UTILITY OF F WAVE MINIMAL LATENCY FOR DIAGNOSIS OF DIABETIC NEUROPATHY

A. R. Gargate¹, A. G. Joshi²

HOW TO CITE THIS ARTICLE:

A. R. Gargate, A. G. Joshi. "Utility of F Wave Minimal Latency for Diagnosis of Diabetic Neuropathy". Journal of Evolution of Medical and Dental Sciences 2014; Vol. 3, Issue 69, December 11; Page: 14728-14736, DOI: 10.14260/jemds/2014/3979

ABSTRACT: BACKGROUND: Diabetes mellitus (DM) is a metabolic disorder which has become a major public health problem worldwide. Its commonest complication is diabetic peripheral neuropathy (DPN). DPN is characterized by combining axonal loss and demyelinating sensory motor peripheral neuropathy. To investigate this condition nerve conduction studies with determination of latency and velocity are commonly used as they are considered to be the most sensitive, reliable, noninvasive and objective means. DPN is believed to affect mainly distal nerve segments. However, it has been recently reported that F-wave study in diabetic patients is very reliable. **AIM:** Aim of the present study was to find out whether F-wave minimal latency (FWML) is having more sensitivity compared to motor nerve conduction study for diagnosis of DPN. METHODS AND MATERIALS: Motor and sensory nerve conduction and F-wave studies of upper and lower extremity nerves were carried out bilaterally in 60 clinically diagnosed patients with Type II diabetes mellitus. These parameters were also studied in 45 age matched controls. **RESULTS:** Sensitivity for distal motor latency (DML) was 53.33% in median, 26.31% in ulnar, 25.8% in peroneal and 41.17% in tibial nerves. Sensitivity for motor amplitude- compound muscle action potential (CMAP) was 56.66% in the median, 66.66% in ulnar, 80.64% in personnel and 72.54% in tibial nerves. Sensitivity for motor conduction velocity (MNCV) was 50% in the median, 47.36% in ulnar, 77.41% in personnel and 72.55% in tibial nerves. Sensitivity for distal sensory latency (DSL) was 37.97% in the median, 23.8% in ulnar, 41.5% in sural nerves. Sensitivity for sensory amplitude (SNAP) was 8.01% in the median, 64.28% in ulnar and 60.37% in sural nerves. Sensitivity for sensory conduction velocity (SNCV) was 40.5% in median, 26.19% in ulnar and 58.49% in Sural nerves. Prolonged FWMLs were found in 73.87% of median, 69% of ulnar, 72.72% of peroneal and 68.96% of tibial nerves. The sensitivity for FWML was 75.7% in median, 81.37% in ulnar, 83.63% in peroneal and 81.7% in tibial nerve. **CONCLUSION:** FWML is a highly sensitive indicator for diagnosis of DPN.

KEYWORDS: Diabetes, peripheral neuropathy, nerve conduction, F-wave study.

INTRODUCTION: Diabetes mellitus (DM) is a metabolic disorder which has become a major public health problem worldwide. The World Health Organization has estimated that the number of adults with diabetes in the world would increase alarmingly from 135 million in 1995 to 300 million in 2025.¹ India leads the world with largest number of diabetic subjects earning the dubious distinction of being termed the "diabetes capital of the world". According to the Diabetes Atlas 2006 published by the International Diabetes Federation, the number of people with diabetes in India currently around 40.9 million is expected to rise to 69.9 million by 2025 unless urgent preventive steps are taken.² Diabetic peripheral neuropathy (DPN) is a common complication of DM. The prevalence of DPN is about 26% in India.³ Reports have revealed that neuropathy, diabetic foot and amputation account for some 18% of the overall burden. The prevalence rate of diabetic foot in the world is about

4.6-12%.⁴ It can be diagnosed by symptoms, signs, clinical examination, nerve conduction studies and other neurophysiological methods. Nerve conductions studies are considered as "Gold Standard" for diagnosis and evaluation of DPN.⁵

In diabetes consistent hyperglycemia damages the microcirculation structure and function resulting in ischemia involving small blood vessles those supply nerves (Vasa nervosum). This results in axonal loss by Wallerian degeneration causing DPN. To diagnose this condition nerve conduction studies with measurement of latency and velocity are commonly used as they are considered to be most sensitive, reliable, objective and non-invasive means.⁶ F-wave is a late muscle response that results from the antidromic activation of motor neurons following electrical stimulation of peripheral nerves.⁷ F-wave allows assessment of the proximal nerve segment which is not accessible by conventional nerve conduction, especially the surreal nerve, is considered to be more impaired than motor nerve conduction.⁹ For this reason, F wave studies have been considered to be of limited value in patients with subclinical diabetic neuropathy.¹⁰ However, studies of proximal as well as distal nerve functions such as F-wave testing may show changes as well. It has been recently reported that F-wave determinations in diabetic patients are very reliable.¹¹

So in the present study all sensory and motor conduction parameters and F-wave parameters of upper and lower extremity nerves were studied in patients with clinical diagnosis of DPN to find out which of these parameters have the highest sensitivity and specificity.

MATERIALS AND METHODS: Sixty patients having type II diabetes mellitus which were referred to the department of Electrophysiology of Krishna Institute of Medical Sciences, Karad were investigated. The patients were referred from Krishna hospital, other hospitals and nursing homes in Karad city as well as the neighboring cities of Western Maharashtra. 38 patients were males and 22 patients were females. Age ranges from 21 to 77 years. The known duration of diabetes was 1year to 25 years. All the patients were having clinical evidence of neuropathy. All the patients were on oral antidiabetic drugs and their blood glucose levels were below 200mg/dl. Institutional ethical committee approval as well as approval from other hospitals and nursing homes was taken for the study.

Inclusion Criteria: were 1) patients who were diagnosed as diabetic by physicians. 2) All these patients were having symptoms of tingling, numbness, hypoesthesia, pain and weakness in extremities with different degree of severity.

Exclusion Criteria were 1) diabetic patients with a history of chronic alcoholism. 4) Patients with other chronic disorders like hypertension, rheumatoid arthritis etc. 5) Patients in which signs of involvement of only median nerve (carpal tunnel syndrome) were present.

Nerve conduction study was also performed on 45 age matched controls those were selected from the non-teaching staff and peons of medical college and hospital of Krishna Institute. In controls 24 were males and 21 were females. Subjects those were having diabetes mellitus, any neurological complaints and h/o alcoholism were excluded from the study.

Patients and subjects were informed the detailed procedure of nerve conduction study and written consent was taken. The electro diagnostic study included motor and sensory nerve conduction of Median and Ulnar nerves on both sides by conventional method.¹¹

For recording sensory and motor nerve conduction, surface metal electrodes were used. For recording motor conduction of Median nerve, recording electrode was placed close to the motor point of Abductor Pollicis Brevis and reference electrode 3cm distal to it at the first metacarpophalangeal joint. A supramaximal stimulus was given at wrist and at elbow near volar crease of brachial pulse. For recording motor conduction of Ulnar nerve, recording electrode was placed close to the motor point of Abductor Digiti Minimi and reference electrode 3cm distal to it at fifth metacarpophalangeal joint. A supramaximal stimulus was given at wrist and at elbow in cubital tunnel behind medial epicondyle. For ulnar nerve stimulation at the elbow arm position was maintained at 135⁰.¹²

For orthodromic sensory conduction of median nerve, surface recording electrode was placed 3cm proximal to the distal wrist crease and a reference electrode at 3cm proximal to recording electrode. For stimulation ring electrodes were fixed on second digit.

For orthodromic sensory conduction of ulnar nerve, recording electrode was placed 3cm proximal to distal palmer crease and a reference electrode at 3cm proximal to recording electrode. For sensory stimulation ring electrodes were fixed on fifth digit. Cathode is placed at first interphalangeal joint and end at 3cm distal to cathode. For both median and ulnar sensory conduction, 20 supramaximal stimuli were delivered and average was recorded. During both median and ulnar sensory conduction recordings, ground electrode was placed between recording and stimulating electrodes. Care was taken to keep same distance between stimulating and recording electrode for both median and ulnar nerves at wrist.

For motor conduction of Peroneal nerve recording electrode was placed on the motor point on the belly of Extensor Digitorum Brevis (EDB) and reference electrode was placed 3cm distal to recording electrode. A supramaximal stimulus was given at ankle on the point midway between the medial and lateral malleoli with feet slightly dorsiflexed. 2nd stimulus was given at upper end of fibula just below head of fibula.

For motor conduction of Tibial nerve recording electrode was placed on the motor point on the belly of Adductor Hallucis (AH) and reference electrode was placed 3cm distal to recording electrode. A supramaximal stimulus was given at ankle between heel and medial malliolus. 2nd stimulus was given in the medial aspect of popliteal fossa.

For sensory conduction of Sural nerve the surface recording electrode was placed midway between heel and lateral malleolus and reference electrode was placed 3cm distal to recording electrode. 20 supramaximal stimuli were delivered and average was recorded. Stimulation of the nerve was done on the posterolateral aspect of the leg obliquely.

For recording of F-wave response the surface recording electrode was placed on a belly of muscle similar to motor nerve conduction study. For median nerve recording electrode was kept on APB muscle, for ulnar nerve it was kept on ADM muscle, for peroneal nerve it was kept on EDB and for tibial nerve it was kept on AH muscle. The F-wave recording was done from relaxed muscle. Conventional supramaximal stimulation was used. The cathode was placed proximal to an ode to avoid nodal block. 10 such stimuli were given. From 10 tracings of F-waves, minimal F-wave latency (FWML) was measured.

Motor and sensory conduction study was performed bilaterally on each nerve. The procedure was explained to patients as well as to the subjects and consent was taken. Patients were asked to lie down on the bed in supine position and extremities were exposed.

For each motor nerve studied following parameters were Measured:

- Distal motor latency.
- Compound muscle action potential amplitude.
- Motor conduction velocity.
- F-wave, minimal latency.

For each sensory nerve studied following parameters were Measured:

- Distal sensory latency.
- Sensory action potential amplitude.
- Sensory conduction velocity.
- During nerve conduction study, laboratory temperature was maintained between 21°C to 23°C. When skin temperature of limb was below 34°C, the limb was immersed in a warm water to correct the temperature.¹²
- For nerve conduction studies, Recorder and Medicare System (RMS) machine from Chandigarh (India) (Model -RMS EMG. EP Mark II, RMS/F/MKT/REV-01) was used.

STATISTICAL ANALYSIS: Microsoft office excels 2013 package was used for statistical analysis. The standard statistical unpaired t test was used to compare nerve conduction parameters in control and patients and p value was calculated. Mean and SD for different parameters were measured in controls and patients.

Normality range was determined from mean and SD of controls (Normal healthy subjects). 95% confidence limit of normality range was determined as mean ± 1.96 SD.

Sensitivity and specificity for each parameter was calculated by standard method.¹³

Nerve	DML	CMAP Amplitude	MNCV	FWML	
Median					
Control	2.91 ± 0.40	15.76 ± 3.63	58.67 ±6.36	25.53 ± 1.71	
Patient	***4.04± 1.97	* 8.19 ± 4.30	*44.70 ± 8.32	***31.26 ± 3.97	
Ulnar					
Control	2.81 ± 0.49	15.80 ± 2.70	56.81 ± 6.23	25.62 ± 1.82	
Patient	***4.20 ± 2.11	* 7.19 ± 3.36	*42.76 ± 6.75	***31.76 ± 4.03	
Peroneal					
Control	3.24 ± 0.76	10.35 ± 2.38	47.29 ± 3.52	48.05 ± 3.74	
Patient	***4.13 ± 1.39	** 2.88 ± 1.68	*35.94 ± 6.05	***59.80 ± 6.06	
Tibial					
Control	3.74 ± 0.63	13.68 ± 3.54	46.03 ± 3.36	47.33 ± 3.43	
Patient	***5.05 ± 1.76	**4.10 ± 2.85	**35.99 ± 6.34	***60.44 ± 7.82	
		Table 1			

RESULTS:

*p< 0.05 **p< 0.01 ***p<0.005

Electrophysiological changes in motor nerve conduction parameters and FWML of upper and lower extremity nerves.

In Tables 1 electrophysiological changes in motor conduction of various nerves in upper and lower extremities are shown. When changes in various parameters of motor conduction in Median, Ulnar, Peroneal and Tibial nerves, 120 each (60 nerves bilaterally), were studied, the following abnormalities were found:

- 1) There was significant increase in DML of all the nerves compared to controls.
- 2) There was significant decrease in CMAP of all the nerves compared to controls.
- 3) There was significant decrease in MNCV of all the nerves compared to controls.
- 4) There was significant increase in FWML of all the nerves compared to controls.

However, the increase in DML and FWML was very highly significant and level of significance for decrease in CMAP and MNCV less.

Nerve	DSL	SNAP Amplitude	SNCV
Median			
Control	2.51 ± 0.32	12 ± 2.45	52.43 ± 5.36
Patient	***3.92±0.89	* 6.42 ± 3.7	*39.75 ± 6.32
Ulnar			
Control	2.72 ± 0.54	14.34 ± 2.68	52.81 ± 4.23
Patient	***4.20 ± 0.11	* 8.02 ± 2.98	*40.16 ± 5.75
Sural			
Control	2.24 ± 0.76	13.35 ± 3.38	49.23 ± 3.00
Patient	***4.23 ± 0.49	** 6.88 ± 1.38	*35.74 ± 4.15
		Table 2	

*p< 0.05 **p< 0.01 ***p<0.005

Electrophysiological changes in sensory nerve conduction parameters of upper and lower extremity nerves.

In Tables 2 electrophysiological changes in sensory conduction of various nerves in upper and lower extremities are shown. When changes in various parameters of sensory conduction in Median, Ulnar and Sural nerves, 120 each (60 nerves bilaterally), were studied, the following abnormalities were found:

- 1) There was significant increase in DSL of all the nerves compared to controls.
- 2) There was significant decrease in SNAP of all the nerves compared to controls.
- 3) There was significant decrease in SNCV of all the nerves compared to controls.

Nerve	Prolonged FWML	Normal FWML	
Median	82 (73.87%)	29 (26.12%)	
Ulnar	79 (69.91%)	34 (30.08%)	
Peroneal	48 (72.72%)	18 (27.27%)	
Tibial	60 (68.96%)	18 (20.68%)	
	Table 3		

Percentage of abnormal F-responses.

Table 3 shows percentage of abnormal F-wave responses. Out of 120 median nerves studied prolonged FWML was present in 82 nerves. Out of 120 ulnar nerves studied, prolonged FWML was present in 79 nerves. Out of 120 perennial nerves prolonged FWML was present in 48 nerves. Out of 120 tibial nerves prolonged FWML was present in 60 nerves.

Parameter	Nerves				
	Median	Ulnar	Peroneal	Tibial	Sural
FWML	75.7%	81.37%	83.63%	81.7%	
DML	53.33%	26.31%	25.80%	41.17%	
СМАР	56.66%	66.66%	80.64%	71.54%	
MNCV	50%	47.36%	77.41%	72.55%	
DSL	37.97%	23.80%			41.50%
SNAP	81.01%	64.28%			60.37%
SNCV	40.50%	26.19%			58.49%
Table 4					

Comparison of Sensitivity for various parameters studied.

Table 4 shows the sensitivity of different nerve conduction parameters. Sensitivity was highest for FWML. This is followed by SNAP (81.01%) in median nerve while CMAP in other nerves studied. The third parameter in the sequence is MNCV.

Parameter	Nerves				
	Median	Ulnar	Peroneal	Tibial	Sural
FWML	95.55%	95.55%	93.33%	93.33%	
DML	91.11%	93.33%	95.55%	91.11%	
СМАР	97.77%	97.77%	100%	97.77%	
MNCV	100%	93.33%	95.55%	100%	
DSL	95.55%	95.55%			88.88%
SNAP	91.11%	95.55%			97.77%
SNCV	100	95.55%			97.77%
Table 5					

Comparison of specificity for various parameters studied.

Table 5 shows specificity for different nerve conduction parameters. Specificity of all the parameters was above 90%. Sensitivity is ability of the test to identify correctly all those who have the disease i.e. true positive. Specificity is ability of the test to identify correctly all those who do not have the disease i. e. true negative.

DISCUSSION: Polyneuropathy is one of the commonest complications of DM. The detection of DPN is an area of ongoing interest for the researchers and clinicians, not only for diagnosing and managing it earlier, but also for understanding the disease which is still under exploration. Mostly nerve conduction studies have been accepted as an essential part of diagnosis of DPN as it has many benefits. In the present study we have done sensory and motor nerve conduction and also FWML.

Then we compared the sensitivity and specificity of various nerve conduction parameters so as to find out which of these parameters are showing higher sensitivity and specificity.

In the present study, we found that in electro diagnostic studies of median, ulnar, peroneal and tibial nerves in DPN patients there was a significant increase in DML and FWML of all these motor nerves. We also found that there was a significant decrease in MNCV and CMAP of some of these nerves. Our results concur with earlier studies.^{14,15}

The interesting finding in our study was that the changes in DML and FWML were very highly significant (p<0.005) than those in MNCV and CMAP (p<0.01). In DM toxicity of glucose leads to damage to the myelin sheath of axons causing degeneration and hampers regeneration of these axons so that nerve conduction is affected. The earlier parameter of motor conduction to get affected is DML. In the present study, 50.69% of the motor nerves which showed motor response were affected with increased DML. These results are consistent with the reports from other researchers.^{16,17} In DPN later effect is decrease in motor velocity due to loss of myelin sheath and then there is axonal loss causing reduction in CMAP. CMAP is a measure of muscle fibre mass. When less number of muscle fibres is activated amplitude of CMAP decreases.

Another finding in this study was that 69.16% of the motor nerves in upper extremity and 58.33% of nerves in lower extremity showed abnormal F-wave response. 254 nerves showed increased FWML. These numbers are significantly higher than those for other parameters of motor nerve conduction. In our study the sensitivity of FWML was 75.7% in median nerve, and above 80% in other nerves studied. This was higher compared to other nerve conduction parameters. The specificity of FWML was above 90% in all the nerves studied. Jung Bin Shin et.al had got similar results in their study of diabetic patients. They concluded that FWML was more sensitive indicator of DPN that either MNCV or CMAP as frequency of abnormal FWML in their study was 67% for median, 56% for ulnar, 18% for peroneal and 21% for tibial nerves.⁶

Another finding in our study was that in 20.41% of the motor nerves studied FWML was increased while other motor conduction parameters like DML, MNCV and CMAP were normal. These findings are consistent with the findings of other workers, which have shown that the F-waves may be considered more sensitive than motor conduction studies in axonal polyneuropathies.^{18,19} Frank Weber in his study found that 45% of axonal polyneuropathies could be identified due to abnormal F-wave response with normal peripheral motor conduction studies.²⁰

F-wave is a late muscle response. A strong electrical stimulus (supramaximal stimulation) is applied to the skin surface above the distal portion of a nerve so that the impulse travels both distally (towards the muscle fiber) and proximally (back to the motor neurons of the spinal cord). These directions are also known as orthodromic and antidromic, respectively. When the orthodromic stimulus reaches the muscle fiber, it elicits a strong M-response indicative of muscle contraction. When the antidromic stimulus reaches the motor neuron cell bodies, a small portion of the motor neurons backfires and orthodromic wave travels back down the nerve towards the muscle. This reflected stimulus evokes small proportion of the muscle fibers causing a small, second CMAP called the F wave.¹² In F-wave study impulse transmission across the entire nerve is studied rather than a segment of nerve. From DSL and DML only distal segment of nerve is tested while from conduction velocity only on a segment of nerve is tested. However, in F wave study proximal as well as distal segment is studied. So this study may be considered more reliable for electrodiagnosis of DPN. Our findings about FWML i.e. FWML is most sensitive indicator for electrodiagnosis of DPN, concur with the studies of Fraser JL and Weber F.^{17,18,19}

In the present study, we found that FWML had maximum sensitivity and specificity in the patients of DPN (Table no. 6 & 7). So FWML may be considered as most sensitive and therefore reliable parameter for electro diagnosis of DPN.

CONCLUSION: FWML is highly sensitive indicator for diagnosis of DPN.

ACKNOWLEDGEMENT: The authors are thankful to the vice chancellor and principal KIMS deemed university, Karad for providing us all the laboratory facilities for carrying out this work. We are also thankful to laboratory technicians of Department of Physiology for their valuable help for operative procedures in the study.

REFERENCES:

- 1. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025: prevalence, numerical estimates and projections. Diabetes care 1998; 21: 1414-31.
- 2. Roglic G, Green A, Sicree R, King H. "Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030". Diabetes Care 2004; 27 (5): 1047–53.
- 3. Pradeepa R, Rema M, Vignesh J. Prevalence and risk factors for diabetic neuropathy in an urban south Indian population: the Chennai Urban Rural Epidemiology Study (CURES-55).
- 4. Wild SH, Roglic G, Sicree R, Green A, King H (2002). Global burden Diabetes Mellitus in the year 2000. Available from: www.who.int.
- 5. de Wytt CN, Jackson RV, Hockings GI, Joyner JM, Strakosch CR. Polyneuropathy in Australian outpatients with type II diabetes mellitus. J Diabetes Complications. 1999; 13 (2): 74-8.
- 6. Shin JB, Seong YJ, Lee HJ. The usefulness of minimal F-wave latency and Sural/Radial amplitude ratio in diabetic polyneuropathy. Yonsi Medical journal 2000; 41: 393-97.
- Panayiotopoulos CP, Chroni E. F-waves in clinical neurophysiology: a review, methodological issues and overall value in peripheral neuropathies. Electroencep Clin Neurophysiol 1996; 101: 365-74.
- 8. Kimura J, Yamada T, Stevland NP. Distal slowing of motor conduction velocities in diabetic polyneuropathy. J Neurolo Sci 1979; 42: 291-302.
- 9. Thomas PK, Tomlinson DR. Diabetic and hypoglycemic neuropathy. Peripheral Neuropathy, Philadelphia; Saunders Press. 1993: 1219-50.
- 10. Mysiw WJ, Colachis SC, Vetter J. F response characteristics in type I diabetes mellitus. Am J Phys MED Rehabil 1990; 69: 112-16.
- 11. Kohara N, Kimura J, Kaji R. Inter-trial variability of nerve conduction studies: multicenter analysis. Electroencep clin Neurophysiol 1995; 97: S66.
- 12. Mishra UK., Kalita J. Clinical neurophysiology, 2nd Ed. Reed Elsevier, India Private Limited, 2008; 32-40.
- 13. Park K. Park's textbook of preventive and social medicine. 20th Ed. Banarsidas Bhanot publishers, 2009: 126-27.
- 14. Pandya NH, Desai KS, Goswami TM. Electrophysilogical changes in sensorimotor nerves in diabetes mellitus and usefulness of nerve conduction studies for early diagnosis of diabetic neuropathy. International journal of Biomedical and Advance research 2013; 4: 187-91.
- 15. Sultana S, Begum N, Ali L. Electrophysiological changes of motor nerves in patients with type 2 diabetes mellitus. JAFMC Bangladesh 2009; 5: 14-7.

J of Evolution of Med and Dent Sci/ eISSN- 2278-4802, pISSN- 2278-4748/ Vol. 3/ Issue 69/Dec 11, 2014 Page 14735

- 16. Zangiabadi N, Ahrari MN, Nakhaee N. The effect of omega-3 fatty acids on nerve conduction velocity and F latency in patients with diabetic polyneuropathy. American journal of Pharmacology and Toxicology 2007; 2: 1-3.
- 17. Trojaborg W. The electrophysilogical profile of diabetic neuropathy. Seminars in Neurology 1996: 16: 123-28.
- 18. Fraser JL, Olney RK. The relative diagnostic sensitivity of different F-wave parameters in various polyneuropathies. Muscle-Nerve 1992; 15: 912-18.
- 19. YCK PJ, Karnes JL, Daube J. Clinical and neurophysiological criteria for diagnosis and staging of diabetic polyneuropathy. Brain 1985; 108: 861-88.
- 20. Weber F. The diagnostic sensitivity of different F wave parameters. J. Neurol Neurosurg Psychiatry 1998, 65: 535-40.

AUTHORS:

- 1. A. R. Gargate
- 2. A. G. Joshi

PARTICULARS OF CONTRIBUTORS:

- 1. Professor, Department of Physiology, Institute of Medical Sciences and Research, Mayni, Satara.
- 2. Professor, Department of Physiology, Krishna Institute of Medical Sciences, Karad.

NAME ADDRESS EMAIL ID OF THE CORRESPONDING AUTHOR:

Dr. A. R. Gargate, Department of Physiology, Institute of Medical Sciences and Research, Mayni Vidyagiri Vita Road, Khatav Taluk, Satara District. Email: ashwinigargate@yahoo.in

> Date of Submission: 24/11/2014. Date of Peer Review: 25/11/2014. Date of Acceptance: 05/12/2014. Date of Publishing: 09/12/2014.