "Generation gap" of diagnosis of DM was noted.

(d) Physical Activity

Activity level was divided into sedentary and active based on a physical activity questionnaire comprising of job related activities and specific questions on exercise and leisure time activities. Housewives, retired persons, office-workers, watchmen, shopkeepers were classified as leading sedentary lifestyle after getting their history of daily activities including exercise and leisurely activities. Daily laborers including farm laborers, construction workers, hotel workers, and plumbers, carpenters, laundry workers, sales men and women were considered as having active lifestyle.

Conflict of Interest

There was no conflict of interest.

Financial Support

This work was not supported by grant from any funding agency or charitable organization.

Statistical Analysis

For comparing discrete variables (sex, metabolic syndrome, microvascular complications) with continuous variables (age, biochemical parameters, anthropometric measurements and blood pressure measurements) Student 't' test was used. For comparing between discrete variables 'Chi-Squared test' was used. Multiple logistical regression analysis was done using sex, metabolic syndrome and microvascular complications as dependent variable and biochemical parameters, anthropometric measurements, and blood pressure measurements as independent variables. Data was analyzed by SPSS statistical software and P value of < 0.05 was considered significant and P value of < 0.01 as more significant. Continuous variables were reported as mean ± standard deviation.

RESULTS

There were 103 participants in the study group. Their characteristics are provided below in Table 1.

Table 1: Characteristics of study group

Characteristics	Median	Mean ± SD
Age (years)	48	48 ± 10.0
Fasting Plasma glucose(mg/dl)	160.2	174.6 ± 46.8
2 hrs OGTT (mg/dl)	250.2	255.6 ± 75.6
Total cholesterol (mg/dl)	202	204.7 ± 41.9
Triglycerides (mg/dl)	191	218 ± 83.4
HDL (mg/dl)	44	44 ± 5.3
Systolic BP (mm Hg)	114	118 ± 18
Diastolic BP (mm Hg)	80	78 ± 8
Waist circumference (cm)	91	90.6 ± 8.7
Body Mass Index(Kg/m^2)	26	25.9 ± 4.5

Study group ages ranged from 25 to 72 years with a mean of 48 ± 10 and a median of 48 years. Mean values of biochemical parameters were: fasting plasma glucose - 174.6 ± 46.8 mg/dl, 2 hours OGTT - 255.6 ± 75.6 mg/dl, total cholesterol – 204.7 ± 41.9 mg/dl, triglycerides - 218 ± 83.4 mg/dl and HDL – 44±5.3 mg/dl. Mean values of other parameters include: systolic BP 118 ± 18 mm Hg, diastolic BP 78 ± 8 mm Hg, waist circumference 90.6 ± 8.7 cm and body mass index 25.9 ± 4.5 Kg/m^2.

Among the study group there were 48 males and 55 females comprising 46.6% and 53.4% respectively. The details are given in table 2.

Table 2: Sex wise distribution of the study group

Sex	Number(103)	Percentage
Male	48	46.6
Female	55	53.4

Age group wise distribution of the males and females belonging to the study group is given in table 3 and figure 1. Majority of the subjects belonged to age group 41 to 50 years which was followed by age groups 51 to 60 years and then by 31 to 40 years.

Table 3: Age group wise distribution of study group

Age (years)	Male	Female	Total number (103)	Percentage
21-30	3	2	5	4.8
31-40	9	13	22	21.3
41-50	16	22	38	36.8
51-60	13	15	28	27.1
>60	7	3	10	9.7

Prevalence of microvascular complications in the study group is mentioned in Table 4. Symptomatic neuropathy was present in 57.3% of subjects, of which 93.2% presented with positive painful symptoms and 6.7% presented with negative symptoms. Objective neuropathy (including asymptomatic neuropathy) was present in 39.8%, of which 68.3% have mild neuropathy and 31.7% have moderate neuropathy. None had severe neuropathy on objective testing. Asymptomatic neuropathy as detected by objective testing was present in 10.7% of total subjects.

Prevalence of retinopathy among the study subjects was 4.9%. Nephropathy as defined by the presence of micro or macro proteinuria was present in 18.4% of study subjects.

Table 4: Microvascular Complications in study subjects

Characteristics	Number (103)	Percentage
Symptomatic Neuropathy	59	57.3
Asymptomatic Neuropathy	11	10.7
Objective Neuropathy	41	39.8
Retinopathy	5	4.9
Nephropathy	19	18.4

Age group wise break up of microvascular complications are given in table 5. Both symptomatic and objective neuropathies have an increasing trend with age while retinopathy and nephropathy does not have a similar relationship.

Metabolic syndrome prevalence among the study group subjects are provided in table 6. Metabolic syndrome was present in 76.6% subjects, of which majority were females. Sex-wise distribution of metabolic syndrome is given in figure 2. Among females 87.3% had metabolic syndrome compared to 64.6% among males. This sex based increase in metabolic syndrome is statistically significant ($P < 0.01$).

Table 5: Age group wise prevalence of microvascular complications

Age group	Symptomatic Neuropathy		Objective Neuropathy		Retinopathy		Nephropathy	
	Number (59)	%	Number (41)	%	Number (5)	%	Number (19)	%
21-30	2	3.4	0	0	0	0	0	0
31-40	16	27.1	7	17	1	20	5	26.3
41-50	16	27.1	10	24.3	0	0	6	31.6
51-60	21	35.6	15	36.6	3	60	5	26.3
>60	4	6.8	9	21.2	1	20	3	15.8

Table 6: Prevalence of Metabolic syndrome

Sex	Total subjects	Subjects with Metabolic syndrome	Percentage
Male	48	31	64.6*
Female	55	48	87.3*
Total	103	79	76.6

*Significant ($P < 0.01$)

Prevalence of surrogate markers of insulin resistance which have a major role in the development of metabolic syndrome is given in table 7.

Among the study subjects, the overall average waist circumference was 90.6 ± 8.7 with males and females having an almost equal average waist circumference of 90.7 ± 8.4 and 90.5 ± 9.0 respectively. The body mass index (BMI) average was 25.9 ± 4.6, with males having an average of 24.9 ± 3.5 and females having an average of 26.9 ± 5.1.

Prevalence of overall abnormal waist circumference and BMI was 76.7% and 84.5% respectively. Among the males 62.5% had increased waist circumference and 79.1% had high BMI. Among the females 89.1% had increased waist circumference and 89% had high BMI.

Percentage of subjects having high TGL was 84.4% overall, with 85.4% in males and 83.6% in females. Total subjects having low HDL was 58.2%, with 41.7% in males and 72.7% in females.

Characteristics of the subjects who had metabolic syndrome are given in table 8 below. Among the subjects who had metabolic syndrome, there was 38% prevalence in the age group of 41-50 years followed by 29% prevalence in the age group of 51-60 years. Symptomatic neuropathy was present in 63% and objective neuropathy was present in 35% subjects. Also retinopathy was present in 5% and nephropathy in 15% of subjects. Among the subjects with metabolic

syndrome, family history of diabetes was present in 57%, sedentary lifestyle in 60% and active lifestyle in the remaining 41%.

Table 7: Prevalence of measures of obesity and surrogate markers of metabolic syndrome

Variables	Overall	Males	Females
Average of measures of obesity (Mean ± SD)			
Waist circumference (cm)	90.6±8.7	90.7±8.4	90.5±9.0
Body mass index (Kg/m^2)	25.9±4.6	24.9±3.5	26.9±5.1
Prevalence of measures of obesity (%)			
Waist circumference (M ≥ 90 cm, F ≥ 80 cm)	76.7	62.5	89.1
Body Mass Index (≥ 23)	84.5	79.1	89.0
Surrogate markers of Insulin Resistance (%)			
High Blood Pressure (mm Hg) (BP ≥130/85)	19.4	16.6	21.8
Hyper triglyceridemia (TGL ≥ 150 mg/dl)	84.4	85.4	83.6
Low levels of HDL (M < 40 mg/dl, F < 50 mg/dl)	58.2	41.7	72.7
Prevalence of Metabolic syndrome by IDF criteria (%)	76.6	64.6	87.3

Table 8: Characteristics of Metabolic syndrome positive study subjects

Metabolic Syndrome positive subjects (n=79)	Number	Percentage
Age Group (years)		
21-30	3	4
31-40	18	23
41-50	30	38
51-60	23	29
>60	5	6
Complications of Diabetes		
Symptomatic Neuropathy	50	63
Objective Neuropathy	28	35
Retinopathy	4	5
Nephropathy	12	15
Family History of diabetes	45	57
Sedentary lifestyle	47	60
Active lifestyle	32	41

The association of metabolic syndrome with age, sex, symptomatic neuropathy, objective neuropathy, retinopathy, nephropathy, fasting glucose, 2hours OGTT, TGL, HDL, systolic and diastolic blood pressure, waist circumference, body mass index was statistically analyzed as detailed above in table 9. Metabolic syndrome was significantly associated with sex ($P < 0.01$), HDL ($P < 0.05$), diastolic BP ($P < 0.05$), waist circumference ($P < 0.01$) and body mass index ($P < 0.01$).

The association of other dependent variables and independent variables among the total study subjects were statistically analyzed. In the Chi square tests, significance was noted between sex and diabetic nephropathy ($P < 0.05$). Also significance was noted between different age groups and both symptomatic neuropathy ($P < 0.05$) and objective neuropathy ($P < 0.01$).

In the 't' test, significance was noted between nephropathy and fasting plasma glucose ($P < 0.05$). Also significance was noted between lifestyle pattern and HDL ($P < 0.05$).

Multiple logistical regression analysis was also done. In this dependent variables like metabolic syndrome, microvascular complications, lifestyle pattern were compared individually with independent variables like biochemical parameters, waist circumference and blood pressure measurements. There was no statistical significance noted.

Table 9: Metabolic syndrome in relation to characteristics

Variables	*P* value
MS and age	0.226^{NS}
MS and sex	0.007**
MS and symptomatic neuropathy	0.195^{NS}
MS and objective neuropathy	0.101^{NS}
MS and retinopathy	0.858^{NS}
MS and nephropathy	0.122^{NS}
MS and fasting glucose	0.238^{NS}
MS and 2 hours OGTT	0.164^{NS}
MS and total cholesterol	0.225^{NS}
MS and Triglycerides	0.383^{NS}
MS and HDL	0.020**
MS and systolic BP	0.441^{NS}
MS and diastolic BP	0.027**
MS and waist circumference	0.000**
MS and body mass index	0.000**
MS and lifestyle	0.919^{NS}
MS and family history	0.477^{NS}

** Significant

NS- Not Significant

MS - Metabolic Syndrome

OGTT - Oral Glucose Tolerance Test

HDL - High Density Lipoprotein

BP - Blood Pressure

Details of the family history of diabetes are mentioned in Table 10. Family history of diabetes was present in 55.3%. Among the total subjects, 34.9% had family history of diabetes in either their parents or children. 20.4% of subjects had family history of diabetes only in their siblings.

Table 10: Pattern of family history in the study group

Family History	Number (103)	Percentage
Family history in subsequent generation	36	34.9
Family history in same generation	21	20.4
Total subjects with family history	57	55.3
Subjects without family history	46	44.7

All the subjects were asked for family history of diabetes and recorded as pedigree chart. The age of diagnosis of diabetes in family members was recorded as per their history. Of the 36 subjects with family history of diabetes in subsequent generation the **mean duration of early presentation was 16.4 ± 7.1 years** with a minimum of 5 years and maximum of 30 years.

Sex wise prevalence of family history is given in table 11. Family history was present in 52% of males and 58% of females.

Table 11: Sex-wise prevalence of family history

Family history	Males		Females	
	Number(48)	%	Number	%
Present	25	52	32	58
Absent	23	48	23	42

Not Significant ($P > 0.05$)

Lifestyle pattern of the study group is given in table 12. Active lifestyle was present in 40.7% and sedentary lifestyle in 59.2%.

Table 12: Lifestyle pattern of the study group

Lifestyle	Number(103)	Percentage
Active	42	40.7
Sedentary	61	59.2

Sex wise lifestyle pattern of the study group is given table 13. Active lifestyle was present in 65% of males and 20% of females. Sedentary lifestyle was present in 35% of males and 80% of females.

Table 13: Sex-wise lifestyle pattern of the study group.

Life style	Male		Female	
	Number(48)	**%**	**Number(55)**	**%**
Active	31	65	11	20
Sedentary	17	35	44	80

Significant ($P < 0.01$)

The reason for attending the Diabetology or Medicine outpatient clinic was asked to the subjects. Among them **76.7% were referred** from other departments of the hospital when there was a suspicion of diabetes. **23.3% of the total subjects presented themselves for diabetes screening**, either as part of master health checkup programme or because of doubts about their glycemic status (due to the symptoms of diabetes or family members having diabetes).

DISCUSSION

This is one of the very few studies specifically designed to study the disease characteristics in **newly diagnosed** diabetics. This is the first study from this part of India which targets exclusively **low socio-economic group**, who form the majority of the Indian population and who depend mainly on government health services. In this study the sample population had fairly equal representation between males (46.6%) and females (53.5%).

Various studies had been published regarding the prevalence of microvascular complications in diabetic population from different parts of India and the world involving different ethnicity. However very few studies had been published regarding the prevalence of microvascular complications in newly diagnosed type 2 diabetes as mentioned in table 14.

The prevalence of diabetic neuropathy varies between different studies depending on the methods used for diagnosis. Generally newly diagnosed diabetics have two types of neuropathy – (i) acute painful neuropathy which is related to uncontrolled hyperglycemia and sudden glucose flux and (ii) the classical neuropathy in diabetes - the chronic distal sensorymotor polyneuropathy (DSPN), which is related not only to hyperglycemia but also the chronic duration of the disease. Even this classical form is prevalent in newly diagnosed diabetics since the pathology of type 2 diabetes starts much earlier

Table 14: Studies on the prevalence of microvascular complications in NEWLY DIAGNOSED type 2 diabetes

Author	Number of subjects	Prevalence of microvascular complications					
		Objective Neuropathy		Retinopathy		Nephropathy	
		Method used	%	Method used	%	Type of albuminuria	%
Eva M. Kohne, et al[105]	2964			Fundus photography (ETDRS Protocol)	37.3		
Mohan Rema, et al[57]	351			Fundus Photography (ETDRS Protocol)	5.1		
Dowse GK, et al[107]	358			Fundus photography	14.8		
Annemieke MW Spijkerman, et al[56]	60	10 gram Monofila-ment	48.3	Fundus photography	1.9	Microalbuminuria	26.7
Richelle J Koopman, et al[54]	132	10 gram Monofila-ment	21.5			Microalbuminuria	21.5
Ranjit Unnikrishnan I, et al[58]	353					Microalbumiuria	23.8
Collins VR, et al[106]	138					Microalbuminuria	26.0

before clinical detection. In this study neuropathy was classified as symptomatic, asymptomatic and objective neuropathy.

The prevalence of symptomatic neuropathy in this study was 57.3% which is substantial. Symptomatic neuropathy includes patients with positive and negative symptoms. Among the symptomatic patients, majority (93.2%) had positive symptoms and only 6.7% had negative symptoms. Positive symptoms indicate either acute painful neuropathy or chronic DSPN and distinguishing these two based on symptoms alone is difficult since the nature of symptoms is common to both. From this predominance of positive symptoms in newly diagnosed diabetcs it is clear that the nature of neuropathy in newly diagnosed diabetes is mainly due to hyperglycemia (acute or chronic) and sudden glucose flux, leading to alteration in nerve function. Negative symptoms which represent a chronic pathology due to irreversible nerve damage were seen only in a minority since the study group included only newly diagnosed diabetics.

Objective neuropathy as detected by quantitative sensory testing (biothesiometry in this study) was detected in 39.8% of subjects. The Hoorn Screening study[56] done in newly diagnosed diabetics coming to general practitioners by Annemieke et al in Netherlands showed a prevalence of diabetic neuropathy as 48.3% by 10 gram monofilament testing. Another study done in United States using secondary analysis of the data from the National Health and Nutrition Examination Survey (NHANES) by Richelle J Koopman, et al,

showed a prevalence of diabetic neuropathy as 21.5% by 10 gram monofilament testing. Both these studies used 10 gram monofilament for detecting diabetic neuropathy, which though easy to use in clinical practice and sensitive, is less accurate for quantitative assessment of the severity of neuropathy when compared to biothesiometry used in this study.

The difference between prevalence of symptomatic neuropathy (57.3%) and objective neuropathy (39.8%) in this study is due to the fact that in early stages of small fiber neuropathy there will not be any objective signs even though positive symptoms are common. The presence of objective neuropathy at the time of diagnosis itself indicates that substantial proportion of patients was affected by chronic DSPN since acute painful neuropathy does not generally produce objective signs. This also emphasizes the ADA recommendation that all type 2 diabetic patients should be screened for microvascular complications at the time of diagnosis itself. Another inference is that substantial damage occurs to the peripheral nerves even at the time of clinical diagnosis since the asymptomatic phase of diabetes could be prolonged in this target population.

Asymptomatic neuropathy which includes subjects with no symptoms but showing abnormality in quantitative sensory testing was present in 10.7% of subjects. These asymptomatic patients also form part of the group with objective neuropathy.

Detection of objective neuropathy, more particularly asymptomatic neuropathy is very important since these groups are prone to develop severe neuropathy and present late to the health facility and hence the dangerous complication of developing diabetic foot ulcer leading to amputation. Another importance of this data is that the study group involved only low socioeconomic group who are prone to walk barefoot and at very high risk for diabetic foot ulcer. This also emphasizes the need to educate the patients regarding the perils of diabetic neuropathy and the importance of proper foot care.

The prevalence of diabetic retinopathy in the present study was 4.9%. Compared to a relatively older study[105] with a large sample, done in United Kingdom as part of the UKPDS study in newly diagnosed diabetics (which showed a very high prevalence of 37.3%), almost all studies[56,57,107] in the past 12 years showed a prevalence of retinopathy in the range between 1.9% and 15%. In many multiethnic studies[107,108] the prevalence of retinopathy in Asian Indians was comparatively low when compared to other ethnic groups. In the present study, the prevalence of retinopathy was 4.9% in low socioeconomic group and it was in line with the prevalence in CURES eye study[57] done in the same geographical area but in the general population without any socio-economic stratification.

Majority of the patients in the present study had mild form of nonproliferative diabetic retinopathy. None of the cases had severe

nonproliferative diabetic retinopathy or proliferative diabetic retinopathy. 80% of subjects with retinopathy had associated nephropathy. This association is well known and demonstrated in many other studies in diabetes.

The prevalence of diabetic nephropathy in the study group was 18.4%. All the subjects with diabetic nephropathy had microproteinuria. Only one subject had macroproteinuria but not included in the study, since the subject had preexisting Henoch-schonlein purpura and was on chronic steroid therapy. There was no major influence of high blood pressure on the development of microproteinuria in this study, since only 15.8% with microproteinuria had high blood pressure with systolic BP ≥130/85mm Hg.

The prevalence of microalbuminuria among newly diagnosed diabetics in different ethnic studies[54,56,106] range between 20% and 30%. In the CURES study[58] done in the same geographical area the prevalence of microalbuminuria was 23.8%. Present study which used microproteinuria as the method for diagnosis of diabetic nephropathy had shown a prevalence of 18.4%.

Metabolic syndrome (MS) which is considered as an important forerunner for both diabetes and cardiovascular disease (CVD) was analyzed in detail in this study among low socioeconomic group subjects. The prevalence of MS in this study was 76.6% among low socioeconomic group. This finding is important in the context that MS is considered a disorder related to high calorie intake and sedentary activity. The target population in this study was generally

expected to involve in jobs which require substantially high physical activity. But this study showed that sedentary lifestyle among low socioeconomic group was present in 60% of the MS positive subjects. The high prevalence of MS along with sedentary lifestyle in this study proves the fact that even the low socioeconomic group population are at increased risk for both diabetes and CVD.

Comparative studies on the prevalence of metabolic syndrome in newly diagnosed diabetics cannot be found in the literature. So studies done in general population and diabetic population from Asian Indians are compared with the study group. Table 15 gives details about comparative studies.

The recent studies done in Delhi and Jaipur in general population by Wasir JS, et al[109] where a subgroup included the diabetics showed a prevalence of MS as 73.5% by IDF criteria. Similarly another study done by Surana SP, et al[110] in Mumbai in diabetics showed a prevalence of MS as 77.2%. Both these recent studies published in 2008 along with other studies[112-115] though used different criteria for diagnosis, showed almost similar prevalence of MS. The present study also had a similar prevalence of MS (76.6%) in newly diagnosed diabetics of low socioeconomic group.

Another important finding of the present study was high prevalence of MS in females (87.3%) than males (64.6%) which was statistically very significant.

Table 15: Studies on the prevalence of metabolic syndrome

Author/target poulation	Total Subjects		Male		Female		Criteria used	Ethnicity (Geographical Area)
	Number	% of MS	Number	% of MS	Number	% of MS		
Wasir JS,Misra A, et al[109] **(Sub group with Diabetes)**	117	73.5	54	74.1	63	73	IDF	North India (New Delhi & Jaipur)
Surana SP, et al[110] **(Diabetics)**	5088	77.2	2908	69.33	2180	87.7	ATP III	West India (Mumbai)
Ramachandran A, et al[111] **(General population)**	475	41.1		46.5		36.4	ATP III	South India (Chennai)
Imam SK et al[112] **(Diabetics)**	233	68.1	116	49.1	117	87.0	IDF	Pakistan(Karachi)

This trend of high prevalence of MS in diabetic females was also shown by a very large study by Surana SP, et al[110] and many other studies. The present study also confirmed the same in newly diagnosed diabetics of low socioeconomic group.

MS was present in substantial number in all the age groups between 31 to 60 years and it was low in the age groups of 21- 30 years and > 60 years. Both these age groups had less number of study subjects compared to the other age groups. The reason for the low prevalence in 21 – 30 years age group could be they are considered to be more active and less obese. But the low prevalence in the >60 years age group could be due to the small size of the sample subjects in that group.

The prevalence of microvascular complications, family history and sedentary lifestyle in metabolic syndrome positive subjects was almost similar to the trend seen in the study group in total, which was discussed earlier.

The association of MS with age, sex, microvascular complications, biochemical parameters, anthropometric measurements, lifestyle and family history was statistically analyzed. There was significant association with sex, HDL, diastolic BP and BMI. The association with waist circumference could be due to the selection bias since only subjects with high waist circumference (obligatory criteria) were considered for defining MS (IDF Criteria).

Table 16: Studies on the prevalence of the measures of - Obesity and Metabolic Syndrome

Author / diabetic status of the study group	Waist circumference (M ≥ 90cm, F ≥ 80cm) %	BMI (> 23Kg/m^2) %	High TGL (≥150 mg/dl) %	Low HDL(mg/dl) (M < 40, F < 50) %	High BP ≥ 130/85 %	Geographical Area
Wasir JS, Misra A, et al[109] **(General population)** sample size – 2050						
Overall	44.5	45.3	26.97	65.21	36.9	North Indians (New Delhi & Jaipur)
Male	39.3	47.0	28.9	43.8	29.1	
Female	48.4	44.0	25.5	81.8	42.8	
Surana SP, et al[110] **(Diabetics-**sample size -5088)						
Overall	46.0	Not done	57.8	52.2	73.3	Western India (Mumbai)
Male	25.7		58.3	43.0	75.1	
Female	73.2		57.2	64.5	71.0	
Mohan V, et al [113] **(Sub group with Newly diagnosed diabetics)** Sample size - 61 Overall	50.8	34.4	52.5	41.0	47.5	South India (Chennai)

Studies featuring the prevalence of measures of obesity are mentioned in table 16. The study by Wasir JS, et al[109] was from the general population. The study by Surana SP, et al[110] was from the diabetic population and study by Mohan V, et al[113] was from a subgroup with newly diagnosed diabetics.

Among the total subjects who participated in the study the prevalence of the measures of obesity such as high waist circumference (76.7%), high BMI (84.5%), high TGL (84.4%) and low HDL (58.2%) were very high in the newly diagnosed low socioeconomic group subjects compared to the studies in general population[109], diabetic population[110], and newly diagnosed diabetic population[113]. When prevalence of measures of obesity in males and females are assessed individually, there was a trend of high prevalence noted in both sex for high - waist circumference, BMI and TGL - on comparsion to other studies[109,110,113.] Low HDL prevalence in males and females was in line with other studies[109.110,113.]

The prevalence of hypertension in total subjects (19.4%), males (16.6%), and females (21.8%) in the present study was comparatively lower to other studies[109,110,113]. The reason for this difference could be that present study was in newly diagnosed diabetics and these subjects may develop hypertension as the duration of diabetes increases along with the worsening of risk factors for obesity and MS.

Presence of family history in the study group was analyzed in detail. There was no significant difference in the prevalence of family history between males and females. Among a total of 55.3% subjects with positive family history, 34.9% had history of diabetes in at least one of their parents and 20.4% had family history in their siblings. This data was very high when compared to a study with a sub group of newly diagnosed diabetics by Mohan V, et al[113] in Chennai which had a prevalence of 19.7%. Thus people from low socioeconomic group have a very high genetic risk when compared to general population as per the results of this study.

Among the 34.9% subjects who had family history of diabetes in subsequent generations, the generation gap for the onset of diabetes based on clinical diagnosis was analyzed. A mean duration of 16.4 ± 7.1 years was obtained. This generation gap of about one to two decades in low socioeconomic group is very significant in formulating the preventive strategies for diabetes.

Contrary to the popular view that people from low socioeconomic group are more active and involve in labour intense jobs, this study had a majority of 59.2% leading a sedentary lifestyle. The sedentary lifestyle was predominant among females (80%) compared to males (35%) and it was statistically significant.

The awareness level of the subjects regarding diabetes was assessed from the data regarding the mode of referral. Only 23.3% subjects were able to present

themselves voluntarily for diabetes screening either because of awareness about symptoms of diabetes or because of family members being affected by diabetes or as part of Master Health Check-up programme. Majority of them (76.7%) were referred from other departments of the hospital. This indicates the fact that still three-fourths of the low socioeconomic group population is not aware of the importance of screening for diabetes and majority are diagnosed accidentally during health visits for other diseases.

Strength of the study

Rigid criteria for inclusion of only newly diagnosed diabetics and diagnosis of diabetes based on fasting plasma glucose and 2 hours OGTT, studying a wide array of disease characteristics in a single study with reference to a particular socioeconomic class, and comparability of the observation with intensely searched published articles done in subjects from different ethnicity and different geographical area make this study strong.

Limitations

Direct ophthalmoscopy was used in place of fundus photography for assessing retinopathy. Microproteinuria was measured instead of microalbumiuria for assessing nephropathy. But this was mainly based on logistical reasons.

Suggestions

Many more large scale multi-centric studies focused on population from low socioeconomic class are needed to validate the findings of this study since such data are of immense value in formulating strategies for targeted health delivery.

CONCLUSION

- Prevalence of microvascular complications in newly diagnosed diabetics of low socioeconomic group were as follows: symptomatic neuropathy – 57.3%, objective neuropathy – 39.8%, retinopathy – 4.9%, nephropathy – 18.4%. These were similar to published studies from general population from the same geographical area.
- Prevalence of metabolic syndrome (76.6%) and measures of obesity in newly diagnosed diabetics in an unexpected manner had a similar trend in low socioeconomic group when compared to data from various studies among general population.
- Significant association ($P < 0.01$) was noted between metabolic syndrome and sex with an increasing trend in females. Similarly association ($P < 0.05$) was found between metabolic syndrome and diastolic blood pressure, HDL and BMI.
- Majority of females of low socioeconomic group had high BMI (89%), and had high prevalence of metabolic syndrome (87.3%) when compared to males of the same class. Significant association ($P < 0.01$) was found between sex and lifestyle with majority of females leading a sedentary lifestyle.

- High prevalence of family history (55.3%) indicates that genetic component could play a major role in the pathogenesis of diabetes in low socioeconomic group diabetics.
- Average generation gap for onset of diabetes based on clinical diagnosis was 16 years in low socioeconomic group.
- Only 23.6% of subjects presented themselves for screening and 76.7% of diabetics were detected by chance during health visits to doctor for some other disease.

SUMMARY

Microvascular complications and metabolic syndrome are well known facts related to type 2 diabetes. However there is paucity of data regarding the disease characteristics in low socioeconomic group. This is the reason for designing a cross sectional study of this type.

Aims and objectives were to find the prevalence of microvascular complications and metabolic syndrome in newly diagnosed type 2 diabetics of low socioeconomic group. Another objective of this study was to find out the generation gap of onset of diabetes in low socio economic group.

The data was collected from a sample of 103 newly diagnosed diabetic subjects belonging to low socioeconomic group. The data was analyzed statistically. The results of the study revealed a prevalence of symptomatic neuropathy (57.3%), objective neuropathy (39.8%), retinopathy (4.9%), nephropathy (18.4%) and metabolic syndrome (76.6%).

Sex, diastolic blood pressure, HDL and lifestyle were important risk factors associated with metabolic syndrome in this study.

One would expect a higher prevalence of microvascular complications in low socioeconomic group, because of the tendency to seek the health facility after a delayed period. This is due to lack of awareness about symptoms of diabetes and its complications and low educational level. Also another expectation is

lower prevalence of metabolic syndrome in low socioeconomic group since they consume less calorie rich diet and involve in labour intense jobs.

However, contrary to these expectations the prevalence of microvascular complications was similar in trend with the studies from general population in the same geographical area. Also the prevalence of metabolic syndrome was similar to the trend observed from studies in general population in India. Hence low socioeconomic group people are not different from general population as far as microvascular complications or metabolic syndrome is concerned. They should be subjected to screening for microvascular complications at the time of diagnosis itself.

Low socioeconomic group females were at more risk of diabetes and cardiovascular disease because of metabolic syndrome, obesity risk factors, and sedentary lifestyle when compared to males.

Future health policies of the government targeting low socioeconomic group population should focus more on creating awareness, not only about diabetes and its complications but also about promoting active lifestyle. Since the onset of diabetes was one to two decades earlier in subsequent generations in this study and majority of the study subjects were diagnosed by chance during health visits for other diseases, focus should be more on detecting cases earlier by targeted screening and initiating appropriate prevention strategies.

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LIST OF FIGURES

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2	Sex-wise distribution of metabolic syndrome positive subjects
3	Lifestyle pattern of study group

Figure 1: Age-wise and sex-wise distribution of the study group

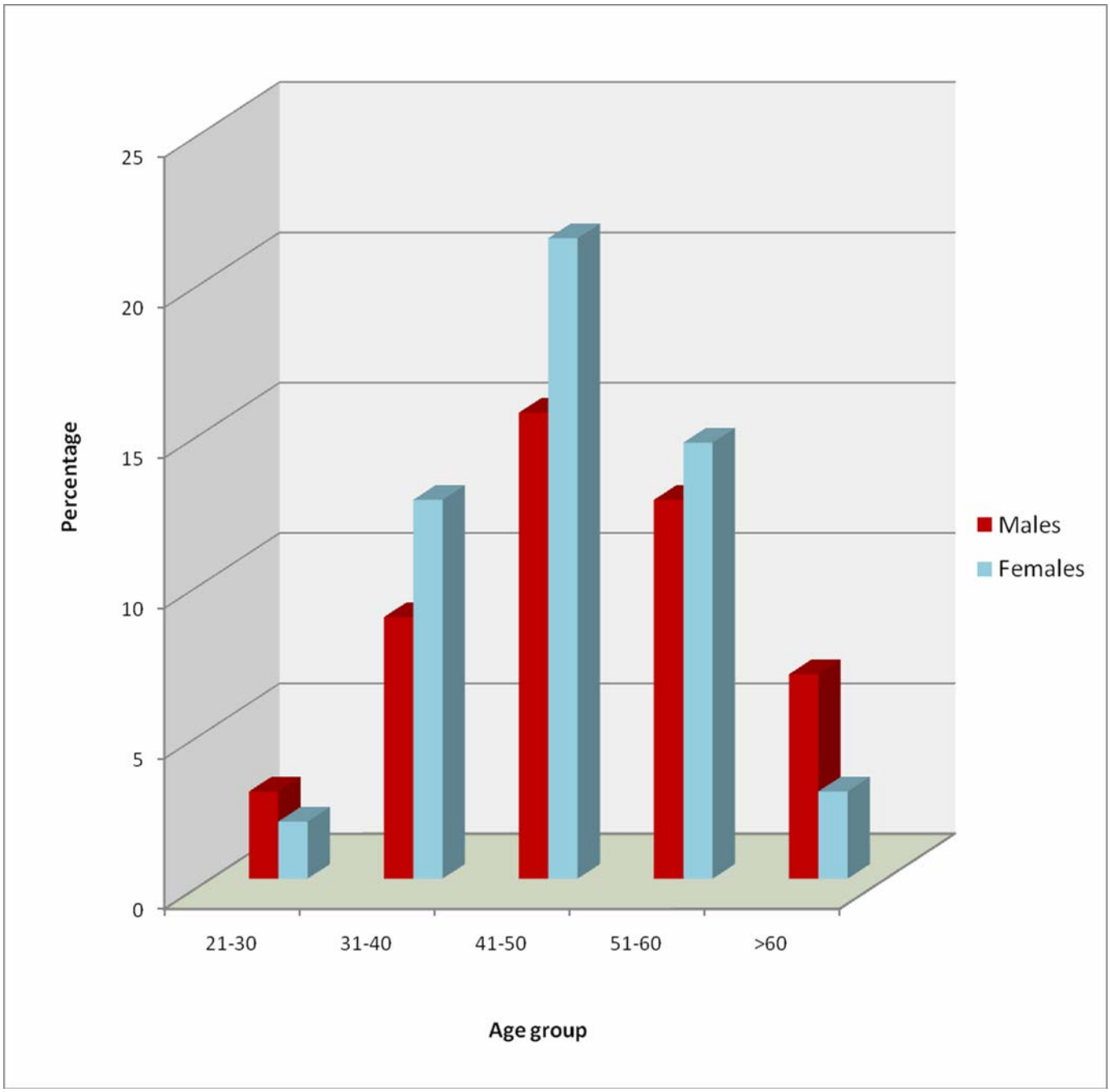


Figure 2: Sex-wise distribution of metabolic syndrome positive patients

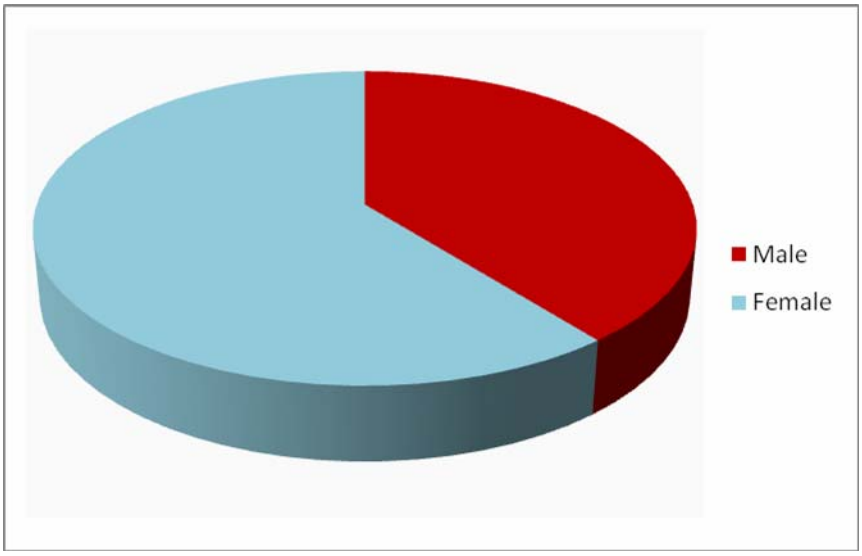
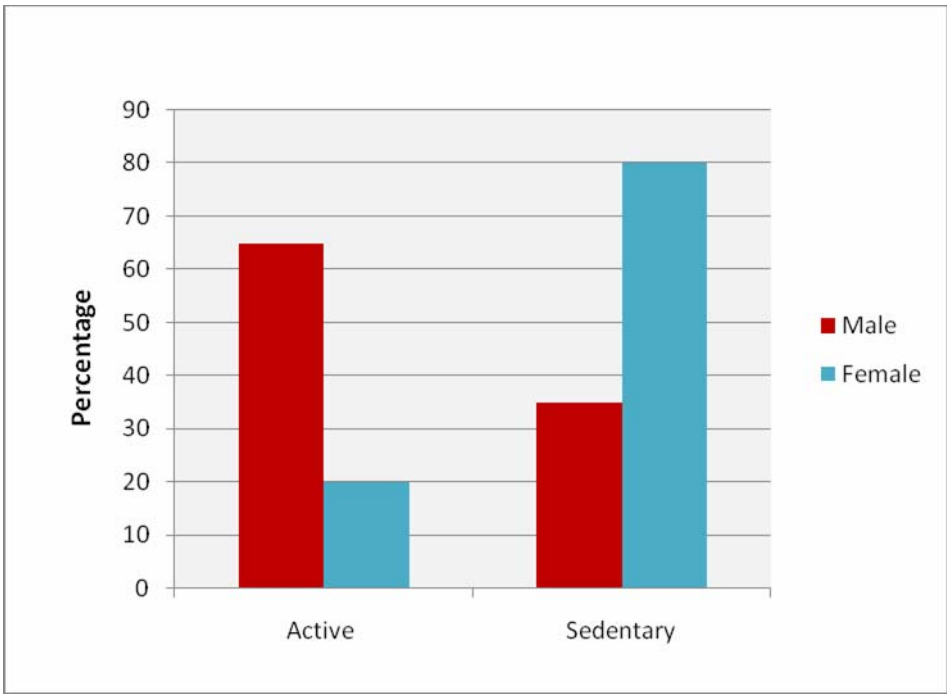


Figure 3: Lifestyle Pattern of study group



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ABBREVIATIONS

DM – Diabetes Mellitus

MS – Metabolic syndrome

IGT – Impaired Glucose Tolerance

IFG – Impaired Fasting Glucose

CVD – Cardio Vascular Disease

ADA – American Diabetic Association

IDF – International Diabetic Federation

JNC – Joint National Committee recommendations

DSPN – chronic Distal Sensorymotor Poly-Neuropathy

OGTT – Oral Glucose Tolerance Test

TGL – Triglycerides

HDL – High Density Lipoprotein cholesterol

LDL – Low Density Lipoprotein cholesterol

BMI – Body Mass Index

BP – Blood Pressure

ACE – Angiotensin Converting Enzyme

ARB – Angiotensin Receptor Blockers

VPT – Vibration Perception Threshold

UKPDS – United Kingdom Prospective Diabetes Study

CURES – Chennai Urban Rural Epidemiological Study

PROFORMA

PREVALENCE OF MICROVASCULAR COMPLICATIONS AND

METABOLIC SYNDROME IN NEWLY DIAGNOSED TYPE 2 DM

Serial No.:	**OP No.:**

Inclusion Criteria: All newly diagnosed Type 2 Diabetics of low socioeconomic group

Exclusion Criteria: T_1 DM, Pregnancy, Therapy with - steroids, ACE inhibitors, ARBs Severely ill patients, Known – kidney disease, heart failure

Name : Age: Sex:

Address:

Pedigree chart

Education:

Occupation:

Income per month:

Socio-economic status:

Family H/O DM: + / -

Generation gap of onset of diabetes:

H/o. GDM / HT/ CAD/Dyslipidemia/Diabetogenic drug therapy

Smoking/Alcohol Diet- veg. /non-veg/ mixed

Reason for attending Diabetology OP:

- During routine evaluation : Medical OP / Surgical OP/ Specialty OP
- Evaluation for surgical fitness / dental procedure fitness
- Referral for other reasons – Infertility / PCOD / Obesity / Others
- Referral from Master Health Check up / Self evaluation

Presenting Symptoms: (for each symptom mention duration)

- Polyuria
- Polydypsia
- Weight loss
- Balanophosthitis
- Vulvovaginitis
- Burning micturition
- Peri-arthritis shoulder
- Non healing wound
- Giddiness
- Visual Symptoms – flashes/floaters/ refractory changes

Sensory symptoms

- Burning sensation
- Pricking, tingling
- Squeezing, constricting
- Throbbing, freezing
- Loss of sensation
- Para/Hypo aesthesia

Motor Symptoms

- Tripping of toes / slipping of slippers / buckling of knees

ANTHROPOMETRIC MEASUREMENTS:

Waist Circumference: cm

Ht: cm, Wt: kg, BMI:

BP: mm/Hg

INVESTIGATIONS:

Fasting Plasma Glucose (mg/dl):

(75 grams) 2 hrs OGTT (mg/dl):

Protein Creatinine ratio:

24 Hrs urine protein:

Fasting Lipid Profile (mg/dl)

Total Cholesterol :

TGL :

HDL :

Urine C&S:

PARAMETERS TO BE OBSERVED :

1. Nephropathy: - Microproteinuria - Macroproteinuria

2. Retinopathy : - Micro aneurysm - Dot/ Blot Hemmorrahage
- Hard exudates - Soft exudates
- Venous dilatations - Venous beading
- Proliferative changes - Macular Edema

3. Neuropathy : Biothesiometry – vibration threshold : Rt. foot -
Lt. foot -

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INSTITUTIONAL ETHICAL COMMITTEE
GOVERNMENT GENERAL HOSPITAL & MADRAS MEDICAL COLLEGE,
CHENNAI-600 003.

Telephone: 044-2530 5000

Fax : 044 – 25305115

K.Dis.No.16328 P & D3/Ethies/Dean/GGH/08 Dated 8/9/2008

Title of the work : "Study of prevalence of Micro-vascular complications and Metabolic syndrome in Newly detected Type 2 Diabetes Mellitus"

Principal Investigator : Dr. A.N. Senthil

Department : Internal Medicine, MMC, ch. 3.

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 10th Sep 2008 at 2 P.M in [illegible], Deans, Chamber, Chennai-3.

The members of the Committee, the Secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The principal investigator and their term are directed to adhere the guidelines given below:

1. You should get detailed informed consent from the patients/participants and maintain confidentiality.
2. You should carry out the work without detrimental to regular activities as well as without extra expenditure to the Institution or Government.
3. You should inform the IEC in case of any change of study procedure, site and investigation or guide.
4. You should not deviate form the area of the work for which I applied for ethical clearance
5. You should inform the IEC immediately, in case of any adverse events or serious adverse reactions.
6. You should abide to the rules and regulations of the institution(s)
7. You should complete the work within the specific period and if any extension of time is required, you should apply for permission again and do the work.
8. You should submit the summary of the work to the ethical committee on completion of the work.
9. You should not claim funds from the Institution while doing the work or on completion.
10. You should understand that the members of IEC have the right to monitor the work with prior intimation.

SECRETARY
IEC, GGH,CHENNAI

CHAIRMAN
IEC, GGH,CHENNAI

DEAN
GGH &MMC, CHENNAI

RKM.5.6(2)

தன்னார்வ ஒப்புதல் படிவம்

ஆய்வின் தலைப்பு

புதியதாக கண்டுபிடிக்கப்பட்ட நீரிழிவு நோயாளிகளிடம் ஏற்படும் நுண்ணிய ரத்த நாளங்கள் சம்பந்தப்பட்ட பின் விளைவுகள் மற்றும் மெட்டபாலிக் சின்ட்ரோம் தொடர்பான மாற்றங்கள் பற்றிய ஆய்வு.

ஆய்வு செய்யும் இடம்

நீரிழிவு நோய் துறை மற்றும் பொது மருத்துவத் துறை, அரசு பொது மருத்துவமனை, சென்னை-1

பங்கு பெறுபவரின் பெயர் :
பங்கு பெறுபவரின் எண் :
பங்கு பெறுவர் இதனை (✓) குறிக்கவும்

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. என்னுடைய சந்தேகங்களை கேட்கவும், அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டள்ளது என அறிந்து கொண்டேன். ☐

நான் இவ்வாய்வில் தன்னிச்சையாக தான் பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகி கொள்ளலாம் என்றும் அறிந்தும் கொண்டேன். ☐

இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்த மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். ☐

இந்த ஆய்வின் மூலம் கிடைக்கும் நகவலையோ, முடிவையோ பயன்படுத்திக் கொள்ள மறுக்கமாட்டேன். ☐

இந்த ஆய்வில் பங்குகொள்ள ஒப்புக்கொள்கிறேன். எனக்கு கொடுக்கப்பட்ட அறிவுரைகளின்படி நடந்து கொள்வதுடன் இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்றும் உறுதியளிக்கிறேன். என் உடல் நலம் பாதிக்கப்பட்டாலோ அல்லது எதிர்பாராத வழக்கத்திற்கு மாறான நோய்குறி தென்பட்டாரோ உடனே இதை மருத்துகூ அணியிடம் தெரிவிப்பேன் என உறுதி அளிக்கிறேன், ☐

இந்த ஆய்வில் எனக்கு இரத்தம், சிறுநீர், எக்ஸ்ரே, ஸ்கேன் பரிசோதனை செய்துகொள்ள நான் முழுமனதுடன் சம்மதிக்கிறேன். ☐

பங்கேற்பவரின் கையொப்பம் ..... இடம் ..... நேதி
கட்டைவிரல் ரேகை

பங்கேற்பவரின் பெயர் மற்றும் விலாசம் .....
ஆய்வாளரின் கையொப்பம் ..... இடம் ..... தேதி
ஆய்வாளரின் பெயர் .....