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Tiny Incredible Urethral

Effect of Aerobic Exercise

Highlights

Flask Paraplegic Reveals

Salivary Dielectric Properties

Discovering Thoughts, Inventing Future

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Effect of Aerobic Exercise Training on Cardiovascular Responses in Type 1 Diabetic Autonomic Neuropathy

By Mohamed Abdulsattar Mohammed Hemida, Prof. Dr. Awny Fouad Rahmy, Dr. Gihan Samir Mohamed & Prof. Dr. Ayman Fathy Kaddah

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Abstract- *Background:* Diabetes Mellitus is a chronic, multifaceted disorder caused by reduction in insulin action and secretion or the both, it's characterized by hyperglycemia and disruption of the metabolism of carbohydrates, fats and proteins, over time, it results in small and large vessels complications and neuropathies. This disease is ranked as the third cause of death and leading factor of blindness. One of the most overlooked of all serious complications of diabetes is cardiovascular autonomic neuropathy (CAN), which encompasses damage to the autonomic nerve fibers that innervate the heart and blood vessels, resulting in abnormalities in heart rate control and vascular dynamics The complications of diabetes mellitus are macro and micro vascular disorders, central, Peripheral and autonomic neuropathy. The autonomic neuropathy is the most common complication of the long standing diabetes Autonomic neuropathy is a well recognised complication of diabetes mellitus, and its incidence has been reported to be 20 - 40%.

Keywords: *aerobic exercise, type 1 diabetes mellitus, cardiac autonomic neuropathy.*

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Effect of Aerobic Exercise Training on Cardiovascular Responses in Type 1 Diabetic Autonomic Neuropathy

Mohamed Abdulsattar Mohammed Hemida [α], Prof. Dr. Awny Fouad Rahmy [σ], Dr. Gihan Samir Mohamed [ρ] & Prof. Dr. Ayman Fathy Kaddah [ω]

Abstract- Background: Diabetes Mellitus is a chronic, multifaceted disorder caused by reduction in insulin action and secretion or the both, it's characterized by hyperglycemia and disruption of the metabolism of carbohydrates, fats and proteins, over time, it results in small and large vessels complications and neuropathies. This disease is ranked as the third cause of death and leading factor of blindness. One of the most overlooked of all serious complications of diabetes is cardiovascular autonomic neuropathy (CAN), which encompasses damage to the autonomic nerve fibers that innervate the heart and blood vessels, resulting in abnormalities in heart rate control and vascular dynamics The complications of diabetes mellitus are macro and micro vascular disorders, central, Peripheral and autonomic neuropathy. The autonomic neuropathy is the most common complication of the long standing diabetes Autonomic neuropathy is a well recognised complication of diabetes mellitus, and its incidence has been reported to be 20 - 40%.

Subjects and Methods: Fifty diabetic patients type-1, diagnosed by concerned Doctor with autonomic neuropathy, with duration of disease more than five years, their age ranged from 45 to 65 years old, they were be chosen from National Institute for Diabetes and Endocrine Glands, They were randomly assigned to two equal groups. Study group included twenty five diabetic patients with autonomic neuropathy, practiced a program of aerobic exercise with intensity from 60 to 75 % of maximal heart rate (HR_{max}) on treadmill for self limiting intensity for 3 sessions / week for three months and received their medical management (16 men and 9 women, mean age was 52.2 ± 4.9 years) that had been received aerobic moderate intensity exercise training on treadmill for 40 minutes, 3 times/week, day after day, for 3 months, while control group included twenty five diabetic patients with autonomic neuropathy they received only their medical treatment. All patients had been evaluated to measure age, Body mass index (BMI), fasting blood glucose, heart rate (HR) responses to valsalva maneuver, HR response to deep breathing, HR response to change of position, systolic blood pressure (BP) response to valsalva maneuver , systolic BP response to sustained hand grip and systolic BP response to change of position. ECG machine and its accessories will be used to do stress test for each patient by attending physician and to monitor heart rate, rhythm, R-R interval and Q-T interval for each patient of both groups. All measurements were done before and after the study program.

Results: After completion of the study, a significant improvement was observed in (BMI), fasting blood glucose, (HR) responses to valsalva maneuver, HR response to deep breathing, HR response to change of position, systolic blood pressure (BP) response to valsalva maneuver, systolic BP response to sustained hand grip and systolic BP response to change of position ($P < 0.05$), when compared to control group.

Conclusion: Aerobic moderate intensity exercise training could improve cardio vascular responses in diabetic autonomic neuropathy. Aerobic exercise is a good method that improve cardiac autonomic neuropathy in type 1 diabetes mellitus.

Keywords: aerobic exercise, type 1 diabetes mellitus, cardiac autonomic neuropathy.

I. Introduction

Diabetes Mellitus is a chronic, multifaceted disorder caused by reduction in insulin action and secretion or the both, it's characterized by hyperglycemia and disruption of the metabolism of carbohydrates, fats and proteins, over time, it results in small and large vessels complications and neuropathies. This disease is ranked as the third cause of death and leading factor of blindness (Boulton AJ et al 2010).

The complications of diabetes mellitus are macro and microvascular disorders, central, Peripheral and autonomic neuropathy. The autonomic neuropathy is the most common complication of the long standing diabetes, It's due to the accumulation of sorbitol in nerve cell that result in abnormal fluid and electrolyte shift, which causes nerve cell dysfunction,. Balanced cardiac ANS function is based on strong impaired cardiovascular ANS function has been associated with type 1 diabetes (T1D) (Stevens et al., 2008).

Data from the 2008 Egypt Demographic and Health Survey (EDHS 2008) were used to show the Prevalence of diabetes for selected socio-demographic

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variables was calculated by gender. Prevalence of co morbid conditions, and risk factors for complications of diabetes, were estimated by gender. Health care utilization among diabetics was estimated. The crude prevalence rate of known diabetes in Egypt in 2008 was 4.07% (0.25). It increased with age, to reach 19.8% among females aged 50-59. Only 18% of males, and 7.8% of females, had a normal body mass index. 37.5% of male diabetics smoked. The prevalence of hypertension among diabetics was 75% for males, and 66.9% for females; of these, only 2% of males, and 14.3% of females, were controlled to < 130/80 mmHg. 13.3% of males had a history of myocardial infarction or stroke. 44.9% of males, and 80.4% of females, had no insurance coverage. More than half of diabetics visited a private physician at their last visit. 9.3% of males, and 3.8% of females, had been hospitalized in the past year. They concluded that Diabetes is highly prevalent among older persons in Egypt. Public health policy should educate the public on the risk factors for diabetes, and should implement guidelines for adequate control of this disease (Naglaa et al 2010).

Autonomic neuropathy is a well recognised complication of diabetes mellitus, and its incidence has been reported to be 20 - 40%. Numerous non-invasive tests have been in use for the diagnosis of cardiac autonomic neuropathy (Ewing DJ et al 1985).

CAN, manifested as changes in HRV, may be detected within 1year of diagnosis in type 2 diabetes and within 2 years of diagnosis in type 1 diabetes (Drake-Holland AJ et al, 2006)

Resting tachycardia. Resting heart rates of 100 bpm with occasional increments up to 130 bpm usually occur later in the course of the disease and reflect a relative increase in the sympathetic tone associated with vagal impairment (Young et al., 2009).

Diabetic autonomic neuropathy (DAN) is classified as subclinical or clinical depending upon the presence or absence of symptoms. A wide spectrum of symptoms affecting many different organ systems can occur, including the cardiovascular, gastrointestinal, genitourinary, pupillary, sudomotor, and neuroendocrine systems (Tesfaye S et al 2005).

One of the most overlooked of all serious complications of diabetes is cardiovascular autonomic neuropathy (CAN), which encompasses damage to the autonomic nerve fibers that innervate the heart and blood vessels, resulting in abnormalities in heart rate control and vascular dynamics (Schumer MP 1998).

Our data and those of others confirm that early in the progression of CAN complicating type 1 diabetes, there is a compensatory increase in the cardiac sympathetic tone in response to subclinical peripheral denervation, CAN may critically influence myocardial substrate utilization (Drake-Holland AJ et al, 2006) and contribute to mitochondrial uncoupling regional ventricular motion abnormalities, functional deficits, and cardio myopathy (Pop-Busui R, 2004)

Aerobic exercise is a physical exercise that intends to improve the oxygen system Aerobic means "with oxygen", and refers to the use of oxygen in the body's metabolic or energy-generating process. Many types of exercise are aerobic, and by definition are performed at moderate levels of intensity for extended periods of time The two types of exercise differ by the duration and intensity of muscular contractions involved, as well as by how energy is generated within the muscle. Initially during aerobic exercise, glycogen is broken down to produce glucose, which then reacts with oxygen (Krebs cycle) to produce carbon dioxide and water and releasing energy. In the absence of these carbohydrates, fat metabolism is initiated instead (Colberg S et al., 2003).

II. Patients and Methods

This study was consists of fifty type 1 diabetes mellitus(IDDM)patients with autonomic neuropathy (36 males and 14 females) attended to the Outpatient Clinic in National Institute for Diabetes and Endocrine Glands. Their age ranged from 45 to 65 years with a mean value of (49 ± 7.2), height ranged from 162 to 181 cm with a mean value of (172 ± 9), and the body weight ranged from 67 to 91 Kg with a mean value of (170 ± 11). Their body mass indexes ranged from 19 to 31 Kg / m^2 with a mean value of (25 ± 3.3 Kg / m^2). The all patients under medical control by specialized physician. All patients were randomly divided into two equal groups.

The study group was twenty five (19 male and 6 female) IDDM patients with autonomic neuropathy, Who practiced aerobic exercise training with a moderate intensity from 60 to 75 % of their HR_{max} for each patient three sessions /week for three months on an electronic treadmill for forty minutes to each session, and Control group include twenty five patients (17 male and 8 female) IDDM, all patients received their medical treatment.

Exclusion criteria: Patients with, Varicose veins, Severe ischemic heart diseases and Chest infection patients were excluded.

Before starting the study, a meeting was done for all patients to explain for all of them our study (patient information sheet PIS) and also to collect consent form of each patient and to record demographic data, fasting blood glucose, heart rate (HR) responses to valsalva maneuver, HR response to deep breathing ,HR response to change of position, systolic blood pressure (BP) response to valsalva maneuver, systolic BP response to sustained hand grip and systolic BP response to change of position. ECG machine and its accessories will be used to do stress test for each patient by attending physician and to

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monitor heart rate, rhythm, R-R interval and Q-T interval for each patient of both groups.

Each patient of study group was asked to perform aerobic exercise training on electronic treadmill with moderate intensity from 60 to 75 % of each individualized (HR_{max}), three times per week for three months for forty minutes of each session, accordingly to self limiting intensity of each patient the program started with:

Warming up phase; for 5 minutes on treadmill with low speed (0 watt) with horizontal line, then the speed of electronic treadmill increased to reach Active phase **(Soligard et al., 2008).**

Stimulus phase; in which each patient of group A performed self limiting exercises on treadmill with individualized moderate intensity from 60 to 75 % of HR_{max}. For 30 minutes **(Laskowski., 2013)**

Cool Down phase; about 5 minutes on treadmill with low speed **(Woods et al., 2007).**

Data were analyzed with SPSS software version 23. The level of significance was set at P≤ 0.05. Paired t-test was applied for each group to compare pre and post values within the same group. Unpaired t-test was applied to compare pre and post values between both groups of the study.

III. Results

Mean value of body mass index (BMI) had shown a significant improve by significantly decreased post exercise in study group (P value = 0.001) as compare to control group which increased significantly (P value = 0.047) (Table 1). In study group The value of Q-T interval had shown significant improve after exercise (P value = 0.001) but in control group had shown significant increase in Q-T interval (P value = 0.001) (Table 1). The reduction of Q-T interval was considered as improvement. In study group R- R interval had shown a significant improve post exercise (P value = 0.001) and no significant change in control group (Table 1). The increment of R- R interval was considered as improvement. The mean value of fasting blood glucose was shown high significant (decrease) improve post exercise (P value = 0.000) and control group had shown significant increase (P value = 0.002) (Table 1).

Table (1) : Changes of Body Mass Index (BMI), Q T interval ,R R interval and Fasting Blood Glucose Pre and Post Program within each group and between groups:

Variables	Study group			Control group			P value for both groups after program
	Pre program	Post program	P Value	Pre program	Post program	P Value	
	Mean ±SD	Mean ±SD		Mean ±SD	Mean ±SD		
BMI	29.2 ± 2.6	27.7 ± 2.3	0.001 S	28.8±1.7	29.2±1.8	0.047	0.018 S
Q T interval	448.8 ± 47.3	414.6 ± 45.3	0.001 S	426.2±34.8	450.4±39.3	0.001	0.023 S
R R interval	487.6 ± 53.3	599.1 ± 49.9	0.001 S	613.6±71.1	574.0±84.4	0.14	0.207
Fasting Blood Glucose	137.4 ± 10.8	137.4 ± 5.0	0.000 S	129.0±6.9	135.6±8.8	0.002	0.001 S

SD=Standard Deviation, Significant level: P≤0.05 S.

The mean value of systolic blood pressure responses to (change position, sustained hand grip and valsalva Maneuver) respectively had shown significant improve after exercise (P value = 0.003) (P value = 0.000) and (P value = 0.008) respectively but in control group had shown significant increase in systolic blood pressure responses to change position, sustained hand grip (P value = 0.000) and (P value = 0.001) (Table 2) and no significant changes in response to valsalva Maneuver) (P value = 0.098) (Table 2).

Table (2) : Changes of systolic blood pressure responses to change position, sustained hand grip and response to valsalva Maneuver Pre and Post Program within each group and between groups:

Variables	Study group			Control group			P value for both groups after program
	Pre program	Post program	P Value	Pre program	Post program	P Value	
	Mean ±SD	Mean ±SD		Mean ±SD	Mean ±SD		
systolic B P response to change position	139.3 ± 6.5	134.8 ± 5.5	0.003 S	137.7± 7.6	143.7± 6.4	0.000 S	0.000 S
systolic B P response to sustained Hand Grip	139.6 ± 6.1	134.1 ± 5.9	0.000 S	138.4± 6.8	142.9± 7.1	0.001 S	0.000 S
systolic BP response to valsalva maneunver	137.6 ± 6.4	134.2 ± 5.8	0.008 S	134.4± 8.5	136.7± 5.6	0.098	0.135

SD=Standard Deviation, Significant level: P≤0.05 S.

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in study group the mean values of the heart rate responses to (change position, Deep breathing and valsalva Maneuver) had shown significant improve post exercise (P value = 0.000), (P value = 0.000) and (P value = 0.001) respectively and in control group had shown significant increase in heart rate responses to change position (P value = 0.009), Deep breathing (P value = 0.026), and no significant changes in heart rate responses to valsalva Maneuver (P value = 0.098) (Table 3).

Table (3) : Changes in Heart rate responses to (change position, Deep breathing and valsalva Maneuver Maneuver Pre and Post Program within each group and between groups:

Variables	Study group			Control group			P value for both groups after program
	Pre program	Post program	P Value	Pre program	Post program	P Value	
	Mean ±SD	Mean ±SD		Mean ±SD	Mean ±SD		
Heart Rate response to change position	98.3±7.6	93.9±5.7	0.000 S	98.3± 6.7	101.6 ± 2.7	0.009 S	0.001 S
Heart Rate response to Deep Breathing	92.6±6.4	88.5±5.6	0.000 S	84.2 ± 6.7	86.7 ± 6.1	0.026 S	0.005 S
Heart Rate response to valsalva maneuver	80.1±4.0	76.3±4.7	0.001 S	87.8 ± 1.6	86.8± 4.7	0.098	0.001 S

SD=Standard Deviation, Significant level: P≤0.05 S

IV. Discussion

In this study, The mean value of BMI was significantly decreased post exercise from (29.2400 ± 2.61852) to (27.76 ± 2.38537). The mean value of fasting blood glucose pre exercise was (137.48 ± 10.85557) and significantly reduced post exercise to (127.00 ± 5.01664). The mean value of systolic blood pressure before exercise (change position, sustained hand grip and valsalva Maneuver) were (139.36 ± 6.52482), (139.68 ± 6.10137) and (137.60± 6.45497) respectively which were significantly changed after exercise by decreasing to (change position, sustained hand grip and valsalva Maneuver) (134.80 ± 5.50757), (134.16 ± 5.91383) and (134.24± 5.84009) respectively. The mean values of the heart rate responses to (change position, Deep breathing and valsalva Maneuver) were (98.36 ± 7.65876), (92.68 ± 6.47251) and (80.12 ± 4.04475) respectively, That were significantly decreased post exercise to (93.96 ±5.78417), (88.56 ± 5.61308) and (76.32 ± 4.75850) respectively. The value of Q-T interval pre exercise was (448.88 ± 47.39666). and significantly reduced post exercise to (414.68 ± 45.37503) (Table 10). The reduction of Q-T interval was considered as improvement. R- R interval pre exercise was (487.60 ± 53.32448) and significantly increased post exercise to (599.12 ± 49.92438), The increment of R- R interval was considered as improvement.

Results of this study were supported by **Neil J et al 2006**, who studied the Differences among the effects of aerobic, resistance, and combined training on HbA_{1c} (A1C) were trivial for training lasting ≥12 weeks, in diabetic patients. There were generally moderate benefits for other measures of glucose control. For other risk factors, although combined training was generally superior to aerobic and resistance training. but there were small additional benefits of exercise on glucose control with increased disease severity. They concluded that All forms of exercise training produce benefits in the main measure of glucose control: A1C. The effects are similar to those of dietary, drug, and insulin treatments. These results were supported by **Thomas H et al 2009** who said that both aerobic and resistance training have important roles in DM. Recent work comparing the individual and combined effects of aerobic and/or resistance training revealed that both forms of exercise were equally beneficial for glycemic control, although aerobic training had a greater effect on body composition, also **Sarika Chaudhary et al 2010** found that BMI and body fat percentage showed significant improvements in both training groups.

Jamie F. Burr 2012 who concluded that Aerobic exercise has significant and particular benefits for people with type 1 diabetes. It increases sensitivity to insulin, improves cholesterol levels, and decreases body fat. The results of this study was similar to **Thomas H et al 2009** who said both aerobic and resistance training have important roles in DM on glycemic control. Also **Alsayd et al, (1999)** who found that after six weeks of exercise training on treadmill with moderate intensity in diabetic patients there was a significant reduction in body weight and BMI. Also **Wing et al; (1988)** found that in diabetic patients exercise had been useful adjunct to diet control in diabetic patients to reduce body weight and BMI. **Klem et al; (1997)** found that exercise improved body composition in diabetic patients that lead to weight loss and reduce BMI. Also **Koullam. Parpa et al 2009 found that** fasting glucose values (FG) and body weight were significantly lower following 12 weeks of training. also **Didangelos T et al 2006** said that Improvement in glycemic control reduces the incidence of CAN and slows the progression there of.

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The results of this study were contradict with Lehmann et al; (1995) they found that moderate exercise training resulted in considerable decrease of body fat particularly in abdomen region but this decrease of the body fat wasn't accompanied with weight loss or reduction of BMI. Also Poirier et al; (1996) found that exercise training for six months in NIDDM didn't significantly changed body weight or BMI. In the current study this reduction of body weight and BMI in group (A) may be attributed to the walking training program was associated with some advises about diet control and weight reduction.

The results of this study showed a significant reduction in fasting blood glucose (FBG) level of group (A) after exercise program while a significant increased in FBG in group (B). This current positive response of FBG in NIDDM patients was supported with the most of the recent studies. These result were supported by Russell et al; (1999), they found that exercise training with moderate intensity lead to increase insulin sensitivity and so reduced blood sugar level and regular exercise improve glycemic control that leads to reduce hypertension and normalized lipid in type II D.M. Also Alsayd et al, (1999) found that moderate aerobic exercise training on treadmill for 6 weeks reduced FBG in type-II diabetic patients. Roger et al; (1988) found that after one week of aerobic exercise, The FBG had been improved via improvement of glucose tolerance test. Also result of Anna Chudyk et al 2011 supporeted our result who said that 645 articles retrieved, 34 met our inclusion criteria; most investigated aerobic exercise alone, and 10 reported combined exercise training. Aerobic alone or combined with resistance training (RT) significantly improved HbA_{1c} −0.6 and −0.67%, respectively (95% CI −0.98 to −0.27 and −0.93 to −0.40, respectively), systolic blood pressure (SBP) −6.08 and −3.59 mmHg, respectively (95% CI −10.79 to −1.36 and −6.93 to −0.24, respectively), and triglycerides −0.3 mmol/L (95% CI −0.48 to −0.11 and −0.57 to −0.02, respectively). Waist circumference was significantly improved −3.1 cm (95% CI −10.3 to −1.2) with combined aerobic and resistance exercise. they concluded that Aerobic exercise improves glycemic control, SBP, triglycerides, and waist circumference in diabetic patients. Hordern M D et al 2009 proved that resisted exercise training for 6 weeks significantly increased rate of glucose disposal and insulin sensitivity in sedentary NIDDM patients, they concluded that discrepancy of blood sugar response to exercise is most likely due to the difference in intensity, volume and duration of exercise. Similler result were founf by Landary and Allen (1992) who found that in diabetic patients after 6-12 weeks of an aerobic exercise, the FBG had been improved, and Schneider et al; (1990) found that after exercise training improve of glucose tolerance and reduce blood sugar level. Lampman et al; (1991) also concluded that after exercise training the FBG had been lowered. Beernbaum et al; (1989) found that after exercise training for 6-12 weeks on a stationary bicycle in Diabetes Mellitus type II the blood glucose level decreased and there was no relationship between the degree of autonomic neuropathy and level of blood glucose fall.

Improvement of FBG can be explained by several mechanisms as exercise training improve impairment of the muscular glucose transport protein system and the decreased of enzymatic activity, which regulate storage and oxidation of glucose in the skeletal muscle (Ebeling et al; 1995). Also exercise training increase the conversation of low oxidative type (II a) fibers that have a greater capillary density and high concentration of the muscle glucose transport system that make them exhibit a greater response to insulin action than type (II b) fibers (Ivy, 1997).

In this study The value of Q-T interval pre exercise was (448.88 ± 47.39666). and significantly reduced post exercise to (414.68 ± 45.37503).The reduction of Q-T interval was considered as improvement. R- R interval pre exercise was (487.60 ± 53.32448) and significantly increased post exercise to (599.12 ± 49.92438), The increment of R- R interval was considered as improvement. Mathur et al 2006 said that QTc prolongation in diabetic subjects stands favourably as an autonomic dysfunction parameter as compared to other autonomic neuropathy function test (ANF) tests. Further, QTc prolongation has linear positive correlation with the degree of CAN. It is inferred from the present observations that QTc prolongation in diabetics with an otherwise normal heart can be used as a diagnostic test for assessment of cardiac autonomic neuropathy and may even be considered as a cardiac autonomic function test with prognostic significance. These results were supported by Veglio et al; (2000) who assessed the relationship between QT interval prolongation and mortality in type 1 diabetic patients. Data on survival after 5 years were obtained from 316 of 379 patients (83.3%) who took part in a study on the prevalence of diabetic neuropathy and QT interval prolongation. They found that mortality at 5 years was 6.32%, patients who survived were significantly younger, had a shorter duration of diabetes, had lower systolic and diastolic blood pressure levels, and had a shorter QT interval corrected for the previous cardiac cycle length (QTc) than subjects who died. In univariate analysis, patients had a higher risk of dying if they had a prolonged QTc or if they were affected by autonomic neuropathy. QTc prolongation was the only variable that showed a significant mortality they concluded that the first cohort-based prospective study indicating that QTc prolongation is predictive of increased mortality in type 1 diabetic patients.

As regarding to Oka et al; (1996), Khan et al; (1987), Veglio et al; (2000) and Ewing et al; (1991), thier studies had been shown that aerobic exercise training at

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moderate intensity of 60–75 % of maximal HR leads to improve and decrease Q-Tc interval in diabetic patients with autonomic neuropathy, This may be due to improvement of sympathetic and parasympathetic nervous system.

Oka et al, (1996) had attempted to clarify the relationship of Q-T interval to alpha and beta sympathetic, as well as, parasympathetic function tests including spectral analysis of R-R interval and systolic blood pressure. Q-T interval in 76 diabetic patients and 76 ages matched healthy control whose R-R interval was comparable. They also investigated the relationship of Q-T interval to various clinical features of diabetes mellitus and to autonomic function tests, Q-T interval in diabetic patients was significantly greater than in healthy control, but were prolonged in patients with long duration of disease as compared with short duration one. There were a significant correlation between Q-T interval and postural hypotension, also between Q-T interval and both high and low frequency component of spectral analysis of R-R interval, whereas, no relation was observed with spectral analysis and systolic blood pressure. An abnormal Q-T interval is an indicator of cardiac sympathetic and parasympathetic nervous dysfunction, but not vasomotor dysfunction.

On the other hand, Laptev DN et al 2012 Studid effect of graded physical exercise on glycemia level and interval QT duration in children and adolescents with type 1 diabetes mellitus. they found that there were two periods of significant and prolonged lowering of glycemia: in 120-420 min and 19-21 hours after exercise. Lowering of glycemia after physical exercise was associated with prolongation of QT interval. Also Zravenboer et al, (1993) investigated the corrected QT interval as a test for diagnosing autonomic dysfunction in 60 type I diabetic patients with proven peripheral neuropathy, Significant increase in QTc interval was observed after dynamic exercise, however, no change in QTc was observed following static exercise, and hence we conclude that static exercises may not be useful in assessing the cardiovascular status of an individual or in predicting cardiovascular events. they concluded that the corrected QT interval should not be used for the diagnosis of the severity of diabetic autonomic neuropathy. The result of study of Suarez GA et al 2005 came in contradict with our result, they studied the relationship between cardiac autonomic neuropathy (CAN) and major cardiovascular events in 2 prospective studies. Specifically, the relationship between baseline CAN and the subsequent incidence of a fatal or nonfatal cardiovascular event, defined as an myocardial infarction MI, heart failure, resuscitation from ventricular tachycardia or fibrillation, angina, or need for coronary revascularization, was examined. The relative risks associated with CAN in these studies were 2.2 and 3.4, respectively, with the latter result just achieving statistical significance ($P<0.05$). There seems to be an association between CAN and major cardiovascular events, but given the small number of events that occurred in each of these studies, The significance of CAN as an independent cause of sudden death has, however, been questioned recently. They suggested that although CAN could be a contributing factor, it was not a significant independent cause of sudden death. Heart failure is, however, common in individuals with diabetes; it is identified in these patients by the presence of neuropathy, even in those without evidence of coronary artery disease or LV dysfunction. Several long-term studies have demonstrated a consistent beneficial effect of regular exercise training on carbohydrate metabolism and insulin sensitivity, which can be maintained for at least 5 years. These studies used exercise regimens at an intensity of 50–80% Vo_{2max} three to four times a week for 30–60 min a session. Improvements in HbA_{1c} were generally 10–20% of baseline and were most marked in patients with mild type 2 diabetes and in those who are likely to be the most insulin resistant. It remains true, unfortunately, that most of these studies suffer from inadequate randomization and controls, and are confounded by associated lifestyle changes. Data on the effects of resistance exercise are not available for type 2 diabetes although early results in normal individuals and patients with type 1 disease suggest a beneficial effect. It now appears that long-term programs of regular exercise are indeed feasible for patients with impaired glucose tolerance or uncomplicated type 2 diabetes with acceptable adherence rates. Those studies with the best adherence have used an initial period of supervision, followed by relatively informal home exercise programs with regular, frequent follow-up assessments. A number of such programs have demonstrated sustained relative improvements in Vo_{2max} over many years with little in the way of significant complications.

Takebayashi K et al 2002 concluded that QTc intervals showed a significant positive correlation with systolic and diastolic blood pressure although it did not correlate with serum lipid concentrations. QTc also tended to be long in obese diabetic subjects (body mass index > 25 and QTc intervals might also be affected by other factors such as arteriosclerotic macroangiopathy and obesity, and not only autonomic nerve function. Therefore it might be considered as an overall index for complications, and not for pure autonomic impairment.

In this study The mean value of systolic blood pressure before exercise (change position, sustained hand grip and valsalva Maneuver) were (139.36 ± 6.52482), (139.68 ± 6.10137) and (137.60± 6.45497) respectively which were significantly improved after exercise by decreasing to (change position, sustained hand grip and valsalva Maneuver) (134.80 ± 5.50757), (134.16 ± 5.91383) and (134.24± 5.84009) respectively.

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Agree with this result Roy et al; (1989) found that in diabetic patients who maximally exercised on bicycle, there was an increase in Systolic blood pressure SBP. Also Alsaydet al, (1999) found a significant decrease in SBP and DBP in type II D.M patients as a response to moderate aerobic exercise training on treadmill for 6 weeks. Also Russell et al; (1999) found that exercise training lead to reduce BP and that similar to finding of Schreider and Ruderman (1990). Also Lehmann et al; (1995) found that cycling exercise training program for three months in diabetic patients significantly reduce SBP and DBP and it was correlated significantly with the change in the physical activity and Lehmann et al; (1995) found that a highly significantly reduction in the SBP and DBP by exercise training to normal range particularly in those diabetic patients who prone to develop neuropathy. Hilsted et al; (1979) found that blood pressure response to exercise training didn't increase to expected level in diabetic autonomic neuropathy patients, and lowered mean SBP and DBP response to comparable relative exercise training in patient with autonomic neuropathy compared with diabetic patients without autonomic neuropathy. Harald E M et al 2012 said that Aerobic interval training is an effective method to lower blood pressure and improve other cardiovascular risk factors. Our result were supported by Jamie F. Burr 2012 who concluded that Aerobic exercise has significant and particular benefits for people with type 1 diabetes. It increases sensitivity to insulin, lowers blood pressure, improves cholesterol levels, and decreases body fat. patients with type 1 diabetes who are physically more active have a lower overall risk of cardiovascular events than their sedentary counterparts. Also Gail and Francis, (1984) concluded that physical exercise training altered the cardiovascular responses to exercise training as decreased heart rate and pressure load on myocardium. Also Gert-van-Dijket al (1994) confirmed that aerobic exercise training is currently promoted as life style modification that lowers the resting BP especially in persons with elevated BP, it was supported with that the dynamic exercise training reduces resting SBP and DBP by approximately 3%and 4 % respectively. On the other hand Campainge and Lampman, (1994) found that patients with type 2DM displayed a greater SBP in response to exercise training. Also Donckier et al; (1989) found that in cardiac autonomic neuropathy there was increasing of SBP in response to exercise training. Vinik et al; (1995) found that patients with cardiac autonomic neuropathy have severely exaggerated increase in SBP and DBP. Also Bottini et al; (1995) found that in diabetic autonomic neuropathic patients, SBP was significantly increased in response to exercise training. Pamella Karoline et al concluded that a single session of aerobic exercise resulted in 24 h BP reductions in individuals with T2D, also 2015 Radice et al; (1996) found that in diabetic autonomic neuropathic patients in response to exercise training there was no significant difference in blood pressure either at rest or at peak of exercise training between diabetic patients with autonomic neuropathy and diabetic patients without autonomic neuropathy and during exercise training diabetic patients showed lower values of SBP and DBP. Agreed with these results, Thomas H et al 2009 who said that both aerobic and resistance training have important roles in DM. Recent work comparing the individual and combined effects of aerobic and/or resistance training revealed that both forms of exercise were equally beneficial for glycemic control, although aerobic training had a greater effect on body composition (except with regard to increasing muscle cross-sectional area). Caution should be used when interpreting these results given double the volume of exercise performed in the combined training. It is recommended that patients with Type 2 Diabetes Mellitus (T2DM) perform both aerobic and resistance training. They concluded that Exercise training in patients with T2DM is feasible, well tolerated, and beneficial to improve cardiovascular risk. It is recommended that patients with T2DM accumulate a minimum of 150 minutes per week of at least moderate-intensity and/or 90 minutes per week of at least vigorous-intensity cardiorespiratory exercise.

The mean values of the heart rate responses to (change position, Deep breathing and valsalva Maneuver) were (98.36 ± 7.65876), (92.68 ± 6.47251) and (80.12 ± 4.04475) respectively, That were significantly decreased post exercise to (93.96 ±5.78417), (88.56 ± 5.61308) and (76.32 ± 4.75850) respectively This improvement of hemodynamic responses come in agreement of Alsayd et al, (1999) he found decreasing in resting HR after moderate aerobic exercise training on treadmill for 6 weeks in NIDDM patients. Also Kahn et al; (1986) found that during exercise training program of diabetic cardiac autonomic neuropathy patients there were lower resting HR, although cardiac autonomic neuropathy have higher resting HR. Wiese et al; (1990) studied heart rate variability (HRV) in diabetic patients with and without autonomic neuropathy in response to orthostatic load and found significant lower in HRV in diabetic patients with autonomic neuropathy. Also Clarie and David (1981) found that strengthening exercise training program for 6 months significantly decreased HR. Gail and Francis, (1984) reported that exercise training program was associated with cardiovascular impairment. This was supported with reducing the HR after the exercise training program. On the other hand, Oka et al; (1995) found that in diabetic with mild autonomic neuropathy the R-R of low frequency component wasn't different from those of healthy subject control or from patients without autonomic neuropathy and R-R of high frequency component was significantly smaller than that of healthy ones. Roy et al; (1989) found that in diabetic patients who maximally

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exercised on bicycle, there was an increase in HR and SBP, they concluded that increasing in resting work product and decrease cardiac output in response to exercise training program in diabetic patients due to decrease parasympathetic activity, While **Bottini et al; (1995)** found that diabetic autonomic neuropathy in response to exercise training program there was a significant increase in HR. Also **Irace et al; (1991)** found a significant increase in HR in response to exercise training program and higher in diabetic autonomic neuropathy than in diabetic without autonomic neuropathy. Also **Howorka et al; (1997)** concluded that in diabetic patients with mild or no autonomic neuropathy who regularly performed endurance exercise training program as stationary bicycle, there was increasing in HR, whereas in definite or severe autonomic neuropathy no effect on HR variability. **Radice et al; (1996)** they studied cardiovascular response to exercise training program in middle aged NIDDM patients with and without autonomic neuropathy, and found that diabetic autonomic neuropathy patients had significant slower recovery of HR and significant higher proportion of blunted increase of HR. **Koullam Parpa et al 2009** studied Effect of High Intensity Interval Training on Heart Rate Variability in Individuals with Type 2 Diabetes. The purpose of their study was to examine the effect of high intensity interval training (HIIT) on cardiovascular autonomic function as determined by HRV, in individuals with diabetes. Their Results demonstrated a statistically significant difference in HRV pre (HRV: 52.80 ± 8.5 ms) compared to post training (HRV: 62.60 ± 11.00 ms), t (13) = -7.46, p = 0.0001. In addition, systolic blood pressure (SBP), diastolic blood pressure (DBP), resting heart rate (RHR), fasting glucose values (FG) and body weight were significantly lower following 12 weeks of training. The beneficial effect on autonomic regulation as a result of exercise training may have clinical importance in preventing adverse cardiovascular events in individuals with diabetes.

Didangelos T et al 2006 said that Improvement in glycemic control reduces the incidence of CAN and slows the progression there of. Glycemic control with a reduction of HbA1c from 9.5 to 8.4 has also been shown to improve HRV with mild autonomic abnormalities; this was not so in cases of advanced autonomic abnormalities. The use of aldose reductase inhibitors such as sorbinil improved resting and maximum cardiac output, and improved MIBG uptake and HRV in patients with mild abnormalities but not in those with advanced CAN. **Vinik A ET AL 2003** concluded that a further decrease in exercise capacity and blood pressure BP is seen in patients with both vagal CAN and orthostatic hypotension. The severity of CAN correlates inversely with the increase in heart rate at any time during exercise and with the maximal increase in heart rate. Thus, CAN contributes to diminished exercise tolerance. Therefore, autonomic testing offers a useful tool to identify patients with potentially poor exercise performance and may help prevent hazards when patients are introduced to exercise training programs. Prolonged QTc causes premature action potentials during the late phases of depolarization. This increases the risk of developing ventricular arrhythmias or fatal ventricular fibrillations. Higher rates of prolonged QTc are seen in females, older patients, high systolic blood pressure or heart rate, and short stature **(Panoulas VF et al 2014).**

Pamella Karoline et al 2015 studed the effects of different intensities of aerobic exercise on 24-hour blood pressure (BP) responses in individuals with type 2 diabetes mellitus (T2D) and prehypertension. [Subjects and Methods] Ten individuals with T2D and prehypertension (55.8 ± 7.7 years old; blood glucose 133.0 ± 36.7 mg·dL^{-1} and awake BP 130.6 ± 1.6/ 80.5 ± 1.8 mmHg) completed three randomly assigned experiments: non-exercise control (CON) and exercise at moderate (MOD) and maximal (MAX) intensities. Heart rate (HR), BP, blood lactate concentrations ([Lac]), oxygen uptake (VO_2), and rate of perceived exertion (RPE) were measured at rest, during the experimental sessions, and during the 60 min recovery period. After this period, blood pressure was monitored for 24 h. thier results indicate that [Lac] (MAX: 6.7±2.0 vs. MOD: 3.8±1.2 mM), RPE (MAX: 19±1.3 vs. MOD: 11±2.3) and VO_2peak (MAX: 20.2±4.1 vs. MOD: 14.0±3.0 mL·kg^{-1}·min^{-1}) were highest following the MAX session. Compared with control group, only MAX elicited post-exercise BP reduction that lasted for 8 h after exercise and during sleep. They concluded that a single session of aerobic exercise resulted in 24 h BP reductions in individuals with T2D, especially while sleeping, and this reduction seems to be dependent on the intensity of the exercise performed.

Sarika Chaudhary et al 2010 evaluated the effects of aerobic and strength training on cardiac variables such as blood pressure, heart rate (HR), and metabolic parameters like cholesterol, high density lipoprotein (HDL), triglycerides and anthropometric parameters of obese women. Their findings of the study indicate statistically significant differences in recovery heart rate [Pre-exercise: 97.40± 5.378 (mean±standard deviation (SD)), post-exercise: 90.70±4.599, t=8.066, P<0.001] and in post-diastolic blood pressure [Pre-exercise: 85±3.265, post-exercise: 86.20±2.820, P<0.001] in aerobic training and in systolic blood pressure [Pre- and post-exercise] in both training groups (P<0.001). Significant differences were observed in very low-density lipoprotein [pre-exercise: 28.10±1.415, post-exercise: 26.86±0.760, t=5.378] and HDL [pre-exercise: 45.40±3.533, post-exercise: 53.60±3.134, t=6.318] levels in aerobic training group with P<0.001. BMI and body fat percentage showed significant improvements in both training groups they concluded that Aerobic training is more beneficial and

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can be used as a preventive measure in patients who are at risk of developing cardiovascular diseases due to obesity.

Sheri Colberg 2013 said that if cardiac autonomic neuropathy (CAN) is present, the heart rate response is abnormal at rest, when standing, and when during strain related to holding the breath (Valsalva maneuver). Blood pressure responses can be abnormal when changing positions or performing isometric exercise. Moreover, the potential for exercise-related dehydration is a concern, as is impaired thermoregulation during activities in environmental extremes, and extra fluids may need to be consumed to protect against both dehydration and hyperthermia. Care must be taken with all components of the exercise prescription. In addition to developing a safe exercise prescription and considering exercise precautions for those with autonomic neuropathy, attention must be given to factors that will assist patients in maintaining a regular physical activity program. Marrero and Size more have developed the Ease of Access Index and Ease of Performance Index to help patients determine how realistic their activity selections are **(Marrero DGet al 1996).**

Aaron I. Vinik et al 2003 concluded that, knowledge of early autonomic dysfunction can encourage patient and physician to improve metabolic control and to use therapies such as ACE inhibitors and β-blockers, proven to be effective for patients with CAN.

The insulin sensitivity, lipid profile, blood pressure, coagulation properties, body composition, and psychological well be improved in diabetic patients by aerobic exercixses **(Mayer et al; 1998).**

Scognamiglio et al; (1995) they investigated role of myocardial contractility recruitment in determining an abnormal left ventricular response to isometric and isotonic exercise in 14 diabetic patients with autonomic neuropathy (A.N), they studied left ventricular and myocardial functions at rest and during exercise by two-dimensional echocardiography, they excluded ischeamic heart diseases by the absence of left ventricular wall motion abnormalities induced by exercises and by coronary angiography, they found that there was an abnormal response of left ventricular ejection fraction to isometric and dynamic exercise in these patients.

Bottini et al; (1995) investigated cardiovascular and plasma catecholamine response during incremental exercise and recovery in diabetic patients with and without autonomic neuropathy, all the patients underwent a submaximal or symptom limited incremental exercise test using a cycle ergometer, air flow and respiratory gases fractions were sampled at the level of the mouth allowing a breath-by-breath analysis of oxygen consumption (VO_{2max}), the heart rate and systolic blood pressure were recorded and venous samples were obtained from the patients at rest and during each minutes of exercise and recovery to measure to measure epinephrine and nor-epinephrine plasma level, the heamodynamic parameters and plasma catecholamine were completed at rest and at 25, 50, 75 and 100 % of the peak of (VO_{2max}), they found that during exercise heart rate, systolic blood pressure, nor-epinephrine, and epinephrine increase was different among diabetic groups being significantly blunted in diabetic patients with autonomic neuropathy.

(Lampman, 1991) said that Physical activity has the potential to yield several health benefits for people with diabetes. These benefits can include improvements in glucose control

V. Conclusion

The result of this study support the importance of using exercise training program as general and especially walking training for IDDM with autonomic neuropathy.

The aerobic exercise training has a positive effect on blood glucose level, heart rate, blood pressure, R-R interval and Q-T interval in IDDM patients with autonomic neuropathy. So the exercise training generally should be recommended as a protective factor against the major risk factors.

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Salivary Dielectric Properties in Oral Cancer (OSCC) Through Time Domain Reflectometry at Microwave Region: The Future Alternative for Diagnosis and Treatment

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Abstract- *Objectives:* Oral cancer is one of the 11 most frequently occurring cancers worldwide and has a higher proportion of deaths per number of cases than breast cancer or cervical cancer because of late detection. In the present study we found out the difference in the dielectric properties of saliva between controls, controls with tobacco habit but having no lesion and patients with squamous cell carcinoma. The dielectric parameters have correlated with histopathological grades and clinical stages of oral squamous cell carcinoma.

Methods: Dielectric relaxation studies have been carried out for saliva of 88 (48 oral cancer and 40 healthy) patients having tobacco habit but no squamous cell carcinoma (SCC) and those having tobacco habit with SCC using picoseconds time domain reflectometry over the frequency range of 10 MHz to 20 GHz at room temperature.

Keywords: *conductivity, dielectric properties, oral squamous cell carcinoma, permittivity, saliva, relaxation time, time domain reflectometry.*

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A. A. Ranade [α], P. B. Undre [σ], S. R. Barpande [ρ], J. V. Tupkari [ω] & S. C. Mehrotra [¥]

Abstract- ***Objectives:*** Oral cancer is one of the 11 most frequently occurring cancers worldwide and has a higher proportion of deaths per number of cases than breast cancer or cervical cancer because of late detection. In the present study we found out the difference in the dielectric properties of saliva between controls, controls with tobacco habit but having no lesion and patients with squamous cell carcinoma. The dielectric parameters have correlated with histopathological grades and clinical stages of oral squamous cell carcinoma.

Methods: Dielectric relaxation studies have been carried out for saliva of 88 (48 oral cancer and 40 healthy) patients having tobacco habit but no squamous cell carcinoma (SCC) and those having tobacco habit with SCC using picoseconds time domain reflectometry over the frequency range of 10 MHz to 20 GHz at room temperature. The above two groups were compared with the control group. Dielectric parameters viz. permittivity (ε_0), relaxation time (τ) and conductivity (σ) have been obtained by fitting complex permittivity spectra to Debye equation. Statistical analysis was done by applying 't' test.

Results: The results show change in dielectric parameters with change in histopathological grades and clinical stage of the OSCC biopsy sample.

Conclusion: The microwave absorption of squamous cell carcinoma patients is more. So microwaves can be used for diagnosis as well as for therapy of oral squamous cell carcinoma. The salivary dielectric parameters can act as useful non-invasive diagnostic tools for cancer detection and determination of histopathological grades of malignancy.

Keywords: conductivity, dielectric properties, oral squamous cell carcinoma, permittivity, saliva, relaxation time, time domain reflectometry.

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I. Introduction

Oral cancer is one of the 11 most frequently occurring cancers worldwide and has a higher proportion of deaths per number of cases than breast cancer or cervical cancer because of late detection. In India, oral cancer is highly prevalent, comprising 35-40% of all malignancies, due to habit of tobacco chewing. Oral cancer refers to all malignancies arising from the lips, the oral cavity, and pharynx *(1)*, and it affects more than 481,000 new patients worldwide. The 90% of oral cancers are oral squamous cell carcinoma. This cancer, when found early, has an 80 to 90% survival rate. Despite this fact and the great treatment advances, the World Health Organization has reported oral cancer as having one of the highest mortality ratios amongst other malignancies with a death rate at five years from diagnosis at 45% *(2,3)*.This high morbidity rate can definitely be attributed to the late diagnosis of the disease *(4)*. At the moment, a lack in national screening programs together with a lack of definitive and satisfactory biological markers *(5-7)* for early oral cancer detection has resulted in late stage diagnosis of oral cancer *(8)*.The routine clinical practice to detect oral cancer is initially made by visual inspection, followed by biopsy of any suspicious lesions found. However, oral cancer can go unnoticed and therefore visual inspection is incapable of effectively screening or detecting cancerous changes in the oral cavity. Such delay in diagnosis may adversely affect patient prognosis. That is why most oral cancer patients present with advanced disease, have secondary tumours and suffer from other co-morbidities. On the other hand, biopsy is an invasive method and this approach increase the emotional trauma to the patient waiting for a diagnosis. New methods for reliable, low-cost, noninvasive, and real-time screening or detection of oral cancer are thus warranted. In recent times, 'light biopsy' with various optical methods, such as Fluorescence, *(9,10)* Raman *(11)* and Elastic Scattering (12) spectroscopy, have been investigated to establish techniques for the screening or detection of oral cancer. However, none of these techniques has been proved to

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be totally reliable in screening or detecting oral cancer and limitations still exist. For example, Fluorescence spectroscopy can be significantly hindered by the presence of tissue scattering and absorption and fail to account for confounding factors such as inflammatory changes that may produce fluorescence emission spectra, resulting in false-positive results. Raman spectroscopy shares the major limitation of other point-detection methods in that only a very small tissue volume is interrogated and it can be very sensitive to mucosal movement. Also, Raman spectroscopy technique is expensive, complex and difficult to adapt for in vivo use due to superimposed optical fiber and auto-fluorescence complicating the spectra. Elastic Scattering spectroscopy is insensitive and imaging is very difficult. Source and detector fibers need to be sufficiently separated for the diffusion approximation to be valid, i.e., >0.5 cm, but at this distance would be insensitive to the size and shape of scattering centers. The intention of this study was therefore to investigate a new approach, namely bioimpedance, for reliable, low-cost, noninvasive, and real-time screening or detection of oral cancer. Bioimpedance is the measurement of the bioimpedance signal, which is obtained by injecting low-level sinusoidal current in the tissue and measuring the voltage drop generated by the tissue impedance. Bioimpedance signal gives information about electrochemical processes in the tissue and can hence be used for characterizing the tissue or for monitoring physiological changes. The electrical properties of tissue vary with the frequency of the applied electric field as seen from α, β and γ–dispersion *(13)*. The α dispersion occurs at low frequencies (10 Hz to 10 kHz) and is mainly affected by the ionic environment that surrounds the cells. The β dispersion (10 kHz to 10MHz) is a structure relaxation. At higher frequencies, the γ–dispersion is found related to water molecules. The α– and β–dispersion regions are more interesting in medical applications, since most changes between pathological and normal tissue occur in this range *(14)*. The present study was carried out in the microwave frequency range from 10 MHz-20 GHz. The electrical properties of saliva were measured at α– and β–dispersion regions.

An increasing number of systemic diseases and conditions, amongst them oral cancer, have been shown to be reflected diagnostically in saliva. Moreover, using saliva as a diagnostic fluid meets the demands for inexpensive, noninvasive, and accessible diagnostic methodology. Whole saliva is the product of the secretions of the 3 major salivary glands (parotid, submandibular, sublingual) and the numerous minor salivary glands mixed with crevicular fluid, bronchial and nasal secretions, blood constituents from wounds or bleeding gum, bacteria, viruses, fungi, exfoliated epithelial cells and food debris *(15,16)*. Saliva has been long proposed and used as a diagnostic medium *(17-19)* because it is easily accessible and its collection is non-invasive, not time-consuming, inexpensive, requires minimal training and can be used for the mass screening of large population samples *(19,20)*. Whole saliva can be collected with or without stimulation. Stimulation can be performed with masticatory movements or by gustatory stimulation (citric acid) *(21)*. Stimulated saliva however, it can be collected in larger quantities, is a little bit altered in content *(22)*. Unstimulated saliva can be collected by merely spitting in a test tube or by leaving saliva drool from the lower lip *(23)* and it is more often used for the diagnosis or follow up of systemic diseases. Saliva has long been used for the monitoring of drug abuse (drugs and addictive substances) such as cocaine, heroin, amphetamine, barbiturates etc. *(24)*. Moreover salivary testing has largely performed for the diagnosis of HIV infection *(25, 26)*. Analysis of salivary parameters such as salivary flow rate, pH, buffer capacity, lactobacillus, and yeast content, presence of IgG, IgM and anti-La auto antibodies and raised protein levels such as that of lactoferrin and cystatin C as has been proposed for the diagnosis of Sjogren's syndrome *(27, 28)*. Concerning cancer diagnostics and follow up altered levels of certain mRNA molecules *(29)* have been detected in saliva in oral cancer patients and of certain proteins in several cancers *(30, 31)*.

In the mouth, the surface layer of cells is replaced about every 2–4 hours; and the turnover time of the oral epithelium is about 4.5 days. If a person is developing an oral cancer, cancer cells can be shed into saliva at very early stage of the cancer; and the number of cancer cells in saliva can be a measure of the cancer stage. Mauk et al., reported that more than 1000 cells/ml and 9000 cells/ml of OSCC cells were separated from tumor stage 1 and 4 patient saliva, respectively *(32)*. This makes saliva an ideal sample for early screening and detection of oral cancers. The impedance-based method has the potential to be a sensitive non-invasive screening method for detecting early stage cancer by detecting cancer cells in saliva, and an approach to obtain quantitative information about cancer stage or to monitor the progress of cancer treatment.

According to the polar and non-polar types of dielectric materials, salivary molecular system can be said to be a polar dielectric system. Saliva acts as a suspension of protein molecules are frequency dependent. Thus, protein relaxation is interpreted in terms of molecular dipole moment and/or in terms of surface conductance. In order to discuss the dielectric properties of biological cell suspensions and thus in turn those of tissue at ultra-high frequencies, we need to have knowledge of dielectric properties of water (which is present upto 99% in saliva). Dispersion of water is of polar origin. Thus, the objective of the present study is undertaken to find out the difference in the dielectric

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properties (parameters) of saliva between controls, controls with tobacco habit but having no lesion and patients with squamous cell carcinoma. It is also undertaken to throw light on the correlation between these dielectric parameters and histopathological grades and clinical stages of oral squamous cell carcinoma and to prepare a database of the bioimpedence measurements in terms of microwave absorption for the use in local hyperthermia treatment and imaging of cancers of soft tissues *(33, 34)*.

II. Materials and Method

Of the patients visiting the outpatient department of Government Dental College and Hospital, Aurangabad, subjects with oral lesions suspicious of malignancy were selected as a study group. Relevant history of each patient was recorded thoroughly. Only those patients who were subsequently diagnosed histopathologically, to have oral squamous cell carcinoma (and verrucous carcinoma) and who had not received any therapy prior to study were included in the oral squamous cell carcinoma (OSCC) group, and the remaining was excluded. The control group mucosal specimens were harvested after informed consent from individuals, who were admitted for incidental elective surgery. These biopsies were all harvested from clinically normal mucosal sites. The mucosal specimens from the control group were taken from an age and sex matched group with unremarkable oral health and no obvious systemic disease.

Accordingly, the subjects for the study were grouped as follows:

Group I (Control): This control group was divided into two subgroups i.e. I (a) and I(b). First group considered of controls (C) i.e. 20 healthy age and sex matched subjects free from any other systemic disease and tobacco related habits. I(b) subgroup consisted of controls (CT) i.e. 20 age, sex and tobacco habit matched subjects (with SCC group) but having no lesion.

Group II (OSCC): 48 (age, sex and habit matched) patients having oral squamous cell carcinoma and verrucous carcinoma. These 48 patients were diagnosed after taking biopsy and were clinically staged as well as histopathological graded. Clinical staging of the patients with OSCC was done using the TNM classification as given by the American Joint Committee for cancer staging and End result reporting (AJCCS) *(35)*. The histopathological grading of OSCC was done according to malignancy grading system proposed by Anneroth et al *(36)*.

A total number of 48 cases of OSCC and verrucous carcinoma cases were screened and all consented to biopsy. Punch biopsies were taken from the representative sites after achieving anesthesia by 2% lignocaine with 1: 80.000 adrenaline.

a) *Procedure for collection of resting (unstimulated) whole (mixed) saliva*

Patient was asked to remain empty stomach or NBM in the morning and also asked to thoroughly brush his teeth without paste and clean his/her mouth. Saliva was allowed to accumulate in the patient's mouth for 5 min and then they were to spit in 30 ml borosil glass air sealed bottles. Then the saliva was poured in centrifuging tubes and immediately centrifuged by using Remi-DGL-721 centrifuging machine at 1000 rpm for 10 minutes.

b) *Experimental Procedure for Analysis of Dielectric Parameters*

Dielectric property measurements were performed immediately after the collecting the saliva. The elapsed time from excision to measurement was between 15-20 minutes. The Time domain reflectometery technique in reflection mode as developed at Dr. Babasaheb Ambedkar Marathwada University has been used for the measurement of dielectric parameters. All details are already described elsewhere *(37, 38)*. The sample cell of digitizing oscilloscope was cleaned with acetone and dried with tissue paper rolls. Then empty cell reading of air i.e. Ra(t) was taken for 30 seconds by keeping the temperature bath on the cell and maintaining the temperature at 35°C to 37°C in order to simulate oral temperature conditions. Then, the filled cell reading i.e. Rx(t) was taken for 30 seconds. For each Saliva sample two readings were taken. Frequency range used during the measurements was 10 MHz to 20 GHz. Procedure was repeated for all saliva samples of control and OSCC groups and the waveform data stored in the oscilloscope memory was transferred to 1.44 MB floppy. The data was analyzed by Fourier transformation method and values of dielectric parameters i.e. dielectric permittivity (ε_0), relaxation time (τ) and conductivity (σ) were obtained and compared with the histopathological grades and clinical stages of the malignancy.

III. Results and Discussions

Oral squamous cell carcinoma (OSCC) comprises 90-95% of all oral malignancies. The five-year survival rate is 80% when diagnosed in early stages, 40% when involvement of regional lymphnodes is present, and less than 20% in case of metastasis. Thus early detection of OSCC not only increases the survival rate but also improves the quality of life by reducing the need for aggressive and disfiguring treatments. Unfortunately, early detection of oral cancerous lesions has proved difficult, because as many as 50% of patients have regional or distant metastasis at the time of diagnosis. The rather high proportion of late diagnosis of OSCC is a clear cause of concern, especially when OSCCs arise over the epithelial surface giving rise to clearly visible changes on the surface.

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Histological and biochemical changes always precede visible signs. The cellular changes in malignancy are also reflected in their electrical properties like permittivity, conductivity and relaxation time. The dielectric properties of biological samples are determined by several important dispersion phenomena whose contributions are normally confined to specific bands in the electromagnetic (EM) spectrum *(13, 14, 34, 39-41)*. The behavior of biological tissues, cell suspensions and saliva at radio frequencies and microwave frequencies is largely determined by the electro-chemical behavior of cells and its cellular structure as well as the intra-cellular fluid in which the cells are suspended and the internal cellular elements, including the nucleus. The cell membrane exhibits capacitance and supports a potential difference across it such that at low frequencies current flows around the cells but at higher frequencies current flow may penetrate the cells.

Moderate variations in the permittivity and conductivity values are reflected by various types of normal tissue, saliva etc. In contrast to these rather homogenous observations, malignant tissues demonstrate substantially increased permittivity and conductivity. These differences are probably attributable to:

1) The physico-chemical bulk properties i.e. properties of body fluids like saliva and tissues which include temperature, electrolyte, protein concentration and pH.
2) Microstructural properties i.e. the geometry of microscopic components.
3) The amount of extracellular fluid.
4) Membrane properties and packing density.
5) Orientation of malignant cells.
6) Changes in the water content-tumour tissues have significantly higher water content than homologous normal tissues. Associated with these differences, one expects that at UHF (ultra high frequency) and microwave frequencies, neo plastic tissues will exhibit somewhat higher permittivity and conductivity values than homologous normal tissues.
7) The rate of necrosis.

At audio and radio frequencies substantial differences are expected between normal and neoplastic tissues, in particular those associated with necrosis in tumour nodules. Schwan et al has described basically three frequency bands within which the permittivity of many biological tissues showed a characteristic decrease with the increase in frequency respectively *(34)*. The γ dispersion was observed at high frequencies and was mainly due to rotation of permanent dipoles of water molecules. The conductivity also exhibited frequency dependence. The β-dispersion was observed at medium frequencies. The present study was carried out in the microwave frequency range from 10MHz-20GHz. In case of solutions or suspensions the β-dispersion was due to rotational relaxation of permanent dipoles. But in case of biological tissues, cell suspensions and saliva etc. the β-dispersion was mainly caused by the Maxwell-Wagner type of relaxation which occurred in any microscopically inhomogeneous medium due to interfacial polarization and dipole relaxation *(42)*. The α-dispersion reflects the relaxation of nonpermanent dipoles which are induced by the displacement of small ions along the charged surface of large molecules or cell membranes. In this study the electrical properties of saliva were measured at α– and β–dispersion regions.

Permittivity depends on polarization which in turn depends on effective dipole moments per unit volume. If polarization increases, then the effective dipole moments per unit volume also increases. Water molecules have high dipole moments. Increased permittivity values thus indicate that the status of water molecules in a given system is changed. Since 99% of saliva is water and the other 1% is composed of organic and inorganic molecules, so the permittivity of the group C, CT and OSCC did not differ much.

Conductivity indicates the presence of mobile ions in the biological system. Thus, if ions increase, then electrical conductivity also increases. If conductivity increases, then microwave absorption is more. Schepps JL, et al showed that conductivity was a more reliable parameter to predict microwave absorption as compared to permittivity *(43)*.

In biological systems electrical currents are carried by both ionic conduction and electron semiconduction. Therefore, the electrical properties of biological systems are dependent on all the physical mechanisms which control the mobility and availability of the relevant ions such as sodium, chloride, potassium, magnesium and calcium *(44-47)*.

Relaxation time depends on the surrounding environment of water molecules. If the relaxation time increases then it means that the surrounding macromolecules are influencing water molecules in such a way that water molecules rotate slower. From the nature of strong forces between the bound water and its neighboring macromolecules it is expected that the relaxation time should be longer than that of free water *(48, 49)*.

In the present study the values of salivary permittivity, relaxation time and conductivity compared among the control group (C), control subjects having tobacco habit but no lesion (CT) group and patients of squamous cell carcinoma (SCC) group. The evaluated values of permittivity, relaxation time and conductivity are represented in Figure 1(a), 1(b) and 1(c), respectively.

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Comparison of the values of permittivity, conductivity and relaxation time according to the group showed in Table 1. It is observed that the mean values of conductivity and relaxation time were higher in the OSCC group compared to the control group, while the mean permittivity was more in the control group compared to the OSCC group.The statistical evaluation of the comparisons was done using 't'test. This test was applied to two groups at a time. From the statistical analysisit is observed that the difference between the values of C and SCC groups for conductivity is statistically highly significant ($p < 0.01$) and that for relaxation time is statistically significant ($p < 0.05$). In case of conductivity parameters the difference of values between CT and SCC group is also found to be statistically highly significant ($p < 0.01$), but the difference of values between C and CT groups is not significant ($p > 0.05$). In case of relaxation time the difference of values between C and CT groups is found to be statistically highly significant ($p < 0.01$), but the difference of values between CT and SCC groups is not significant ($p > 0.05$). In case of permittivity parameter the difference of values between C and CT, C and SCC and CT and SCC groups are not found to be statistically significant ($p > 0.05$).

The values of conductivity, relaxation time and permittivity within the SCC group were correlated with the histopathological grading and clinical staging. These values were also compared within different grades and stages. In the sample of 48 patients having squamous cell carcinoma only two grades were found (grade I and grade II). In which 9 cases belonged to grade I and 30 cases belonged to grade II.

The differences between the mean values of conductivity, relaxation time and permittivity of different histopathological grades were calculated and statistical evaluation was done using t'testare recorded in Table 2. It is observed that the mean permittivity and conductivity values of OSCC increased from grade I to grade II, but the mean relaxation time decreased from grade I to grade II.The difference between the mean conductivity values of grade I and grade II diseases is found to be statistically highly significant ($p < 0.01$) and that between the mean permittivity is found to be statistically significant ($p < 0.05$). The difference between the mean relaxation time values of grade I and grade II diseases is found to be statistically highly significant ($p < 0.001$).

In the sample size of 48 squamous cell carcinoma patients, 5 cases belonged to stage I, 6 cases belonged to stage II, 29 cases belonged to stage III and 8 cases belonged to stage IV.Comparison of the values of permittivity, conductivity and relaxation time according to the clinical stages in OSCC group showed in Table 3. The statistical evaluation was done using unpaired 't'test.From this table it is found that the mean value of permittivity of stage I is lowest than stage II, III and IV. The value of stage II is higher than stage IV but lower than stage III. The mean values of conductivity of stage II, III and IV are greater than those of stage I. The value of stage III is lower than that of stage II and greater than stage IV.The mean value of relaxation time of stage IV was higher than stage II, but lower than stage III. While the mean value of relaxation time of stage I is greatest than Stage II, III and IV.

In case of mean conductivity values the difference between stage I and stage II disease is also highly significant ($p < 0.01$). The differences between stage I and stage II is also significant ($p < 0.01$), but that between stage I and stage IV is not significant ($p > 0.05$). In case of mean relaxation time difference between the values of stage I and stage II, stage I and stage III and stage I and stage IV diseases are all statistically highly significant ($p < 0.001$). In case of mean permittivity, the differences between values of stage I and stage II, stage I and stage III and stage I and stage IV diseases are all statistically highly significant ($p < 0.001$). Thus, the mean conductivity and permittivity values show an increasing trend with increase in clinical stages whereas the mean relaxation time values show a decreasing trend for the same. The results were analyzed as follows: [Figure 1(a), 1(b) and 1(c)].

In the present study the mean values of conductivity(S/m) were significantly increased in oral squamous cell carcinoma (0.2527 ± 0.0850) as compared to the C (0.1939 ± 0.0436) and CT (0.1684 ± 0.0581). The difference between the mean conductivity values of C and CT groups was not found to be statistically significant. The mean values permittivity showed to statistically significant differences between C (74.54 ± 3.1133) and CT (77.099 ± 5.9407), CT and OSCC (74.81 ± 16.1001) and C and OSCC groups. These findings were similar to those of the earlier workers, who reported that the values of permittivity and conductivity were more in cancerous tissues as compared to normal tissues *(43, 50-52)*.

The mean relaxation time values were significantly increased in OSCC group (12.9079 ± 4.6749) as compared to the control (C) group (11.2980 ± 1.0090). The mean relaxation time values were significantly increased in the control (CT) group as compared to control (C) group i.e. 12.3870 ± 0.6706 in CT group vs 11.2980 ± 1.0090 in C group. The difference between the mean relaxation time values of CT and OSCC groups was not found to be statistically significant.

The values of the dielectric parameters, in the present study were correlated with the different clinical stages and histopathological grades of OSCC. The mean values conductivity and permittivity increased and relaxation time values decreased from grade I to grade II malignancy respectively and the differences between the two were statistically significant. Thus the values of dielectric parameters correlated well with the histopathological grades of OSCC and the difference

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was found to be statistically significant. The available literature did not reveal any study in which correlation between dielectric parameters and histopathological grades was done. Hence comparison with reported literature was not possible. The correlation of histopathological grades of OSCC with the dielectric parameters, however, cannot be ignored, because histopathology depicts the actual cellular picture of the disease process.

The mean conductivity and permittivity values increased and relaxation time values decreased from stage I to stage II, stage I to stage III and stage I to stage IV. The differences between the mean values of the above stages were statistically significant except that of stage I and stage IV conductivity values. The differences between the mean values of all three dielectric parameters for stage II and III, stage III and IV and stages II and IV however, were not statistically significant. Diagnostic accuracy of clinical staging depends on the use of advanced diagnostic aids.

In the present study higher values of permittivity and conductivity were observed in the OSCC group as compared to those of the control group. As stated previously, increase in conductivity causes an increase in microwave absorption *(43, 52)*. The microwave absorption of cancer cells is greater than that of normal cells. Thus, from the present study it could be inferred that the differences in microwave absorption of normal and cancer saliva can help us to develop techniques for diagnosis oral cancer.

IV. Conclusions

Salivary Dielectric Properties in Oral Cancer (OSCC) Through Time Domain Reflectometry at Microwave Region have been reported. The present study shows that the salivary conductivity of squamous cell carcinoma patients is more than that of the normal subjects. Hence, the microwave absorption of squamous cell carcinoma patients is more. So microwaves can be used for diagnosis (imaging and detection) as well as for therapy (hyperthermia treatment) of oral squamous cell carcinoma. Also salivary dielectric parameters can act as useful non-invasive diagnostic tools for cancer detection and determination of histopathological grades of malignancy. Further, salivary relaxation time can be useful as an indicator of the possible occurrence of oral squamous cell carcinoma in subjects having tobacco habit. The present study also shows that the clinical stages and dielectric values have to be carried out to determine the dose of microwave radiation according to clinical stages of malignancy.

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Table 1 : Values of permittivity, conductivity and relaxation time for the control (C) group, control subjects having tobacco habit but no lesion (CT) group and patients of oral squamous cell carcinoma (OSCC) group.

	Permittivity			Conductivity (S/m)			Relaxation time (ps)		
	C	CT	OSCC	C	CT	OSCC	C	CT	OSCC
Min.	65.05	52.42	11.87	0.1414	0.0514	0.1173	8.77	11.08	6.86
Max.	77.98	79.86	90.36	0.2928	0.2781	0.5064	12.7	13.59	38.74
N	20	20	48	20	20	48	20	20	48
Mean	74.54	77.099	74.81	0.1939	0.1684	0.2527	11.30	12.39	12.91
S.D.	±3.1133	±5.9407	±16.1001	±0.0436	±0.0581	±0.0850	±1.009	±0.6706	±4.6760

Table 2 : Values of permittivity, conductivity and relaxation time for different histopathological grades of oral squamous cell carcinoma (OSCC).

	Permittivity		Conductivity (S/m)		Relaxation time (ps)	
	Grade I	Grade II	Grade I	Grade II	Grade I	Grade II
Min.	11.70	11.87	0.1175	0.1172	10.22	6.86
Max.	82.22	82.12	0.5064	0.4881	38.74	21.32
N	9	39	9	39	9	39
Mean	67.62	70.71	0.2345	0.2569	16.50	12.07
S.D.	±25.2678	±13.5778	±0.1152	±0.0777	±8.000	±2.5806

Table 3 : Values of permittivity, conductivity and relaxation time for different clinical stages of oral squamous cell carcinoma (OSCC) group.

	Permittivity				Conductivity (S/m)				Relaxation time (ps)			
	Stage I	Stage II	Stage III	Stage IV	Stage I	Stage II	Stage III	Stage IV	Stage I	Stage II	Stage III	Stage IV
Min.	11.87	69.89	50.40	26.93	0.1799	0.1768	0.1172	0.1799	9.99	8.43	8.92	6.86
Max.	75.70	75.57	90.36	82.22	0.2909	0.3654	0.5064	0.3255	21.32	12.46	38.74	15.54
N	5	6	29	8	5	6	29	8	5	6	29	8
Mean	47.76	73.14	73.35	70.18	0.2333	0.2644	0.2567	0.2412	16.20	10.66	13.04	12.02
S.D.	±32.90	±2.345	±9.6963	±18.27	±0.0557	±0.0800	±0.0987	±0.0502	±4.9767	±1.6827	±5.2227	2.9098

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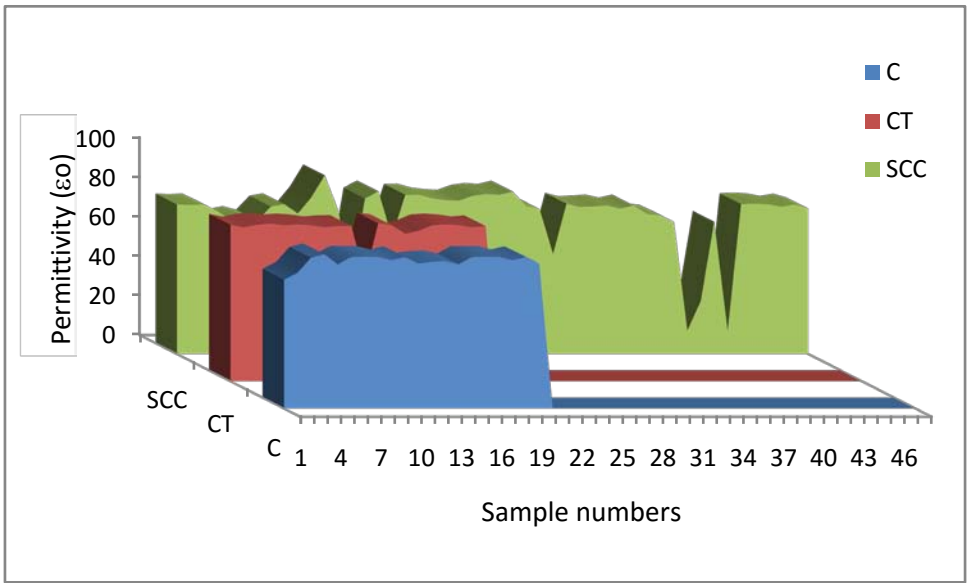


Figure 1 (a) : The evaluated values of permittivity for the control (C) group, control subjects having tobacco habit but no lesion (CT) group and patients of oral squamous cell carcinoma (OSCC) group.

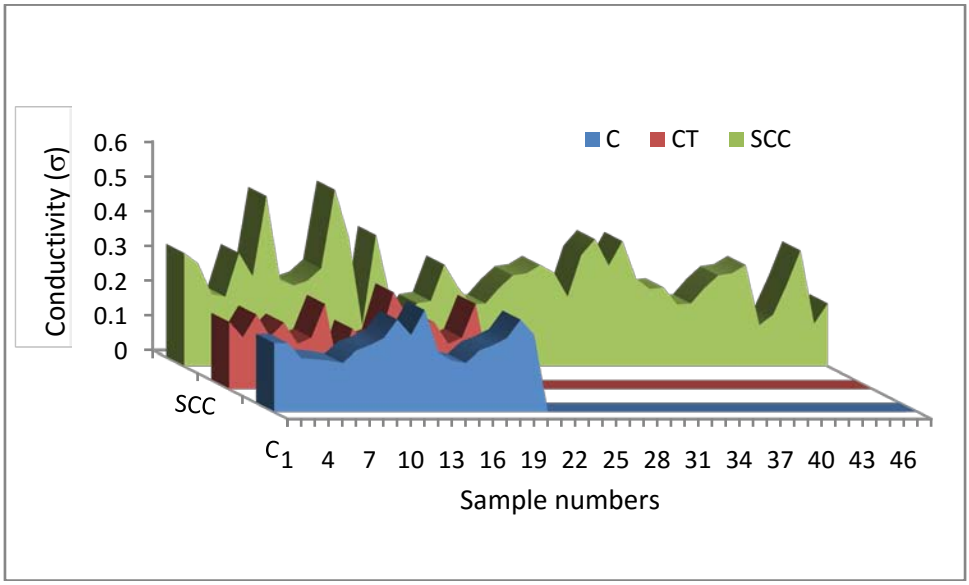


Figure 1 (b) : The evaluated values of conductivity for the control (C) group, control subjects having tobacco habit but no lesion (CT) group and patients of oral squamous cell carcinoma (OSCC) group.

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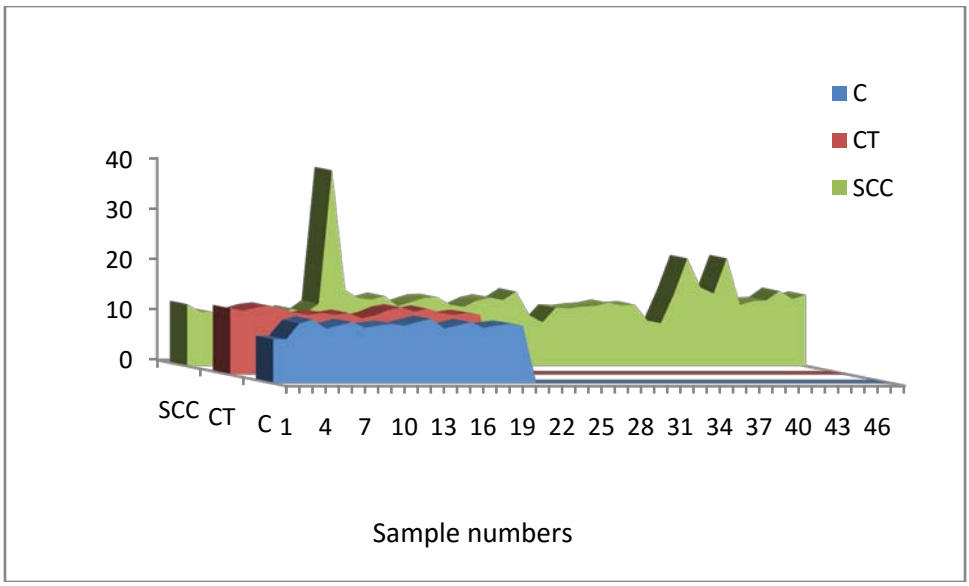


Figure 1 (c) : The evaluated values of relaxation time for the control (C) group, control subjects having tobacco habit but no lesion (CT) group and patients of oral squamous cell carcinoma (OSCC) group.

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A Flask Paraplegic Reveals a Sero Positive to HIV

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Summary- Flask paraplegic during the infection by the virus of human immunodeficiency (HIV) are very strong and with multiple etiology. The author report a case of flask paraplegic which was the circumstance to discover HIV sero positive with a patient.

The aim was to illustrate the difficulties of etiology diagnostic despite the realization of tom densitometry and of medullar IRM. It was a young lady with had 27 years of age who had been admitted for chronic cough, flask paraplegic and a retention of urine. The analysis during her admission notified a flask paraplegic, some sphincterien troubles, without sensibility troubles. There was no signal neither of Babinski nor amyotrophic. The examination of respiratory organ notified a syndrome of pulmonary bilateral condensation. The CT Scan of sacred lamb rachis focused on some discal protrusions of lamb sacred, and the IRM showed an aspect of inflammatory myelite. The pulmonary radio showed interstitial pneumopathy with a right scissurite. The research of some BAAR became negative. The retroviral became HIV positive and the quantity of lymphocytes TCD4 at 118 cellular/ mm3 with a viral charge of 74 782 copies/ ml. The diagnostic of myelite caused by HIV combined to pneumopathy was retained.

Keywords: *flask paraplegic, chronic cough, HIV/aids.*

GJMR-F Classification : *NLMC Code: WC 140*



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The neurologic manifestation like flask paraplegic could be the revelation of HIV infection. Their presence justifies the practice of HIV serology.

Keywords: flask paraplegic, chronic cough, HIV/aids.

I. Introduction

The nervous system is often a target organ affected during the HIV infection. This contact can be caused either by an opportunist infection, or by a pathology or of HIV neurotropism itself. In Africa, and in west countries, the contact of neurologic infection by HIV are frequent (37%). They occupied the third position of affection during this virose, after the digestive manifestations and of the body (1,5). If some get in touch with the secondary affection at immune depression, others correspond to direct contact of nervous system by HIV (2, 3, 4). We report a case of myelite combined with HIV as an aim to remind the gravity of this neurologic infection during Aids.

II. Observation

Female patient of 27 years having before zona intercostals, was admitted for chronic cough urine retention and absolute impotence function of inferior members. The beginning of the illness could be up to about two weeks through the appearance of productive cough which brought her to consultation where treatment was given without success. It is at the appearance of a urine retention and of an impotence function of inferior members at brutal occurrence that she has been referred to Yalgado Ouédraogo hospital for a better caring.

The examination at her admission notified a general conserved state, conjunctives well anicterique colored, a temperature of 39°5, without neither hydratation, nor nutritious, nor linens. The examination of nervous system gave a clear conscious, a flask paraplegic with 0/5, with abolition of osteoarticulary reflexes, without neither sensibility troubles nor Babinski.

The analysis of pulmonary organ gave a syndrome of bilateral pulmonary condensation. The pulmonary radiography notified a bilateral pneumopathy with right scissurite.

The research of BAAR in spits was in fructuous. It was the same in the case of cryptocoque research and of some others bacteria in LCR. The CT Scan of lamb rachis sacred aimed some discal protrusions of lamb sacred vertebras L3-L4 ; L4-L5 ; L5-S1 (cf diagram 2) and IRM of 27th august 2015 showed the inflammatory myelite aspect (cf diagram 1).

The HIV serology became positive to HIV1 and the rate of lymphocyte TCD4 was = 118 cell/mm^3 on 31/07/2015 with viral charges of 74782 copies /ml. Under the treatment of antiretroviral and anti biotherapy the process was favorable but it persisted the flask paraplegic despite the reduction sessions. She was discharged from hospital on 01/09/2015

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Diagram1: Picture of lamb rachis sacred at IRM



Diagram 2 : Picture of CT scan o lamb rachis sacred

III. Commentary

The acute myelite is rare during the HIV infection contrary to the chronic form. It often manifestes by a through paraplegic. The most paraplegic are combined to HIV infection. Only 7 to 10% of spastic paraplegic are only combined to HTLV-1 (5, 6). The myelite can be isolated or associated at HIV encephalopathy. It can be associated Herpes Simplex virus and varicelle Zona virus. It often occurred on the case of immune depressed like in the neurological complication of patients living with HIV (PvHIV). The opportunist infections most frequently incriminate are infections with cytogalovirus (CMV), herpes, tuberculosis, toxoplasmose.

IV. Conclusion

The neurological manifestations of HIV/AIDS are varied often strong ant more specific. If some of them are of easy diagnostic, others can required an unavailable sophisticated diagnostic under the tropic. They can the revelation of HIV infection. We have to practice the HIV serology before any neurological as paraplegic.

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A Tiny Incredible Urethral Carcinoma: Dimension may be Deceptive- A Case Report

By Sujata Sarangi, Sanghamitra Mukherjee, Manisha Mahata, Gopinath Barui & Tushar Kanti Das

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Abstract- Primary urethral carcinoma is a very rare urinary tract cancer with very few reported cases all over the world. Owing to limited trials and research work due to the rarity there is no standardization of the treatment protocol. We report a case of a 60 yrs female presenting with hematuria who underwent surgical resection of urethra and was diagnosed to be a case of Primary Urethral adenocarcinoma.

Keywords: *urethra, adenocarcinoma, primary.*

GJMR-F Classification : *NLMC Code: WP 460*



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A Tiny Incredible Urethral Carcinoma: Dimension may be Deceptive-A Case Report

Sujata Sarangi [α], Sanghamitra Mukherjee [σ], Manisha Mahata [ρ], Gopinath Barui [ω] & Tushar Kanti Das [¥]

Abstract- **Primary urethral carcinoma is a very rare urinary tract cancer with very few reported cases all over the world. Owing to limited trials and research work due to the rarity there is no standardization of the treatment protocol. We report a case of a 60 yrs female presenting with hematuria who underwent surgical resection of urethra and was diagnosed to be a case of Primary Urethral adenocarcinoma.**

Keywords: urethra, adenocarcinoma, primary.

I. Introduction

Primary urethral cancer is an extremely rare lesion comprising less than 1% of the total incidence of all genitourinary malignancies. [1]The age of presentation is generally above 75years and a female predominance[2,3] has been reported with urethral carcinoma taking up only 0.02% of all female cancers. [4] It presents most commonly with hematuria, infections and urethral diverticulum. Location of tumor origin, as well as histology, can affect management and prognosis. The rarity of the disease prevents prospective studies in order to determine the best treatment outcomes.

II. Case Report

A 60 year old female presented to the surgery outdoor with complaints of frank bleeding per urethra for 5 days. The patient did not have any burning sensation while micturition, no lower abdomen pain and was a febrile at the time of examination. Apart from the hematuria patient was otherwise stable, had no other significant past history of disease apart from being hypertensive for 10 years.

Routine work up of the patient showed the blood parameters to be normal. Urine examination under microscope showed plenty of RBCs. The urine culture report was insignificant. Straight X-ray and trans-abdominal ultrasonography did not reveal the presence of any stone or any obvious abnormality in the urinary tract.

Plain MRI of Pelvis revealed a small ill-defined, altered signal intensity area involving the anterior urethra at the level of the vaginal vault with maintained fat planes with adjacent structures.(Fig 1)

Biopsy was taken from this part of the urethra and on histopathological examination, it was proved to be urethral adenocarcinoma, enteric type (Fig 2, Fig 3). The patient underwent surgical resection of the urethra and the specimen was sent for histopathological examination along with the proximal urethral margin.

Gross examination of the specimen showed a single grayish white tubular structure measuring 2.5x1.0x1.0 cm. The proximal urethral margin was sent separately in two pieces altogether measuring 1x0.8x0.5 cm. Whole of the sent tissue was processed.

Microscopic examination revealed histological structure of urethra lined by squamous epithelium with focal areas of ulceration and partly by transitional epithelium along with dense chronic infiltrate in submucosa and muscle. No residual tumour tissue was seen. The proximal margin was unremarkable.

Patient is under close follow up.

III. Discussion

Primary urethral cancer is an extremely rare and aggressive condition with less than 2000 reported cases. [5]The overall incidence is less than 1% of the total incidences of malignancies [5] and 0.02% of the female malignancies [6]. This carcinoma has female predominance. [7]The origin of this carcinoma is debatable. It may be from Mullerian duct, urethritis glandularis, Skene's glands or mixed origin. Because of the limited knowledge, it is often difficult to manage this malignancy. There is difference in anatomy of urethra of male and female hence it leads to individualized approach for each patient. The etiology of urethral adenocarcinoma mainly includes irritative stimuli like urinary tract infection or diverticula which leads to epithelial metaplasia, dysplasia and finally carcinoma. [8] The symptoms vary but it presents most commonly with bleeding followed by other presentations like irritative voiding, dyspareunia, an extra urethral mass, pelvic pain and complaints of obstruction or incontinence in advanced cases. A detailed history, physical examination, urine cytology, urethrocystoscopy, intravenous urography, urethrocytography, CT scan and MRI are very useful diagnostic tools.[8]A careful physical examination should be done comprising of palpation of external genitalia for any abnormalities, pelvic examination with careful inspection and palpation of urethra especially in case of females, bimanual examination under general anaesthesia and digital rectal examination [9]. The role of urine cytology is limited. Diagnostic urethrocystoscopy and biopsy is the primary mode for diagnosis of a urethral tumour in terms of tumour extent, location and underlying histology. [10] The

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urethra consists of five layers- mucosa submucosa and three muscle layers. For in females, as in our case the histological type depends on the location of the tumour in the urethra. Distal tumours are generally Squamous cell carcinoma as that part has squamous lining and proximal part generally has urothelial or adenocarcinoma as it is lined by transitional epithelium. The most common type of urethral carcinoma is the urothelial type(54-65%),[9] followed by Squamous Cell Carcinoma and Adenocarcinoma. The adenocarcinoma of urethra may show enteric, colloid or signet ring histology. All of them may be present singly or in combination. Clear cell type is a another very rare variety. The confirmatory diagnosis is made by urethrocystoscopy, biopsy and histopathological examination. MRI and CT scan help in assessing local tumour extent and lymphatic and distant metastasis[7]. The stage of the disease is a important prognostic factor. In advanced stages, it has been reported that the 3 year survival rates is 56% and there is no five-year survival rate.[2,3] It has also been reported that the squamous type has better prognosis than adenocarcinoma. [7]The treatment protocol of urethral adenocarcinoma is controversial as very less research has been done due to rarity of the disease. The treatment options include local excision to anterior pelvic exanteration along with neo or adjuvant chemotherapy or radiotherapy. Local excision has shown high incidences of metastasis and recurrence.In case of posterior urethral involvement, radical cystectomy with pelvic diversion and pelvic lymphadenectomy is the preferred course whereas in anterior urethral involvement, partial or total urethrectomy can be tried.[2,3] For less than 2cm lesions radiation along with surgery and adjuvant chemotherapy has been suggested, whereas for bigger lesions brachytherapy/ extended beam radiation can be tried.[2]. Despite all this, the treatment protocols of urethral carcinoma remain debatable but combination therapy has proved to be useful according to some studies.

IV. Conclusion

As urethral carcinoma has been found to be a very rare and aggressive tumour prone to recurrence and distant metastasis, it is highly essential that the tumour be diagnosed, staged and treated as early as possible as the advanced cases are known to show slim chances of survival. Hence, we report this case to increase awareness about this fatal tumour and to focus on the importance of histopathology for its diagnosis.

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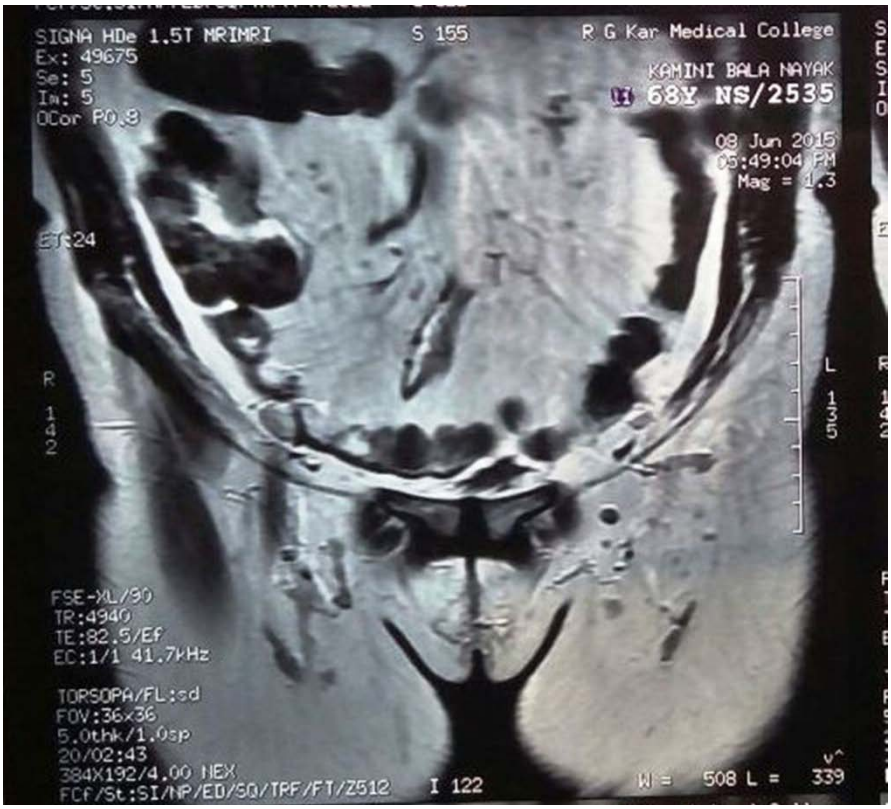


Figure 1 : Ill-defined, altered signal intensity area involving the anterior urethra at the level of the vaginal vault with maintained fat planes with adjacent structures

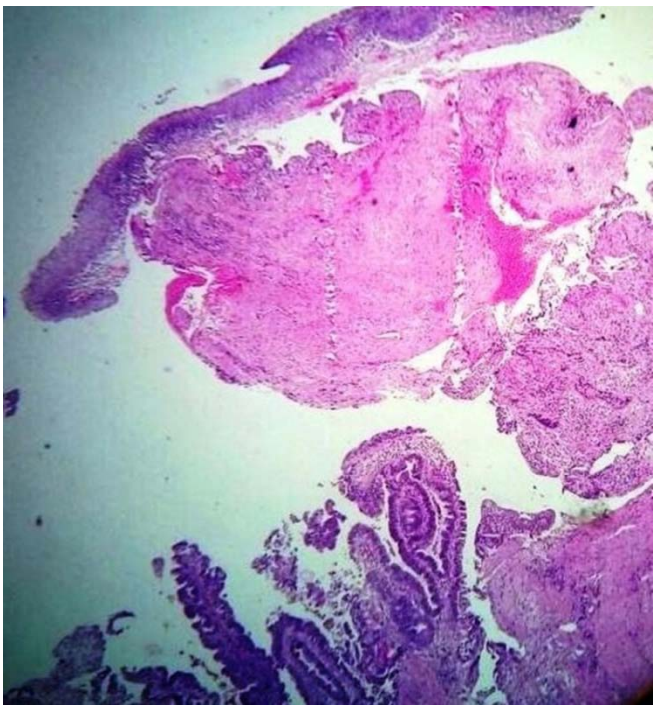


Figure 2

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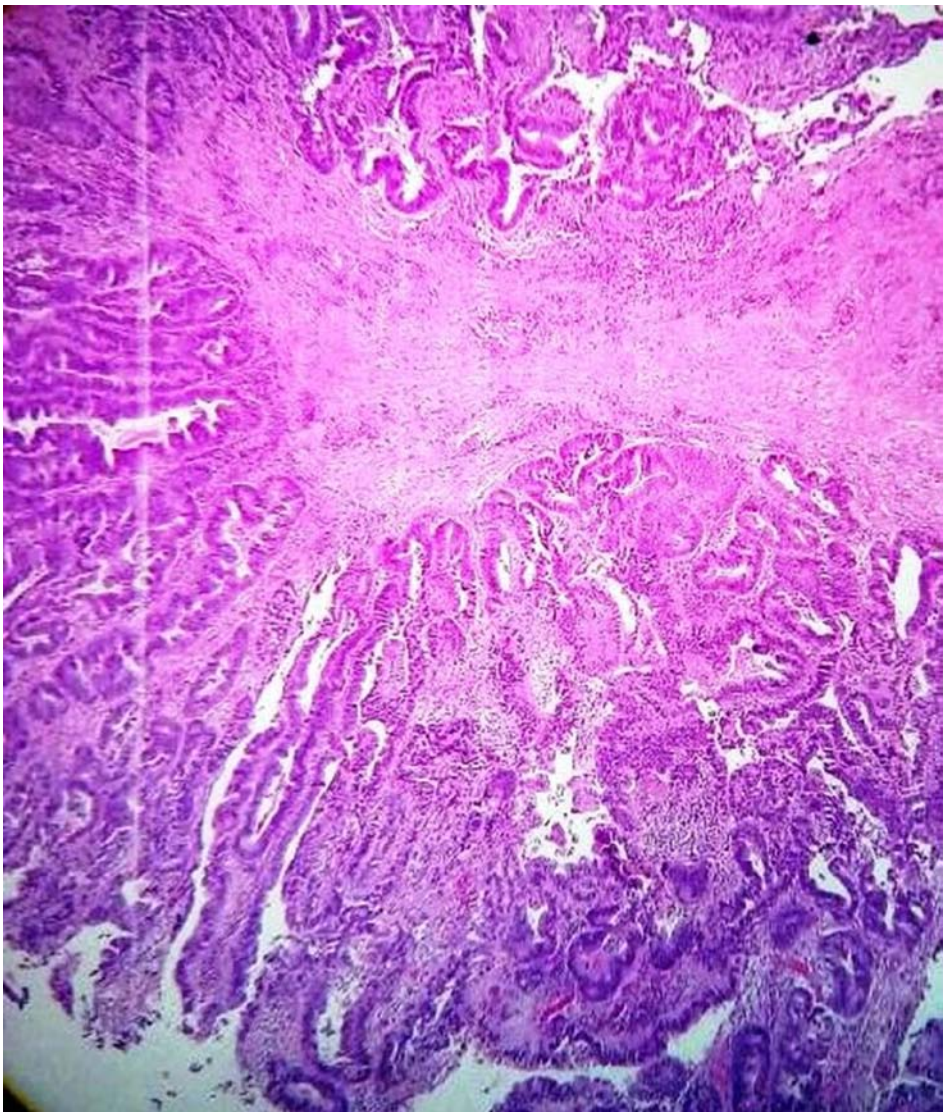


Figure 3

Figure 2 and 3 : Microscopy reveled urethral transitional epithelium beneath which there are areas of adenocarcinoma (enteric type)

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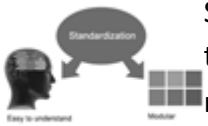


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The Editorial Board reserves the right to make literary corrections and to make suggestions to improve briefness.

It is vital, that authors take care in submitting a manuscript that is written in simple language and adheres to published guidelines.

Format

Language: The language of publication is UK English. Authors, for whom English is a second language, must have their manuscript efficiently edited by an English-speaking person before submission to make sure that, the English is of high excellence. It is preferable, that manuscripts should be professionally edited.

Standard Usage, Abbreviations, and Units: Spelling and hyphenation should be conventional to The Concise Oxford English Dictionary. Statistics and measurements should at all times be given in figures, e.g. 16 min, except for when the number begins a sentence. When the number does not refer to a unit of measurement it should be spelt in full unless, it is 160 or greater.

Abbreviations supposed to be used carefully. The abbreviated name or expression is supposed to be cited in full at first usage, followed by the conventional abbreviation in parentheses.

Metric SI units are supposed to generally be used excluding where they conflict with current practice or are confusing. For illustration, 1.4 l rather than 1.4 × 10-3 m3, or 4 mm somewhat than 4 × 10-3 m. Chemical formula and solutions must identify the form used, e.g. anhydrous or hydrated, and the concentration must be in clearly defined units. Common species names should be followed by underlines at the first mention. For following use the generic name should be constricted to a single letter, if it is clear.

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All manuscripts submitted to Global Journals Inc. (US), ought to include:

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Abstract, used in Original Papers and Reviews:

Optimizing Abstract for Search Engines

Many researchers searching for information online will use search engines such as Google, Yahoo or similar. By optimizing your paper for search engines, you will amplify the chance of someone finding it. This in turn will make it more likely to be viewed and/or cited in a further work. Global Journals Inc. (US) have compiled these guidelines to facilitate you to maximize the web-friendliness of the most public part of your paper.

Key Words

A major linchpin in research work for the writing research paper is the keyword search, which one will employ to find both library and Internet resources.

One must be persistent and creative in using keywords. An effective keyword search requires a strategy and planning a list of possible keywords and phrases to try.

Search engines for most searches, use Boolean searching, which is somewhat different from Internet searches. The Boolean search uses "operators," words (and, or, not, and near) that enable you to expand or narrow your affords. Tips for research paper while preparing research paper are very helpful guideline of research paper.

Choice of key words is first tool of tips to write research paper. Research paper writing is an art.A few tips for deciding as strategically as possible about keyword search:

- One should start brainstorming lists of possible keywords before even begin searching. Think about the most important concepts related to research work. Ask, "What words would a source have to include to be truly valuable in research paper?" Then consider synonyms for the important words.
- It may take the discovery of only one relevant paper to let steer in the right keyword direction because in most databases, the keywords under which a research paper is abstracted are listed with the paper.
- One should avoid outdated words.

Keywords are the key that opens a door to research work sources. Keyword searching is an art in which researcher's skills are bound to improve with experience and time.

Numerical Methods: Numerical methods used should be clear and, where appropriate, supported by references.

Acknowledgements: Please make these as concise as possible.

References

References follow the Harvard scheme of referencing. References in the text should cite the authors' names followed by the time of their publication, unless there are three or more authors when simply the first author's name is quoted followed by et al. unpublished work has to only be cited where necessary, and only in the text. Copies of references in press in other journals have to be supplied with submitted typescripts. It is necessary that all citations and references be carefully checked before submission, as mistakes or omissions will cause delays.

References to information on the World Wide Web can be given, but only if the information is available without charge to readers on an official site. Wikipedia and Similar websites are not allowed where anyone can change the information. Authors will be asked to make available electronic copies of the cited information for inclusion on the Global Journals Inc. (US) homepage at the judgment of the Editorial Board.

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The Editorial Board and Global Journals Inc. (US) recommend the use of a tool such as Reference Manager for reference management and formatting.

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Figures: Figures are supposed to be submitted as separate files. Always take in a citation in the text for each figure using Arabic numbers, e.g. Fig. 4. Artwork must be submitted online in electronic form by e-mailing them.

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22. Never start in last minute: Always start at right time and give enough time to research work. Leaving everything to the last minute will degrade your paper and spoil your work.

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24. Never copy others' work: Never copy others' work and give it your name because if evaluator has seen it anywhere you will be in trouble.

25. Take proper rest and food: No matter how many hours you spend for your research activity, if you are not taking care of your health then all your efforts will be in vain. For a quality research, study is must, and this can be done by taking proper rest and food.

26. Go for seminars: Attend seminars if the topic is relevant to your research area. Utilize all your resources.



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27. Refresh your mind after intervals: Try to give rest to your mind by listening to soft music or by sleeping in intervals. This will also improve your memory.

28. Make colleagues: Always try to make colleagues. No matter how sharper or intelligent you are, if you make colleagues you can have several ideas, which will be helpful for your research.

29. Think technically: Always think technically. If anything happens, then search its reasons, its benefits, and demerits.

30. Think and then print: When you will go to print your paper, notice that tables are not be split, headings are not detached from their descriptions, and page sequence is maintained.

31. Adding unnecessary information: Do not add unnecessary information, like, I have used MS Excel to draw graph. Do not add irrelevant and inappropriate material. These all will create superfluous. Foreign terminology and phrases are not apropos. One should NEVER take a broad view. Analogy in script is like feathers on a snake. Not at all use a large word when a very small one would be sufficient. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Amplification is a billion times of inferior quality than sarcasm.

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33. Report concluded results: Use concluded results. From raw data, filter the results and then conclude your studies based on measurements and observations taken. Significant figures and appropriate number of decimal places should be used. Parenthetical remarks are prohibitive. Proofread carefully at final stage. In the end give outline to your arguments. Spot out perspectives of further study of this subject. Justify your conclusion by at the bottom of them with sufficient justifications and examples.

34. After conclusion: Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium though which your research is going to be in print to the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects in your research.

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Key points to remember:

- Submit all work in its final form.
- Write your paper in the form, which is presented in the guidelines using the template.
- Please note the criterion for grading the final paper by peer-reviewers.

Final Points:

A purpose of organizing a research paper is to let people to interpret your effort selectively. The journal requires the following sections, submitted in the order listed, each section to start on a new page.

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To make a paper clear

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- Insertion a title at the foot of a page with the subsequent text on the next page
- Separating a table/chart or figure - impound each figure/table to a single page
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In every sections of your document

· Use standard writing style including articles ("a", "the," etc.)

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· Use paragraphs to split each significant point (excluding for the abstract)

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· Present your points in sound order

· Use present tense to report well accepted

· Use past tense to describe specific results

· Shun familiar wording, don't address the reviewer directly, and don't use slang, slang language, or superlatives

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An abstract is a brief distinct paragraph summary of finished work or work in development. In a minute or less a reviewer can be taught the foundation behind the study, common approach to the problem, relevant results, and significant conclusions or new questions.

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- Fundamental goal
- To the point depiction of the research
- Consequences, including definite statistics - if the consequences are quantitative in nature, account quantitative data; results of any numerical analysis should be reported
- Significant conclusions or questions that track from the research(es)

Approach:

- Single section, and succinct
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- A conceptual should situate on its own, and not submit to any other part of the paper such as a form or table
- Center on shortening results - bound background information to a verdict or two, if completely necessary
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- Exact spelling, clearness of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else

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- Explain the value (significance) of the study
- Shield the model - why did you employ this particular system or method? What is its compensation? You strength remark on its appropriateness from a abstract point of vision as well as point out sensible reasons for using it.
- Present a justification. Status your particular theory (es) or aim(s), and describe the logic that led you to choose them.
- Very for a short time explain the tentative propose and how it skilled the declared objectives.

Approach:

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- If use of a definite type of tools.
- Materials may be reported in a part section or else they may be recognized along with your measures.

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- Report the method (not particulars of each process that engaged the same methodology)
- Describe the method entirely
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- Simplify - details how procedures were completed not how they were exclusively performed on a particular day.
- If well known procedures were used, account the procedure by name, possibly with reference, and that's all.

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- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings - save it for the argument.
- Leave out information that is immaterial to a third party.

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The page length of this segment is set by the sum and types of data to be reported. Carry on to be to the point, by means of statistics and tables, if suitable, to present consequences most efficiently.You must obviously differentiate material that would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matter should not be submitted at all except requested by the instructor.



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Content

- Sum up your conclusion in text and demonstrate them, if suitable, with figures and tables.
- In manuscript, explain each of your consequences, point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation an exacting study.
- Explain results of control experiments and comprise remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or in manuscript form.

What to stay away from

- Do not discuss or infer your outcome, report surroundings information, or try to explain anything.
- Not at all, take in raw data or intermediate calculations in a research manuscript.
- Do not present the similar data more than once.
- Manuscript should complement any figures or tables, not duplicate the identical information.
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Approach

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- Put figures and tables, appropriately numbered, in order at the end of the report
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- Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work
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- Give details all of your remarks as much as possible, focus on mechanisms.
- Make a decision if the tentative design sufficiently addressed the theory, and whether or not it was correctly restricted.
- Try to present substitute explanations if sensible alternatives be present.
- One research will not counter an overall question, so maintain the large picture in mind, where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

- When you refer to information, differentiate data generated by your own studies from available information
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Topics	Grades		
	A-B	**C-D**	**E-F**
Abstract	Clear and concise with appropriate content, Correct format. 200 words or below	Unclear summary and no specific data, Incorrect form Above 200 words	No specific data with ambiguous information Above 250 words
Introduction	Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited	Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter	Out of place depth and content, hazy format
Methods and Procedures	Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads	Difficult to comprehend with embarrassed text, too much explanation but completed	Incorrect and unorganized structure with hazy meaning
Result	Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake	Complete and embarrassed text, difficult to comprehend	Irregular format with wrong facts and figures
Discussion	Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited	Wordy, unclear conclusion, spurious	Conclusion is not cited, unorganized, difficult to comprehend
References	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring

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