Int J Pharm Bio Sci 2015 April; 6(2): (B) 1445 - 1453

Research Article **Neurobiology**

International Journal of Pharma and Bio Sciences **ISSN 0975-6299**

EVALUATION OF VISUAL EVOKED POTENTIAL (VEP) IN THE OFFSPRING OF TYPE II DIABETIC PARENT(S).

ANITHA A*[1], JANANI R[2] AND SUDHARSHINI P[3]

*[1]*Professor and HOD,NeuroPhysiology,Government Villupuram Medical College, Villupuram, Tamilnadu, India.*
[2]*Janani R , Physiology , Government Villupuram Medical College, Villupuram, Tamilnadu, India.*
[3]*Sudharshini P, Community Medicine, Government Villupuram Medical College, Villupuram, Tamilnadu, India.*

ABSTRACT

Metabolic abnormalities in Diabetes Mellitus can involve ganglionic and preganglionic elements in the entire retina and macular region causing Visual disturbances.Subclinical CNS dysfunctions have been reliably detected by Visual evoked potentials in patients with uncomplicated diabetes and normal brain CT scan. The offspring of diabetic parents have a higher risk of diabetes in future and a possibility of Diabetic retinopathy.This study aims at evaluating visual evoked potential in asymptomatic offspring of diabetic parents.150 individuals in each group(case and controls) were enrolled after Written and informed consent . Institutional ethical Committee approval was obtained., VEP readings were taken using the standard procedure as given by Recommended Standards for Visual Evoked Potential, Guidelines 9B.RESULT;The statistical analysis revealed significant difference in controls and offspring of diabetic parents in terms of P100 latency in both left and right eye ($P<0.05$).The offspring of diabetic parents may be screened with VEP ,as , prolongation of P100 latency a direct sign of retinal damage and demyelinationcould add the risk to the fact that they may be in a pre-diabetic stage without clinical manifestation,but there may be subclinical optic pathway involvement which mandates active intervention to reduce the co-morbidly associated with Diabetes.

KEYWORDS; Diabetes Mellitus - Visual evoked potentials –P 100 Latency - offspring – subclinical - retinal damage

*Corresponding author

ANITHA A
Professor and HOD,NeuroPhysiology,Government Villupuram Medical College,Villupuram, Tamilnadu, India.

INTRODUCTION

The World Health Organization estimates that > 180million people worldwide have diabetes and its incidence is likely to be doubled by the year 2030. According to the Diabetes Atlas 2013 published by the international Diabetes Federation, the number of the people with diabetes in India currently around 65 million is expected to rise to 80 million by 2030. The injurious effects of hyperglycemia may be due to macro vascular complications such as coronary artery disease, peripheral artery disease and stroke or may be microvascular complications such as diabetic nephropathy, diabetic peripheral neuropathy and central neuropathy(Wild S,et al 2004)[1]. The impairment of the central nervous system is a frequent microvascular complication of diabetes but the exact pathophysiology seems to be multifactorial, similar to genesis of diabetic peripheral neuropathy (T.T.Varkonyi et al,2002)[2]. Metabolic abnormalities in DM can involve ganglionic and preganglionic elements in the entire retina and macular region. Visual disturbances may attribute to macular edema. In addition neural conduction also may be delayed (Sema Garg, Richard M Davis [2009])[3]. Vision threatening retinopathy is rare in type 1 diabetic patients in the first 3 to 5 years of diabetes or before puberty. During the next two decades nearly all type 1 diabetic patients develop retinopathy (Heravian J, et al 2012)[4]. Up to 21% of patients with type 2 diabetes have retinopathy at the time of first diagnosis of diabetes and most developed some degree of retinopathy overtime (Fong DS,et al 2003)[5]. Subclinical CNS dysfunctions have been reliably detected by evoked potentials in patients with uncomplicated diabetes and normal brain CT scan (T. Das, et al 2001)[6]. · On measuring Visual evoked potential for Diabetic patients, abnormal changes in latencies of the visual evoked potentials, especially delay of P100 was noted.(Yaltkaya, et al 1988)[7](Dolu, et al 2003)[8]. Abnormalities of central nervous system and related pathways can be measured by evoked potential studies in an efficient a manner sub clinically and was used as an important diagnostic method (T. Das, et al, 2001)· Of all the evoked potentials visual, auditory and somatosensory are widely used for clinical purposes (F L Mastalgia, 1983)[9]. Diabetic retinopathy occurs both in type 1 and 2 and has been shown that nearly all type 1 and 75% of type 2 will develop retinopathy with 15 years duration (Klein R, et al 1984)[10,11]Hence it is possible to detect asymptomatic diabetic retinopathy sub clinically before its clinical diagnosis by using visual evoked potential. In the event of metabolic inflammation, it seems that the first-order neurons get attacked readily, which negatively impact neuronal regulatory cascades . With diffuse involvement of the retina, including the macula and the periphery, both the ERG and VEP have been documented to be absent (Mohanapriya chelladuralet al 2015)[12] . Not many studies have been found to be done in the offspring of diabetic parents using Visual evoked potential as the modality. Studies done by Brinciotti M, et al in 2007 and 2011 [13] measured visual evoked potential in offspring of diabetic mothers also showed prolongation of P100 latency in offspring. Hence the offspring of diabetic parents may be prone to development of diabetes in future, which can be detected sub clinically by measuring visual evoked potential. Our study aims at evaluating visual evoked potential in offspring of diabetic parents (maternal diabetes, paternal diabetes and both).

AIM

To evaluate the Visual evoked potential in offspring of Diabetic parent(s)

METHODOLOGY

150 individuals in each group (case and controls) were considered. Written and informed consent was obtained from the subject in regional language if they are more than age of 16, or from their parents if they are younger than 16 years. Institutional ethical Committee approval was obtained.

INCLUSION CRITERIA

- Offspring of diabetic parent(s) on the WHO criteria with
  - Normal blood pressure
  - Normal glucose level
  - without refractive error (refractive error is corrected by spectacles)
  - Normal BMI.
- AGE**:**15 to 24
- Both male and female.

EXCLUSION CRITERIA

- Offspring of non-diabetic parent(s).
- Offspring of diabetic parents, whose parents also have associated illness such as
  - Hypertension
  - Obesity
  - Hyper/hypothyroidism.
- Offspring of diabetic parents with
  - Altered blood pressure
  - Altered glucose level
  - Obesity
- AGE:>24 and < 15

Age, BMI and gender matched healthy subjects attending Master Health Check-Up in our Hospital was taken as controls.By using the MEDICAID POLYRITE instrument, VEP readings was taken by standard procedure as given by Recommended Standards for Visual Evoked Potential, Guidelines 9B: Guidelines on Visual Evoked Potential published by American Neurophysiology society in 2008.

EQUIPMENT SETUP

MONTAGE

- Channel 1-FPz-Reference electrode.
- Vertex-Cz-ground electrode
- C-Oz-active electrode.

STIMULATION

- Black and white checkerboard was used. Distance between subject and screen was maintained as 100cm.
- Contrast- 80%
- Size of pattern- 14 X 16 minutes.
- Rate of stimulation- 4-8Hz.
- Mean luminance of the central field-50cd/$m^{2.}$
- Background Luminance- 20 -40cd/m^2.

VEP PARAMETERS

The following parameters were considered during the study:

- Latency of N75 msec
- Latency of P100 msec
- Latency of N145 msec
- Amplitude of P100 – N 75 µV

STATISTICAL ANALYSIS

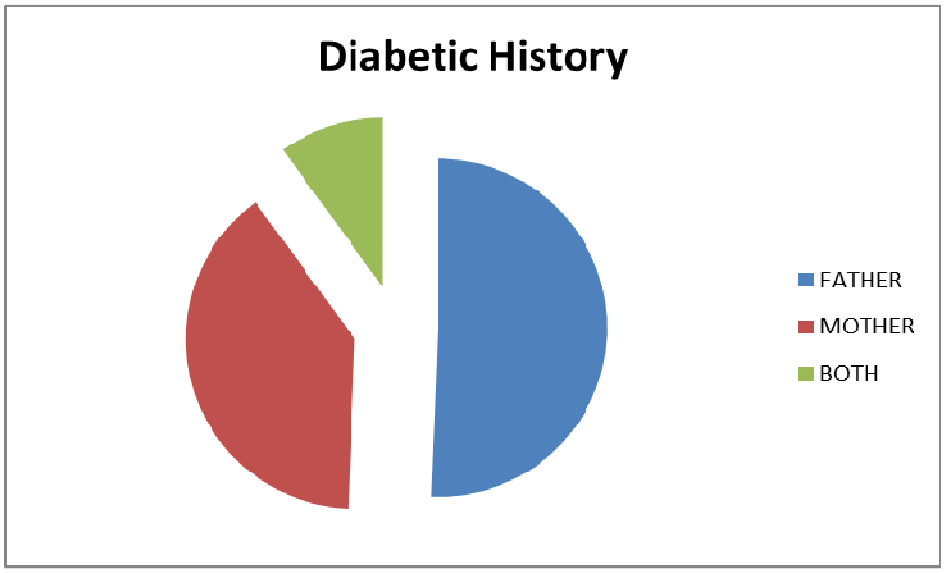
- The statistical analysis was done using SPSS software 20.0 versions.
- The parameters was analysed using Student independent unpaired't' test.

$P<0.05^{*}$ is considered as significant; $P<0.01^{**}$ is considered as highly significant

RESULTS

Overall 150 offspring of diabetic parents (figure 2) was compared with 150 ages, BMI and sex matched normal controls (Figure 1). Mean age was 19.34 in cases and 19.48 in controls (P-value = 0.655).

Figure 1
DIABETIC FAMILY HISTORY OF THE SYUDY POPULATION



The central role played by the mitochondria in insulin secretion and signal transduction conclude that mutations in mt-DNA predisposes greater risk of type 2 diabetes developed in the offspring of affected women when compared to affected (Meigs JB, et al). The study population also highlights the Maternal Diabetic Preponderance. As detailed in table 1,there was significant difference in controls and offspring of diabetic parents in terms of P100 latency in both left and right eye ($P<0.05$).However there was no significant change regarding the other parameters of VEP.

Table 1
One-way ANOVA tested the differences between the three groups

PARAMETER	DIABETIC HISTORY OF PARENT	n	MEAN	STANDARD DEVIATION	P-VALUE
P100 L	FATHER	76	102.44	3.86	.025*
	MOTHER	59	102.92	3.18	
	BOTH	15	107.35	2.22	
	TOTAL	150	103.02	3.86	
P100 R	FATHER	76	103.00	3.98	.430
	MOTHER	59	103.47	4.03	
	BOTH	15	105.40	1.77	
	TOTAL	150	103.32	3.844	

In the overall population including case and control, the number of offspring of both parent diabetic (group 3) was considerably lesser than the either parent diabetic (group 2 and 3).This result coincides with the genetic study done by Poulton J,et al in 2002. comparative analysis within the case population, there was significant (p=0.025) increase in the P100 latency of the left eye of offspring of both the parents (group 3) when compared with the offspring of maternal and paternal diabetes (group 1 and 2).

TABLE 2

PARAMETER	STUDY GROUP	n	MEAN	STANDARD DEVIATION	P-VALUE
P100 L	Offspring of diabetics	150	103.02	3.86	**0.028***
	Control	150	101.50	2.87	
P100 R	Offspring of diabetics	150	103.32	3.84	**0.011***
	Control	150	101.62	2.63	

One-way ANOVA was used to test the differences between the three groups.

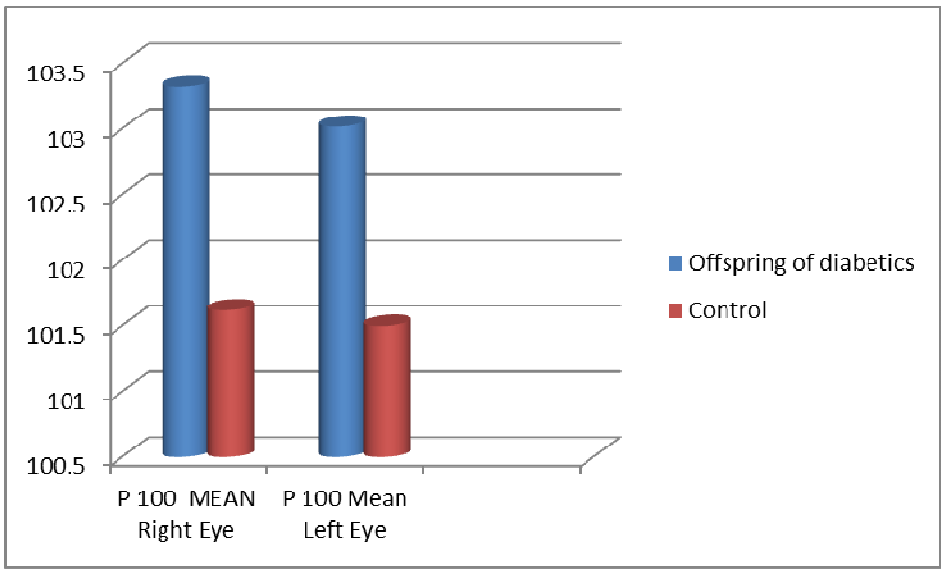
- GROUP 1: History of Paternal diabetes only
- GROUP 2: History of maternal diabetes only
- GROUP3: History of either parents diabetic (both maternal and paternal).

TABLE 2
One-way ANOVA was used to test the differences between the three groups

PARAMETER	DIABETIC HISTORY OF PARENT	n	MEAN	STANDARD DEVIATION	P-VALUE
P100 L	FATHER	76	102.44	3.86	.025*
	MOTHER	59	102.92	3.18	
	BOTH	15	107.35	2.22	
	TOTAL	150	103.02	3.86	
P100 R	FATHER	76	103.00	3.98	.430
	MOTHER	59	103.47	4.03	
	BOTH	15	105.40	1.77	
	TOTAL	150	103.32	3.844	

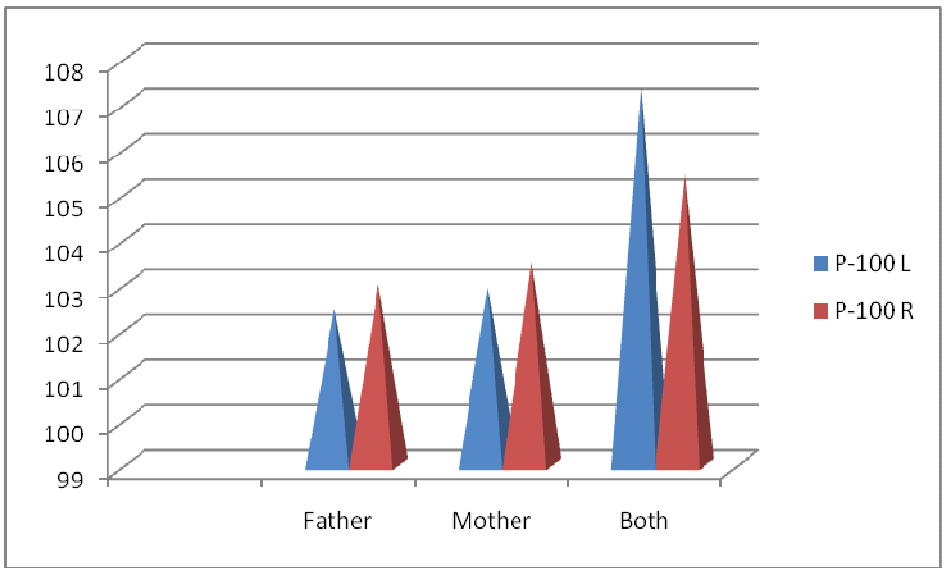
There was no significant difference in latencies of offspring only with maternal diabetes (group 2) and offspring only with paternal diabetes (group 1).But, there is significant delay in the latency P100 of left eye in offspring of both the parents (group 3) than group1 and group2 (table 2).And we found no correlation between the age of onset of diabetes in the parents to the VEP of the offspring.

Figure 2
Comparative analysis of the P 100 Latency between the study and Control Group



Statistically significant monocular delay was also noticed in the Right P -100 latency than the Left Eye P -100 Latency(p-0.01). This monocular prolongation of latency may be due to asymmetrical involvement of retina (Ramachandran A) . The unilateral VEP abnormality, obtained by full field monocular stimulation is likely to be due to prechaismal involvement of the visual pathway.

Figure 3
Comparison of P 100 Latency of RIGHT and LEFT Eyes Among OFFSPRING'S of Paternal, Maternal and Both Diabetic Parents.



The lifetime risk of developing diabetes is ~40% in offspring of one parent with type 2 diabetes, and approaching 70% if both parents have diabetes (Lyssenko V, et al 2013).Hence offspring of both parents diabetic (group 3) have a higher risk of DM.In accordance, when we did comparative analysis within the case population, there was significant (p=0.025) increase in the P100 latency of the left eye

of offspring of both the parents (group 3) when compared with the offspring of maternal and paternal diabetes (group 1 and 2)

DISCUSSION

In type 2 Diabetes, the odds ratio for offspring of a single affected parent is 3.5 compared to those with no parental diabetes history and it increase to 6.1 if both the parents are affected(Meigs JB, et al 2000)[14]. Type 2 Diabetes as mentioned is a multifactorial disorder in which variants of mitochondrial DNA would play an important role. Mitochondrial DNA is maternally inherited and highly polymorphic. The central role played by the mitochondria in insulin secretion and signal transduction conclude that mutations in mt-DNA predisposes greater risk of type 2 diabetes developed in the offspring of affected women when compared to affected Men**.** (Maassen JA, et al 2004)[15] Hyperglycemia and insulin resistance could also promote inflammation, and may be a factor of linking diabetes to the development of atherosclerosis. Elevated glucose levels could promote inflammation by increased oxidative stress . When the generation of ROS exceeds cellular defense mechanism, the unstable molecules interact with biological macromolecules such as lipids, proteins and DNA and leads to structural changes as well as functional abnormalities especially First order Neurons (V.C.Renju 2012)[16] VEP is a simple, sensitive and objective technique for evaluating impulse conduction along the Visual pathways. Diabetes Mellitus is a common cause for Visual evoked potential abnormalities, which could be explained by the presence of retinopathy or optic nerve involvement. Delay in the latency of the main positive wave P100 is very sensitive in detecting retinopathy (Heravian J,et al 2012)[17].Visual impairment in retinopathy may be due to macular edema and retinal thickening which may even lead to visual loss (M. Rema & R. Pradeepa 2007)[18].VEP is also a valuable method to detect diabetic preretinopathy in type 1 DM and hence helps in subclinical detection of retinopathy (Karlica D,et al 2010)[19].Optic nerve involvement due to Type II DM occurs prior to the onset of symptoms which also can be detected by VEP by prolongation of 100 latency (Heravian J,et al 2012) . In our study there is a significant delay in the P100 latencies in both eyes of cases when compared with controls. This result is in accordance with study of Brinicoitti, who recorded the VEP in offspring of mothers having gestational diabetes and concluded the presence of delay in P100 latency. In the overall population including case and control, the number of offspring of both parent diabetic (group 3-5%) was considerably lesser than the either parent diabetic (group 2 and 3-45%).This result coincides with the genetic study done by Poulton J,et al[20] in 2002 which the overall population including case and control only 3.6% had both parent diabetic while either parent incidence was about 32.8%(David MM, et al) [21]. But the lifetime risk of developing diabetes is ~40% in offspring of one parent with type 2 diabetes, and approaching 70% if both parents have diabetes (Lyssenko V, et al 2013)[22].Hence offspring of both parents diabetic (group 3) have a higher risk of DM. In accordance, when we did comparative analysis within the case population, there was significant (p=0.025) increase in the P100 latency of the left eye of offspring of both the parents (group 3) when compared with the offspring of maternal and paternal diabetes (group 1 and 2).This monocular prolongation of latency may be due to asymmetrical involvement of retina (Ramachandran A) [23]. The unilateral VEP abnormality, obtained by full field monocular stimulation is likely to be due to prechaismal involvement of the visual pathway.

To summarize

- Optic nerve involvement due to Type II DM occurs prior to the onset of symptoms which also can be detected by VEP by prolongation of 100 latency.
- The central role played by the mitochondria in insulin secretion and signal transduction conclude that mutations in mt-DNA predisposes greater risk of type 2 diabetes developed in the offspring of affected women when compared to affected Men But the lifetime risk of developing

diabetes is ~40% in offspring of one parent with type 2 diabetes, and approaching 70% if both parents have diabetes.Hence offspring of both parents diabetic (group 3) have a higher risk of DM and so a higher risk of Retino –Optic Conduction Delay.

- The monocular prolongation of latency may be due to asymmetrical involvement of retina. The unilateral VEP abnormality, obtained by full field monocular stimulation is likely to be due to prechiasmal involvement of the visual pathway.

CONCLUSION

Type 2 diabetes parents' offspring showed significant delay in the P100 latencies of visual evoked potentials of both right and left eye when compared with the controls. Comparison within the case group, offspring of both parents diabetic showed prolongation of P100 latency of the left eye than the offspring of either parents having diabetes. Keeping these findings in mind, we may conclude that offspring with both parents diabetic have a higher risk of diabetes in future and higher chance of retinal involvement. There was no significant difference between the latencies of maternal and paternal diabetes. The prolongation of P100 latency is a direct sign of retinal damage and demyelination. Hence the offspring of diabetic parents may be screened with VEP, as, prolongation of P100 latency could add the risk to the fact that they may be in a pre-diabetic stage without clinical manifestation with their blood sugar levels normal,but there may be subclinical optic pathway involvement which causes the delay in the latency.Active Intervention module, scheduled on this target population reduces the morbity and mortality.

ACKNOWLEDGEMENT

The authors of this study gratefully acknowledge the receipt of Funding by ICMR, support and help provided by the Institution , all the staff of the Department of Physiology and the Department of Ophthalmology.

REFERENCES

1. Wild S,et al "Global prevalence of diabetes estimates for the year 2000 and projections for 2030" Diabetes care; 27(5):1047-53. 2004
3. 2 T.T.varkonyi et al, "Impairment of visual evoked potentials":An early central manifestation of diabetic neuropathy?" *Diabetes care;* 25(9):1661.,2002 Sema Garg, Richard M Davis "Diabetic retinopathy screening update" *Clinical* diabetes; 27(4):140-5. 2009
4. Heravian J, etal "Pattern visual evoked potential in patients with Type II Diabetes mellitus" *J Ophthalmic Vis* Res; 7(3):225-230. 2012
5. Fong.D.S,et al "Diabetic retinopathy" *Diabetes care* October;27(10):2540-2553, *2004*
6. T. Das, et al "Studies on central nervous system function in diabetes mellitus," *Journal of the Indian Medical* Association, 99(2), 84–89, 2001
7. Yaltkaya et al. "Visual evoked potentials in diabetes mellitus"*Acta Neurol Scand Mar; 77(3):239-41, 1988*
8. Dolu et al, " Evaluation of central neuropathy in type II diabetes mellitus by multimodal evoked potentials" *Acta neurol.Belg., , vol.103, 206-211., 2003*
9. F L Mastalgia, W M Carroll. "Evoked potentials in neurological diagnosis" *Journal list Br Med J (Clin Res Ed) v.28;page6356; 1982 Dec.*
10. Klein R, et al "The Wisconsin epidemiologic study of diabetic retinopathy II. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30." *Arch Ophthalmol; 102: 520-6, 1984*
11. Klein R, et al "The Wisconsin epidemiologic study of diabetic retinopathy II. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30." *Arch Ophthalmol; 102: 520-6, 1984*

12. Mohanapriya chelladurai, NEURODEGENERATIVE AND NEUROINFLAMMATORY DISARRAYS IN PROGENIES AND ADULTS , Int J Pharm Bio Sci Jan; 6(1): (B) 636 - 648 , 2015
13. BrinciottiM, et al, "Effects of Maternal Diabetes on Visual Evoked Potentials and Early Psychomotor Development of the Offspring"*Journal of Diabetic Care dec.30 (12):e128), 2007*
14. Meigs JB, et al "Paternal transmission of type 2 diabetes: the Framingham Offspring Study" *Diabetes dec; 49(12):2201-7, 2000*
15. Maassen JA, et al "Mitochondrial Diabetes: Molecular mechanisms and Clinical presentation" *Diabetes Feb; 53S1*:*S103-S109, 2004*
16. V.C.RENJU, oxidative stress, sialic acid and total antioxidant status in patients with type2 diabetes mellitus, Int J Pharm Bio Sci Oct; 3(4): (B) 789 – 795, 2012
17. Heravian J,et al "Pattern visual evoked potential in patients with Type II Diabetes mellitus" *J Ophthalmic Vis Res;7(3):225-230, 2012*
18. M. Rema & R. Pradeepa "Diabetic retinopathy: An Indian perspective"*Indian J Med Res 125, March, pp 297-310, 2007*
19. Karlica D,et al "Visual Evoked Potential Can Be Used to Detect a Prediabetic Form of Diabetic Retinopathy in Patients with Diabetes Mellitus Type **I"***Coll. Antropol.* 34 *2: 525–529, (2010)*
20. Poulton J, et al "Type 2 diabetes associated with a common mitochondrial variant: Evidence from a population - based case-control study" *Human Molecular Genetics, , vol11 No13 1581-15832002*
21. David MM, et al "Epidemiology of Type 1 Diabetes"*Endocrinol Metab Clin North Am. Sep 2010; 39(3):481-497.*
22. Lyssenko V, et al "Genetic Screening for the Risk of Type 2 Diabetes*" Diabetes care August; 36(s2):s120-126, 2013*
23. Ramachandran A "Genetic Epidemiology of NIDDM among Asian Indians" *Ann Med. Dec;* 24(6):499-503, 1992.