# Clinical Evaluation of Maternally Inherited Type-2 Diabetes and Deafness in a Tertiary Care Hospital at Puducherry

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## ABSTRACT

**Introduction:** Maternally Inherited Diabetes and Deafness (MIDD), a specific clinical syndrome results in sensory neural hearing defect in diabetes population which may lead to A3243G mutation in tRNALeu (UUR) gene.

**Materials and methods:** A prospective case control study, the non probability convenient sampling technique was followed in this study. The subjects were divided into non diabetic and diabetic with maternal inheritance groups. Hundred patients with the strong maternal history of diabetes is group 1 and hundred non diabetic individuals with no maternal history of diabetes is group 2. Blood and urine samples were collected and analyzed biochemical parameters among the two groups. In addition, audiometric analysis was also carried out for those groups.

**Results:** The mean age of onset of diabetes was 41 years and deafness was 51 years. The mean plasma glucose, Glycosylated Hemoglobin(HbA1C), Serum Insulin, Insulin Resistance, Cholesterol, Triacyl glycerides, Very Low Density Lipoprotein(VLDL), Low Density Lipoprotein, Serum Urea, Serum Uric acid, Serum Creatinine and Albumin to Creatinine Ratio (ACR) levels in patients were significantly higher whereas High Density Lipoproteins(HDL) and urine creatinine levels were significantly low as compared with controls. The mean Body Mass Index (BMI) is slightly higher in patients as compared with control group.

**Conclusion:** The study helps us to understand that the Maternally Inherited Diabetes and Deafness syndrome severely alters the insulin resistance level, ACR ratio and lipid profile which may lead to multiple organ disorder at early age of diabetes.


**Keywords:** Insulin Resistance, Albumin Creatinine Ratio, Lipid Profile, Glycosylated Hemoglobin, Mutation, Cholesterol

## INTRODUCTION

Diabetes is considered to be one of the epidemic disease in terms of incidence and healthcare complications seen worldwide.[1] The epidemiological data over the past decades have shown that the pattern and clinical profile of type 2 diabetes mellitus are highly prevalence in India compared to the western countries including lower Body Mass Index (BMI) and earlier onset of diabetes. The type 2 diabetes mellitus is a metabolic disorder characterized by hyperglycemia showing different patterns of inheritance. The one among the inheritance is attributed to the mutation in the gene present in the mitochondrial DNA and is transmitted from mother to her progeny and it is termed as mitochondrial diabetes.[2] The patients suffering from the maternally inherited diabetes generally not over weighted and the onset of the disease at an early age. The major defect in maternally inherited diabetes have shown that less secretion of insulin by pancreatic β cells.[3] Many previous reports in the literature have identified maternal pedigrees with mitochondrial DNA (*mt*DNA) mutations, having diabetes mellitus associated with sensorineural hearing impairment (nonsyndromic deafness).[4] MtDNA mutations are linked with a variety of diseases, ranging from rare muscular syndromes to common disorders like diabetes mellitus and Alzheimer's disease (Wallace 1994).[5] Underlying mechanisms of these complications have to be addressed clearly. Therefore, the clinical and biochemical profile of maternally inherited type 2 diabetes mellitus with deafness were characterized in the present study.

## MATERIAL AND METHODS

This study was prospective case control study. Patients were selected from Aarupadai Veedu Medical College and Hospital, Puducherry. The study was conducted from Jan-2012 to Dec-2017. The inclusion criteria were the patients with type 2 diabetes with maternal inheritance with or without sensory neural deafness. The sample size was 200 and the subjects were sub divided into two groups, non diabetic control with no maternal history (n=100) and patients with maternal inheritance (n=100). The BMI was calculated for both the groups by dividing weight in Kg by height in meter square.

The plasma glucose was estimated by enzymatic dependent colorimetric method.[6] Glycosylated hemoglobin was determined by particle enhanced immunoturbidimetric

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method. In this method $HbA1_C$ is estimated directly without measurement of total hemoglobin.[7] Insulin was determined by using Enzyme immunoassay method and Insulin resistance was calculated by the Homeostasis Model Assessment Insulin Resistance Score (HOMA-IR score).[8-9] Serum cholesterol and Serum triglyceride (GPO-PAP - method) were estimated by Enzymatic method.[10-11] Serum HDL-Cholesterol was estimated by precipitant method using auto-analyzer kit. LDL-Cholesterol and VLDL-Cholesterol were calculated according to Friedwald's equation.[12-13] Serum Urea, Uric acid and Creatinine were estimated by GLDH-UV kinetic method, Uricase method and Jaffe's method respectively using auto-analyzer kit.[14-16] Serum total protein was measured by Biuret method and Serum albumin was measured by Bromocresol Green(BCG) method using auto-analyzer kit.[17-18] Urine microalbumin was measured by turbilatex method and urine creatinine was measured by Jaffes method.[19] ACR value was calculated by using urine microalbumin and creatinine. Puretone thresholds were measured using GSI 68 diagnostic audiometer in a sound treated room. Modified Hughson – Westlake method was used to obtain the thresholds at 250 Hz, 500 Hz, 1KHz, 2 KHz, 4 KHz, 6 KHz and 8 KHz for Air conduction and 500 Hz, 1 KHz, 2 KHz and 4KHz for Bone conduction.[20] Pure tone average was obtained at 500 Hz, 1 KHz and 2 KHz. Hearing impairment was categorized as minimal (16 – 25 dB), mild (26 – 40 dB), moderate (41– 55 dB), moderately severe (56 – 70 dB), severe (71 – 90 dB) and profound (91 dB and above).

The statistical data were analyzed by SPSS software (Statistical Package for Social Sciences) for windows version 20 using independent sample t test. The results were expressed as Mean ± SD. The p values which is < 0.05 was considered to be statistically significant in this study.

## RESULTS

The results have been summarized and Mean and SD (Standard Deviation) of control subjects and diabetes

| Parameters | Non-Diabetics (100) | Diabetics (100) | p value |
|---|---|---|---|
| Plasma Glucose (F) | 85.25± 22.42 | 175.96± 58.29 | <0.001 |
| Plasma Glucose (PP) | 110.59±27.58 | 275.42±84.76 | <0.05 |
| HbA1C | 4.65± 0.9474 | 7.48± 1.68 | <0.001 |
| Urine glucose | - | 48% | - |
| Insulin | 8.63± 3.24 | 14.31± 6.32 | <0.05 |
| HOMA-IR | 4.49±1.97 | 15.73±7.76 | <0.05 |

**Table-1:** Comparison of plasma glucose, glycosylated hemoglobin levels, Urine glucose, Insulin and HOMA-IR (mean ± SD) of patients with maternally inherited T2DM with control group.

| Parameters | Non-Diabetics (100) | Diabetics (100) | p value |
|---|---|---|---|
| Cholesterol | 188.76±10.15 | 231±23.35 | <0.001 |
| Triglycerides | 143.85±6.12 | 199.93±18.09 | <0.05 |
| HDL | 45.84±6.81 | 34.141±5.78 | <0.001 |
| VLDL | 27.67±6.21 | 39.98±8.78 | <0.001 |
| LDL | 114.6±9.11 | 156.88±12.64 | <0.001 |

**Table-2:** Comparison of Serum Cholesterol, Serum Triglycerides, Serum HDL, Serum VLDL and Serum LDL (mean ± SD) of patients with maternally inherited T2DM with control group.

| Parameters | Non-Diabetics (100) | Diabetics (100) | p value |
|---|---|---|---|
| Serum Urea | 21.29±8.33 | 42.82±8.58 | <0.05 |
| Serum Uric acid | 5.45±1.26 | 7.51±1.49 | <0.05 |
| Serum Creatinine | 1.01±0.102 | 1.37±0.18 | <0.001 |

**Table-3:** Comparison of plasma Urea, Plasma Uric Acid and Plasma Creatinine (mean ± SD) of patients with maternally inherited T2DM with control group.

| Parameters | Non-Diabetics (100) | Diabetics (100) | p value |
|---|---|---|---|
| Urine Creatinine | 191.12±76.18 | 84.47±24.11 | <0.05 |
| Microalbumin | 13.41±8.59 | 66.55±30.12 | <0.05 |
| ACR Value | 7.55±5.46 | 84.03±41.32 | - |

**Table-4:** Comparison of Urine Creatinine, Microalbumin and ACR (mean ± SD) of patients with maternally inherited T2DM with control group.

| Parameters | BMI | p value |
|---|---|---|
| Non-Diabetics (100) | 25.09±4.50 | <0.05 |
| Diabetics (100) | 26.58±3.59 | <0.05 |

**Table-5:** Comparison of BMI of patients with maternally inherited T2DM with control group.

| Parameters | Non-Diabetics (100) | Diabetics (100) | p value |
|---|---|---|---|
| Serum total protein | 7.35±0.40 | 6.97±0.40 | <0.05 |
| Serum Albumin | 4.83±0.49 | 4.14±0.23 | <0.05 |
| Globulin | 2.54±0.43 | 2.82±0.38 | <0.05 |
| A/G ratio | 2.03±0.54 | 1.51±0.24 | - |

**Table-6:** Comparison of Serum total protein, albumin, globulin and A/G ratio of patients with maternally inherited T2DM with control group

study groups are shown in tables 1 to 6. Table 1 shows the distribution of plasma glucose (Fasting and Post prandial), glycosylated hemoglobin levels, urine glucose, Insulin and HOMA-IR levels of patients with maternally inherited type 2 diabetes mellitus with control group. Mean plasma glucose and glycosylated hemoglobin level in patients of maternally inherited type 2 diabetes mellitus was significantly higher ($p< 0.001$) as compared with control group. Whereas low significant statistical difference in insulin and HOMA-IR was observed in comparison of diabetic patients with control group. Nearly 48% of the diabetic patients were found to have trace to higher level of glucose in urine.

Table 2 shows the variation of serum cholesterol, serum triglyceride levels, HDL, VLDL and LDL levels of patients with maternally inherited type 2 diabetes mellitus with control group. Serum cholesterol, serum triglyceride, LDL and VLDL level of patients with maternally inherited type 2 diabetes mellitus was significantly higher ($p< 0.001$) as compared with control subjects. Whereas the HDL level of maternally inherited type 2 diabetes mellitus was significantly lower ($p< 0.05$) as compared with control subjects.

Table 3 shows the variation of serum Urea, serum Uric acid and serum Creatinine levels of patients with maternally inherited T2DM with control group. Serum Urea, serum Uric acid and serum creatinine levels of patients with maternally inherited type 2 diabetes mellitus was significantly increases ($p< 0.05$, $<0.001$) as compared with control subjects.

Table 4 shows the variation of Urine creatinine, micro albumin and ACR values of patients with maternally inherited type 2 diabetes mellitus with control group. Urine albumin and ACR levels of patients with maternally inherited type 2 diabetes mellitus was significantly increases ($p< 0.05$) and urine creatinine was significantly decreased ($p< 0.05$) compared with control subjects.

Table 5 shows the variation of BMI patients with maternally inherited type 2 diabetes mellitus with control group. BMI values of patients with maternally inherited type 2 diabetes mellitus was slightly higher compared with control subjects.

Table 6 shows the variation of Serum total protein, serum albumin, serum globulin and A/G ratio of patients with maternally inherited type 2 diabetes mellitus with control group. Serum total protein, serum albumin and A/G ratio were significantly decreased whereas Serum globulin was significantly increased in patients with maternally inherited type 2 diabetes mellitus compared with control subjects.

## DISCUSSION

In the present study, 100 type 2 maternally inherited diabetes patients were recruited to understand the clinical and biochemical profile of maternal inherited diabetes. Out of which 54 were males and 46 were females with mean age of onset of diabetes was 41 years. In the present study the BMI of Maternally Inherited Diabetes patients was found to be slightly higher due to the onset of diabetes was less than 5-10 years for 70% of the recruited patients. The glycemic profile of our recruited subjects was found better when compared to the other studies indicating type 2 diabetes mellitus with insulin resistance.

It is believed that type 2 diabetes mellitus with maternal inheritance may result in multi organ complications. One among the complication will be impaired hearing and it is very difficult to pinpoint exact cause of deafness. In our present study out of 100 patients 65 subjects were found to be impaired hearing loss out of which 14 faces severe complication, 20 faces moderate complication and 31 faces mild complication. This complication is mainly due to several environmental and genetic factors however several studies have shown the involvement of mitochondrial DNA mutation in the pathogenesis of diabetes and deafness.

In our study the patients with diabetic complication had significantly higher serum cholesterol, serum triglycerides and low HDL level when compared to the normal individual. However, dyslipidemia is an important characteristic feature seen in type 2 diabetes mellitus. The dislipidemia condition is observed in the recruited patients with maternally inherited diabetes which may results in micro vascular complications in the future.

Another significant finding in our study was higher prevalence of microalbuminuria in patients with maternally inherited type 2 diabetes mellitus. The ACR value was significantly higher and microalbuminuria is present in patients with maternally inherited type 2 diabetes mellitus which is an earlier index for the future renal failure which may lead to nephropathy.

In the present study it was observed that the A/G ratio was found to be lower which reveals that the decreased synthesis of albumin by the liver in the maternally inherited type 2 diabetes patients which may be due to several liver complications.

## CONCLUSION

The maternally inherited type 2 diabetes is a distinct clinical entity. The clinical and biochemical profile of maternally inherited type 2 diabetes mellitus also shows several complications such as hearing loss, micro vascular complications, nephropathy and liver complications. The observed clinical findings of maternally inherited diabetes might be the outcome of a combination of genetic or

environmental factors. The prevalence of diabetes with deafness may be due to mutation in mitochondria tRNALeu gene which may be a contributing etiological factor for MIDD.

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