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Discovering Thoughts, Inventing Future

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Contents of the Issue

i. Copyright Notice
ii. Editorial Board Members
iii. Chief Author and Dean
iv. Contents of the Issue

1. Echocardiographic Profile in Newly Diagnosed Patients with Obstructive Sleep Apnoea (OSA) and Normal LV Ejection Fraction: A Prospective Study. *1-7*
2. A narrative review on HPV vaccination among boys and men. *9-12*
3. Effect of Cigarette Smoking on Trace Elements among Residents in Khartoum State, Sudan. *13-18*
4. Simulation model for breast cancer management in India. *19-22*
5. Human Papilloma Virus: An Oncogene. *23-25*

v. Fellows
vi. Auxiliary Memberships
vii. Preferred Author Guidelines
viii. Index

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Echocardiographic Profile in Newly Diagnosed Patients with Obstructive Sleep Apnoea (OSA) and Normal LV Ejection Fraction: A Prospective Study

By Anender Kaur Dhariwal, Prakash Sanzgiri, Charan Reddy KV, Vidya Suratkal & Suresh Vijan

Abstract- OSA is considered as an independent risk factor for cardiovascular morbidity and mortality. Hypertension, atrial fibrillation, heart failure with reduced ejection fraction, stroke and metabolic syndrome are also known to be associated with OSA. Each of these conditions are associated with 2D-ECHO abnormalities and often present with increased hospitalization rates or morbidity. However, echocardiographic parameters in newly detected OSA, without any other associated illness, is poorly defined. The aim of this study is to evaluate systolic and diastolic dysfunction using 2D speckle tracking in patients with newly diagnosed OSA and normal left ventricle ejection fraction. The association between diastolic dysfunction, Global Longitudinal Strain (GLS), LV hypertrophy, LV mass, estimated pulmonary artery pressures and severity of OSA was also studied. The results indicated that most of the patients with OSA, without any other cardiovascular diseases, exhibited normal left ventricular (LV) ejection fraction (EF), but had clinical signs and symptoms of LV systolic dysfunction.

Keywords: *obstructive sleep apnoea, left ventricular ejection fraction, echocardiography, systolic dysfunction.*

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Echocardiographic Profile in Newly Diagnosed Patients with Obstructive Sleep Apnoea (OSA) and Normal LV Ejection Fraction: A Prospective Study

Anender Kaur Dhariwal [α], Prakash Sanzgiri [σ], Charan Reddy KV [ρ], Vidya Suratkal [ω] & Suresh Vijan[¥]

Abstract- OSA is considered as an independent risk factor for cardiovascular morbidity and mortality. Hypertension, atrial fibrillation, heart failure with reduced ejection fraction, stroke and metabolic syndrome are also known to be associated with OSA. Each of these conditions are associated with 2D-ECHO abnormalities and often present with increased hospitalization rates or morbidity. However, echocardiographic parameters in newly detected OSA, without any other associated illness, is poorly defined. The aim of this study is to evaluate systolic and diastolic dysfunction using 2D speckle tracking in patients with newly diagnosed OSA and normal left ventricle ejection fraction. The association between diastolic dysfunction, Global Longitudinal Strain (GLS), LV hypertrophy, LV mass, estimated pulmonary artery pressures and severity of OSA was also studied. The results indicated that most of the patients with OSA, without any other cardiovascular diseases, exhibited normal left ventricular (LV) ejection fraction (EF), but had clinical signs and symptoms of LV systolic dysfunction.

Keywords: obstructive sleep apnoea, left ventricular ejection fraction, echocardiography, systolic dysfunction.

I. Introduction

Obstructive sleep apnoea (OSA) is a common condition affecting nearly 5-15% of adult population in both developing and developed countries. Prevalence increases with age, obesity, and other chronic diseases.OSA is considered as an independent risk factor for cardiovascular morbidity and mortality. Left ventricular systolic function is generated by radial and longitudinal fibre shortening. Radial shortening is predominantly dependent on the contraction of circumferential myocardial fibres, which are more resistant to ischemia. However, longitudinal shortening is generated by both longitudinal sub-endocardial and sub-epicardial fibres, where the sub-endocardium is more vulnerable to myocardial ischaemia. Hence, assessment of LV longitudinal function is considered as a sensitive marker for early detection of the left ventricular systolic dysfunction.

A recent meta-analysis that compared left ventricular ejection fraction (LVEF) and Global longitudinal strain (GLS) in predicting major adverse cardiac events in patients with different cardiovascular diseases reported that GLS had superior prognostic value to EF for predicting all-cause mortality, cardiac death, malignant arrhythmia, hospitalization due to heart failure, urgent valve surgery or heart transplantation and acute coronary ischemic events[1]. The potential of Continuous positive airway pressure (CPAP) therapy to reverse functional and structural remodeling of the heart has been confirmed in several studies.

The present study was undertaken to evaluate early systolic and diastolic dysfunction using 2D speckle tracking in patients with newly diagnosed OSA with normal left ventricle ejection fraction. The association between diastolic dysfunction, LV hypertrophy, LV mass, estimated pulmonary artery pressure with severity of OSA, studied using Apnoea-hypopnoea Index (AHI).

II. Material and Methods

The current work is based on single centre, observational, non-randomised prospective study, which was undertaken to assess and highlight the Echocardiographic parameters in patients having Hypertension, Atrial Fibrillation, Heart failure with reduced ejection fraction, Stroke and Metabolic syndrome, which are known to be associated with OSA. Each of these medical conditions cause 2D-Echo abnormalities with high morbidity and increased hospitalization rates. However, 2D-echocardiographic parameters in newly detected OSA, without any other associated illness, is poorly defined. In this study we had selected such patients and sub-grouped them based on the severity of sleep apnoea.

a) Patients selection

Inclusion criteria: This was an observational study of 50 patients (included both inpatients and outpatients-males & females above 18 years), recently diagnosed to have Obstructive sleep apnoea by polysomnography (PSG), with rigid exclusion criteria. Patients with OSA often have co-existing disorders that are prone to diastolic dysfunction such as aging, obesity, hypertension and diabetes. Obstructive sleep apnoea (Apnoea hypopnoea index >5 episodes/hr), satisfying the inclusion and exclusion criteria were selected in study after written informed consent. Patients were graded as mild (AHI ≥5), moderate (AHI ≥15) and

Author α σ ρ ω ¥: Department of Clinical and Interventional Cardiology, Lilavati Hospital and Research Center, Bandra, Mumbai, India.
e-mail: dr.sanzgiri@gmail.com

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severe (AHI ≥ 30) obstructive sleep apnoea as per American academy of sleep medicine[2].

Exclusion criteria: Patients excluded in this study had central sleep apnoea, coronary artery disease or electrocardiographic changes suggestive of myocardial infarction, global LV systolic dysfunction (LVEF<50%) or a history of congestive heart failure, diabetes mellitus, moderate to severe valvular heart diseases, hypertrophic cardiomyopathy, history and clinical features of restrictive or chronic obstructive pulmonary disease or asthma, arrhythmias like atrial fibrillation, previous diagnosis of OSA and/or the previous use of continuous positive airway pressure therapy (CPAP), chronic renal impairment (serum creatinine > 112μmol/L), individuals with systemic and metabolic diseases which could adversely affect the cardiac function and cigarette smoking were excluded. Also excluded were patients <18 years, pregnant females, and those with prior surgical treatment for Obstructive sleep apnoea, and those who are unwilling or uncooperative patients.

b) Methods

Overnight fully attended PSG monitoring was performed with the Alice 4 Sleep System (Respironics Inc., Murrysville, PA, USA) using standard recording technique. All Echocardiographic examinations were performed by an experienced cardiologist who was blinded for the results of polysomnography. All measurements were performed with the subjects in the left lateral decubitus position by M-mode, two dimensional, and Doppler ultrasound echocardiography. The equipment used was Vivid I (GE healthcare, Horten, Norway). Basic measurements of left ventricular dimensions in diastole and systole, thickness of inter-ventricular septum (IVS), left ventricular posterior wall (LVPW) and LV Mass (LVM) were measured by the M-mode technique and LVM was divided with body surface area to obtain LVM index (LVMI). LVH was said to be present when the LVMI crossed the reference upper limits of 95g/m2 in females and 115g/m2 in males (2015 chamber quantification)[10].

LVEF was measured using biplane Simpson's method according to the recommendation of European Association for Echocardiography. LV Global longitudinal strain was measured using commercially available 2D strain software (EchoPAC PC, version 6.0, GE Healthcare, Horten, Norway). Those with GLS of less than -20% were labeled as low GLS and those with GLS≥-20% were labeled as normal GLS (2015 chamber quantification guidelines)[3]. LV diastolic dysfunction was evaluated according to the guidelines of the American society of Echocardiography. Right ventricle dimension (RVD) and right ventricular fractional area change (RVFAC) were also measured.

III. Discussion

Repeated episodes of hypoxia, hypercapnia, microarousals, and changes in intra-thoracic pressure, trigger pathophysiological mechanisms such as sympathetic hyperactivity, oxidative stress, systemic inflammation, hypercoagulability and endothelial dysfunction which can lead to the development of vascular disease. Hypertension, commonly seen in OSA, is the most common risk factor for LVH. However, *Hedner et al (1990)*[4] reported that OSA patients had a thicker LV wall and LV mass, and their mass index to body surface area, was approximately 15% higher among normotensive OSA patients than in normotensive control subjects. In the present study, the percentage of subjects having mild, moderate and severe OSA were 38%, 30% & 32% respectively *(Table-1)*. Amongst the subjects with mild, moderate and severe OSA, the percentage of LVH was 10.5%, 60% and 93.8% respectively. A statistically significant association between OSA and LVH was observed *(Table-2).* Recurrent episodes of hypoxaemia and increased sympathetic activity observed during OSA would also contribute to development of LVH in patients with OSA, and would correlate with severity, duration of OSA and degree of hypoxemia.

Wachter group (2013)[5] reported that moderate-to-severe OSA is independently associated with diastolic dysfunction. The prevalence of diastolic dysfunction in their study increased with the severity of sleep apnoea from 44.8% (none) to 56.8% (mild) to 69.7% (moderate-to-severe sleep apnoea) (p-0.002). The degree of diastolic dysfunction also increased with sleep apnoea severity. e' was significantly reduced in OSA and E/e' was significantly increased with increasing severity of OSA5. Similar pattern was noted in our study. We observed 42.1% of cases with mild OSA, 73.3% with moderate OSA & 75.1% (grade I diastolic dysfunction-43.8%, grade II- 31.3%)of cases with severe OSA had diastolic dysfunction. There was a significant association (p-0.0034) between grades of OSA and diastolic dysfunction. AHI was the only significant predictor of diastolic dysfunction in our study group; more the AHI, more likely is the patient to have diastolic dysfunction (*Table-5).*

The percentage of subjects with mild, moderate and severe OSA having PAH were 5.3%, 20% and 43.8% respectively. There was a statistically significant association (p-0.035) between grades of OSA and PAH. Patients with severe OSA had greater predisposition to having pulmonary hypertension on first detection of OSA. However all of them had normal RV function *(Table-4).* In our study, the estimated LVEF was no different in all subgroups of OSA. LV hypertrophy, LV mass and left ventricular mass index (LVMI) was increased in moderate and severe OSA groups. GLS was statistically abnormal in moderate and severe OSA

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groups. Mean Pulmonary artery pressure (mPAP) was significantly increased in moderate and severe OSA sub-groups *(Table-3).* Systolic LV function is commonly estimated by assessing LV ejection fraction. But fall of LVEF is a rather late echocardiographic finding. This is due to the fact that normal value of LVEF does not always imply normal LV systolic function. On the other hand, diastolic function is often impaired in OSA. Myocardial ischemia and oxidative stress are the pathophysiological explanations of these disturbances.

The recent development of the 2D-STE (speckle-tracking echocardiography) enables accurate and reliable measurements of both the global and regional myocardial strain and strain rates. The limitations of EF in assessing systolic function and predicting prognosis in the context of LV hypertrophy (or increased LV wall thickness) are well recognized. STE has gained increasing clinical popularity in this setting as a means of identifying early, subtle systolic dysfunction in the context of normal LVEF, aiding diagnosis of rarer causes of LV hypertrophy, such as hypertrophic cardiomyopathy (HCM) or cardiac amyloidosis (CA).It can also be used to predict and assess short and long term prognosis with the study of global longitudinal strain (GLS), which is an accurate echocardiographic method of early LV dysfunction[6]. 50% of OSA cases had low GLS (GLS< -20%) and 50% had normal GLS (GLS≥ -20%).

Estimated LVEF was no different in all subgroups of OSA. LV hypertrophy, LV mass and left ventricular mass index (LVMI) was increased in moderate and severe OSA groups. GLS was statistically abnormal in moderate and severe OSA groups. Mean mPAP was significantly increased in moderate to severe OSA subgroups (*Table-3*). None of the subjects with mild OSA had low GLS, while 60% of subjects with moderate OSA and all 100% of subjects with severe OSA had low GLS. There was a significant association (p-1.86E-08) between grades of OSA and low GLS *(Table-6). Altekin et al (2012)*[7] used 2D-speckle tracking echocardiography (2D-STE) to evaluate subclinical LV systolic dysfunction in patients with OSA patients with preserved LVEF and without any confounding diseases that may result myocardial dysfunction. In their study, the mean GLS values for mild, moderate & severe OSA patients were -25.3±-1.67, -20.22±-2.4 & -16.62±-2.48 respectively, almost similar to our findings[7,8]. In moderate OSA patients, the GLS values decreased with the severity of the disease.

Our study showed that decreased longitudinal systolic deformation occurs early in OSA patients despite normal LVEF and that Longitudinal systolic deformation is strongly associated with the severity of OSA, with AHI being a independent predictor of GLS. The possible explanation for this is that the apnoea-hypopnea periods affect the sub-endocardially located longitudinal fibres thereby, increasing LV wall tension and preload caused by the OSA leading to LV longitudinal systolic dysfunction. In order to decrease LV wall tension and protect myocardial function, LV hypertrophy and remodeling develops as compensatory mechanisms. As the LV hypertrophy and concentric remodeling progresses, the sub-endocardial myocardial layer responsible for the longitudinal shortening becomes more susceptible to ischemic apoptosis and fibrous transformation, resulting in reduced LV longitudinal shortening in the early stages of the OSA. This conclusion also supports the theory that the longitudinal fibres are affected in the early stages of OSA, as they are sub-endocardially located & are more susceptible to myocardial ischemia caused by the recurrent apnoea-hypopnea episodes of the OSA. Haruki et al have shown that after effective CPAP therapy for a period of 3 months, AHI and minimal oxygen saturation were significantly improved, with an elimination of sleep-induced GLS abnormality in OSA patients[9].

Pulmonary hypertension (PH) in OSA is often overlooked.PH secondary to OSA is usually mild to moderate. 27%–30% of patients with OSA without left ventricular dysfunction or hypoxemic lung disease have PH. It was previously considered that PH is a manifestation of long standing OSA. However, our study has demonstrated that PH can be present at the first detection of OSA, and is directly related to severity of OSA. OSA is associated with a higher mortality among patients with PH than without PH. In presence of PH, treatment modality specific to OSA associated with PH should be planned. The possible coexistence of other conditions (pulmonary parenchymal disease, Mitral regurgitation, auto-immune disease, obesity hypoventilation syndrome, chronic pulmonary thromboembolism), which worsen PH, should be considered as it requires a different management strategy. The majority of patients with OSA experience cyclical oxygen desaturation during sleep. These episodes can last from few seconds occurring several times an hour followed by arousals with complete or partial recovery of oxygen saturation. This cumulative effect of intermittent hypoxia can lead to PH[10].The findings in our study can be summarized as follows:

1). Left ventricular hypertrophy (LVH) was present in 52% (26 out of 50) patients. There was a significant association between various grades of OSA and LVMI. The LVMI was higher in subjects with moderate and severe OSA as compared to mild OSA, albeit the difference was not significant. 2)62% of newly diagnosed OSA patients in our study had diastolic dysfunction (grade I diastolic dysfunction -52% and grade II diastolic dysfunction- 10%), of which 67.74% had LVH and 54.84% had history of hypertension. 3).The prevalence of diastolic dysfunction increased with the severity of OSA. There was a statistically significant

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association (p- 0.0034) between severity of OSA and diastolic dysfunction. AHI was the only significant predictor of diastolic dysfunction; more the AHI, more likely is the patient to have diastolic dysfunction. 4).Apnoea hypopnoea index was found to be a significant predictor of GLS. None of the subjects with mild OSA had low GLS, while 60% of subjects with moderate OSA and all 100% of subjects with severe OSA had low GLS. There was a statistically significant association (p-1.86E-08) between grades of OSA and low GLS. Thus, a decreased longitudinal systolic deformation (measured as GLS) occurs early in OSA patients despite normal LVEF and that longitudinal systolic deformation is significantly associated with the severity of OSA, with AHI being a significant predictor of GLS. 5) The percentage of subjects with mild, moderate and severe OSA having PAH were 5.3%, 20% and 43.8% respectively. There was a statistically significant association (p-0.035) between grades of OSA and PAH. Patients with severe OSA had greater predisposition to having pulmonary hypertension on first detection of OSA. However all of them had normal RV function.

IV. Conclusion

All newly diagnosed patients with OSA should undergo detailed echocardiographic evaluation to see diastolic function and strain imaging should also be performed in them even if have a normal LV ejection fraction. New cases of OSA patients without clinically diagnosed cardiovascular diseases usually present with early signs of cardiac hypertrophy, LV diastolic or LV systolic dysfunction as seen by abnormal GLS and pulmonary artery pressures. The severity of the OSA also appears to play a major role in LV re-modeling. Hence, early therapeutic interventions can be undertaken to reverse many of abnormalities like LVH, diastolic and systolic dysfunction[11].

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Table 1: Distribution of OSA grades among study subjects. The percentage of subjects having mild, moderate & severe OSA were 38%, 30% and 32% respectively.

Sleep Study: OSA grade	No patients	%
Mild (AHI ≥ 5)	19	38.0%
Moderate (AHI ≥ 15)	15	30.0%
Severe (AHI ≥ 30)	16	32.0%
Total	50	100.0%

Table 2: Association among the cases between- OSA grade and echocardiography LVH

Sleep Study: OSA grade		Echocardiography: LVH		Total
		Present	Absent	
Mild	No.	2	17	19
	%	10.5%	89.5%	
Moderate	No.	9	6	15
	%	60.0%	40.0%	
Severe	No.	15	1	16
	%	93.8%	6.3%	
Total	No.	26	24	50
	%	52.0%	48.0%	

Table 3: Comparison of various echocardiography variables between OSA grades

Echo Variables	Sleep Study: OSA grade	Mean	SD	Median	IQR	F-value	p-value
LVEF (Simpson's)	Mild	60.79	2.30	60.00	3.00	2.601	0.085
	Moderate	59.27	3.11	59.00	5.00	Difference is not significant	
	Severe	59.06	1.91	59.50	3.00		
	Severe	39.94	2.96	40.00	5.00		
mPAP	Mild	18.21	2.68	18.00	3.00	14.371	0.00076
	Moderate	21.60	5.15	20.00	2.00	Difference is significant	
	Severe	25.06	6.77	22.00	14.00		
IVS (mm)	Mild	10.51	0.91	10.50	1.10	39.421	8.88E-11
	Moderate	12.19	0.72	12.00	1.30	Difference is significant	
	Severe	13.07	0.94	13.20	1.60		
PW (mm)	Mild	10.28	0.92	10.00	1.50	38.659	1.18E-10
	Moderate	11.86	0.74	11.90	1.10	Difference is significant	
	Severe	12.77	0.86	12.95	1.30		
LV mass (g)	Mild	143.68	38.48	135.00	65.00	27.299	1.36E-08
	Moderate	209.67	44.98	199.00	70.00	Difference is significant	
	Severe	248.38	44.68	254.00	72.00		
LVMI (g/m2)	Mild	75.21	21.62	70.00	39.00	20.174	4.73E-07
	Moderate	102.07	18.18	105.00	28.00	Difference is significant	
	Severe	119.69	22.35	119.50	41.00		
GLS	Mild	23.86	1.53	24.00	2.20	122.779	2.18E-19
	Moderate	19.67	1.33	19.40	2.20	Difference is significant	
	Severe	16.17	1.46	15.90	2.40		

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Table 4: Association among the cases between- OSA grade and echocardiography: PAH

Sleep Study: OSA grade		Echocardiography: PAH		Total
		Mild PH	No PH	
Mild	No.	1	18	19
	%	5.3%	94.7%	
Moderate	No.	3	12	15
	%	20.0%	80.0%	
Severe	No.	7	9	16
	%	43.8%	56.3%	
Total	No.	11	39	50
	%	22.0%	78.0%	

Table 5: Association among the cases between-OSA grade and grade of diastolic dysfunction

Sleep Study: OSA grade		Grade of Diastolic dysfunction			Total
		No diastolic dysfunction	Grade I	Grade II	
Mild	No.	11	8	0	19
	%	57.9%	42.1%	0.0%	
Moderate	No.	4	11	0	15
	%	26.7%	73.3%	0.0%	
Severe	No.	4	7	5	16
	%	25.0%	43.8%	31.3%	
Total	No.	19	26	5	50
	%	38.0%	52.0%	10.0%	

Table 6: Association among the cases between sleep Study: OSA grade diastolic dysfunction and echocardiography GLS

Sleep Study: OSA grade		Echocardiography: GLS		Total
		Low	Normal	
Mild	No.	0	19	19
	%	0.0%	100.0%	
Moderate	No.	9	6	15
	%	60.0%	40.0%	
Severe	No.	16	0	16
	%	100.0%	0.0%	
Total	No.	25	25	50
	%	50.0%	50.0%	

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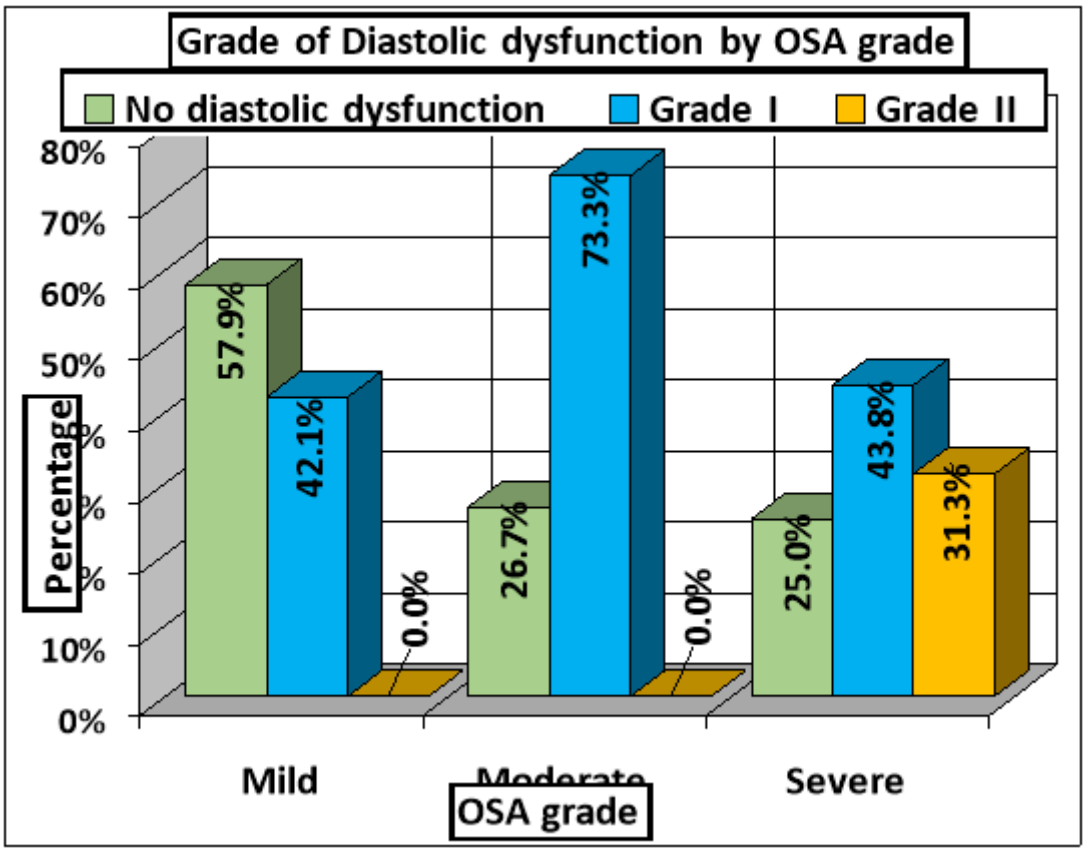


Figure 1: The mean age of study of study subjects (n=50) with newly diagnosed OSA was 47.16 ± 2.902 years, 42% were females and 58% were males

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A narrative review on HPV vaccination among boys and men

By Vinod K Ramani & Radheshyam Naik

Abstract- Apart from cervical cancer, Human papillomavirus (HPV) infection is associated with head and neck as well as other anogenital cancers such as vulva, vagina, anus, and penis. HPV vaccine provides specific protection against the disease and its subsequent manifestations.

Vaccination programs for men tend to improve population-level control of HPV infection and directly prevent HPV related disease such as anogenital warts and oropharyngeal cancers in males. HPV vaccine does not treat existing infection or lesions/cancer and is intended for individuals before initiation fo sexual activity or any other form of exposure to HPV.

Many programs across the globe do not include vaccination for boys because of the cost and little recognition of the emerging epidemic of HPV associated cancers in men. In the Indian context, as screening is not feasible for non-cervical HPV associated cancers, its incidence mostly among men will continue to rise until the present generation of vaccinated adolescents reaches their middle-age.

Vaccination will reduce transmission rates and increase herd immunity. This in-turn, will prevent not just cervical cancers but also other HPV-associated malignancies among men and women.

GJMR-F Classification: *NLMC Code: QW 806*

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A narrative review on HPV vaccination among boys and men

Vinod K Ramani [α] & Radheshyam Naik [σ]

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Vaccination will reduce transmission rates and increase herd immunity. This in-turn, will prevent not just cervical cancers but also other HPV-associated malignancies among men and women.

I. Introduction

Apart from cervical cancer, Human papillomavirus (HPV) infection is associated with head and neck as well as other anogenital cancers such as vulva, vagina, anus, and penis. Worldwide ~70% of cervical cancer could be attributed to HPV types 16 and 18. HPV vaccine provides specific protection against the disease and its subsequent manifestations[1].

An important etiological agent in squamous cell carcinoma of the tonsil, base of tongue and anus, includes one of a subset of mucosal high-risk human papillomaviruses (HPVs) principally 16 and 18. Apart from causing cervical cancer among women, it significantly contributes to squamous cell carcinoma of the larynx, head and neck, penis, vulva and vagina[2].

In India[1], the crude incidence rate of cervical cancer per 100,000 during 2018 was 14.9, and the age-standardized rate was 14.7. The global measures were 15.1 and 13.1, respectively. It ranks second among the leading causes of female cancers. Among women aged 25-64 years, screening coverage every three years for cervical cancer is 3.1%. The age-standardized rate for cervical cancer mortality in India was 9.2 per 100000 women during 2018. The age - specific mortality rate of cervical cancer among women aged 15-44 years of age in India during 2018 was 3.9%. The demographic profile of India includes 32.7% of its population living in urban areas.

The average worldwide incidence of anal cancer is 1 per 100,000. Its incidence is high among men who have sex with men (MSM), women with a history of cervical or vulvar cancer, the immunosuppressed population including HIV-infected, and patients with a history of organ transplantation. The incidence of anal cancer is high among women when compared with men[1].

Cancers of the vulva and vagina are rare among women with worldwide estimated new cases of 27,000 and 13,000 respectively, in the year 2008. Among vulvar cancers, only the basaloid/warty lesions are often associated with detection of HPV DNA (deoxyribonucleic acid). Penile cancer's incidence worldwide is estimated to be 22,000 cases, strongly correlating with those of cervical cancer[1].

Among the head and neck cancers, current evidence suggests that HPV type 16 is associated with tonsil cancer, the base of tongue cancer, and other oropharyngeal cancers. The crude incidence rate per 100,000 and year 2018 for oropharyngeal cancer in India was 2.6 (Male: 2.2, Female: 0.4)[1]. Among human cancers, ~5% are caused due to HPV infection with HPV16 being the major genotype. HPV infection mainly with the genotype 16 could be attributed to >90% of anal cancers[1].

The peak prevalence of HPV infection among women is in their late teens and twenties and steadily declines throughout the subsequent decades. However, men acquire the infection during the late teens, and there is no change in prevalence during the subsequent decades[2].

Gardasil from Merck company is one of the available prophylactic HPV vaccines, which is approved by the United States Food and Drug Administration (USFDA) during 2006. This quadrivalent vaccine protects against HPV types 6, 11, 16 and 18. During 2009, USFDA approved Cervarix from GlaxoSmithKline company as a bivalent vaccine against genotypes 16 and 18. During 2014, a nine-valent vaccine 'Gardasil 9' from Merck was approved, which offers protection against five additional oncogenic genotypes (31, 33, 45, 52 and 58) in addition to the types 6, 11, 16 and 18. The primary target group for vaccination includes

Author α σ: Preventive Oncology unit', Healthcare Global Enterprise Ltd., KR Road, Bangalore. e-mails: drvinod.r@hcgel.com, radheshyam_n@yahoo.com

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adolescents aged 9-13 years, with catch-up vaccination until the age of 26 years[3]. The vaccine is ideally intended for individuals before initiation of sexual activity and exposure to HPV, as it may not benefit existing infection or disease.

The proportion of girls and women as well as boys and men in an Australian study[3], showed a significant reduction in the development of genital warts after the implementation of the National HPV Vaccination program during 2007.

Cost-effectiveness is the primary argument for the HPV vaccination program among males. The recommendation in Countries such as the USA, Canada, Austria, and Australia includes gender-neutral vaccination[4].

II. Methods

'Pubmed' database was used for searching relevant articles. Search terms used include 'HPV vaccination among males'; 'Effectiveness of male HPV vaccination program'; the results of this search yielded research articles that contextually detailed the concerned concepts. The criterion used for reviewing these abstracts includes their relevance to the defined review question. This review includes 13 studies that address the determinants of HPV vaccination uptake.

III. Discussion

In India, screening tests such as PAP smear and HPV testing are already existent for cervical cancer, which is not the case with oropharyngeal cancers. The absence of screening tests results in many such patients presenting with advanced disease involving regional lymph nodes. It is of interest to note the increasing incidence of anal cancer among both the sexes, as well as the presentation of disease in an advanced stage[5]. Some reasons for low vaccination rates in various studies include inadequate provider recommendations, parent opposition, lack of policies mandating HPV vaccination during school enrolment, and absence of school-based immunization program[5].

The sexual behavior with both female and male sexual partners determines the incidence risk of acquiring HPV infection and the likelihood of its clearance. A consequential predictor of both HPV infection and persistence is having either >10-lifetime female sexual partners or >2 recent male anal sex partners[5].

Choi[6] et al.'s study on the 2012-2013 United States National Immunization survey teen dataset shows that 56% of females received at least one dose of HPV vaccine when compared with 28% of males. In this study[6], the interaction between gender and socio-demographic variables in predicting vaccination was found to be significant. Such variables include age, ethnicity, mother's education level, healthcare coverage, and Provider recommendation for vaccination. There has been a lag time of five years for male vaccination to become a routine when compared to female vaccination program. The customary parental reason for avoiding vaccination to their children includes 'healthcare provider not recommended' for males (24%) and 'vaccine not necessary' for females (18%).

Predisposing conditions such as cancer and acquired immunosuppression (among transplant recipients, cancer patients, chronic inflammatory conditions on immunomodulatory drugs, and HIV patients) increase the morbidity of HPV. Such prepubescent boys need to be vaccinated, which could prevent the impact of HPV disease in the future else it becomes a lost opportunity in our fight against HPV disease[4]. There is a scope for post-exposure prophylactic HPV vaccination in boys and men (as well as girls and women). Although direct evidence from clinical trials is limited (given the clinical heterogeneity of the problem and timescale for significant outcomes such as progression to invasive cancer), indirect evidence (women with the cervical disease) provides a compelling rationale regarding the benefits of quadrivalent vaccination[7].

Many programs across the globe do not include vaccination for boys because of the cost and little recognition of the emerging epidemic of HPV associated cancers in men. As screening is not feasible for non-cervical HPV associated malignancies, the incidence of HPV-associated cancers (mostly among men) will continue to rise until the present generation of vaccinated adolescents reaches their middle-age[5]. Primary level of prevention could address this burden, where-in HPV vaccination is provided to both boys and girls.

HPV vaccination program for young adolescent girls leads to dramatic reductions in cervical high-grade precancerous lesions, as well as genital warts. Among girls, sero-surveillance of circulating vaccine-related HPV types also shows a reduction[6]. It is imperative to monitor the incremental impact of universal vaccination of pre-adolescent boys as a component of the immunization schedule. Although population-wide cervical screening programs are currently prevailing, it may not be prudent to advocate screening for HPV infection or related disease in males. The real-time effectiveness of HPV vaccination among males could be monitored through precise surveillance strategies, which in-turn depends on the healthcare infrastructure and existing models of disease surveillance such as sexually transmitted infection (STI) networks[4]. Sentinel surveillance of circulating genital HPV types is a surrogate marker for vaccine effectiveness in males. In such a setting, we need to consider the sampling methods, appropriate anatomical sites for specimen collection, and the sensitive assays which need to be utilized. The epidemiological challenge for assessing the

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impact of HPV vaccination in the male population includes analyzing the effect of herd protection.

An indicator of the vaccine's impact among the male population includes changes in the prevalence of genital HPV genotypes among young, sexually active men. Such markers are more of an indicator of viral deposition than of significant host infection, due to the high rate of HPV DNA clearance detected in males[8]. Surveillance strategies should include a combination of short (HPV prevalence) and long term (anogenital warts, cancers) outcome measures, including those for specific target populations such as MSM and HIV infected men (at high risk for HPV infection and associated disease).

Among heterosexual men, the keratinized epithelial cells from the penile shaft need to be ideally sampled avoiding other deposits from the surface. Comparative studies do not show any difference in the HPV detection rates between swabbing with and without abrasion[8]. This swabbing technique promotes compliance as it is less uncomfortable for participants. Among men who have sex with men (MSM), anal sampling is the ideal site for sampling as HPV is frequently detected here than on the penis or scrotum.

Due to female vaccination, there is a continuing decline in male HPV genoprevalence[8]. This confounding factor is of epidemiological interest when we intend to accurately measure the impact of male vaccination on the male infection (additional decline beyond that due to female vaccination). MSM cannot be covered by such herd protection, and they need to be protected with vaccination.

For measuring the impact of the vaccination programs, sero-surveillance could contribute towards measuring immunological response to vaccination. Exposure to HPV DNA does not always result in a serological response, and vaccination results in higher antibody titers when compared with natural infection. Although geno-prevalence survey is invasive in nature sero-prevalence cannot substitute for geno-prevalence as a measure of circulating virus[8].

Unlike cervical cancer screening, lack of screening tests for anal and oropharyngeal cancers has led to an increase in incidence, particularly among men. Unlike the HPV negative cancers at these sites, HPV positive ones tend to occur in younger age groups (40 to 60 years), present at a later stage leading to higher mortality and cause significant morbidity after therapy, thus impairing the quality of life[2].

The seroconversion rate among women is ≥70% after detectable cervical HPV infection, with antibodies against the major coat protein L1. However among men, this rate is only ≥20-30%. Among girls and women, an effective prophylactic vaccine against HPV 6, 11, 16 and 18 tends to significantly reduce the infection and disease. Even though the antibody response is poor among men for natural infection, the humoral immune response to the virus-like particle vaccine results in 100% seroconversion. Trials with the quadrivalent 'Gardasil' vaccine have shown efficacy against infection and disease, in context to preventing 6/11 genital warts among men who have sex with women and 6/11/16/18 anal intraepithelial neoplasia among men who have sex with men[2].

Some of the determinants which influence compliance among men for vaccination include their attitude towards HPV vaccination and self-efficacy (ability to visit the clinic three times for vaccination). Other socio-psychological determinants such as social influences and specific attitudinal constructs like outcome beliefs and anticipated regret were also significantly associated with an intention for HPV vaccination[8]. As assessed in Marra E. et al.'s study[9],out-of-pocket payment had a significantly negative effect on HPV vaccination intent among male clients of the STI clinic in Amsterdam.

Duncan et al[10] address the gendered influences on the acceptability of HPV vaccination among men. Parents tend to accept the sexuality of adolescent boys to a greater extent when compared with girls and tend to perceive protecting children from harm as their duty. These deliberations reflect on their motivation for HPV vaccination among boys. However, the low awareness about its benefits for boys given the well favored belief that it accords protection to girls, and the stigma in receiving a women's vaccine in conjunction with the lack of Provider recommendation for boys, are the obstacles for HPV vaccine acceptability.

The cost-utility of girls-only HPV vaccination program needs to be input into a model for estimating the quality-adjusted life years (QALYs) gained and the net costs for the health system. Simulation modeling activity for HPV vaccination should include preventing of events such as anogenital warts, cervical intraepithelial neoplasia (CIN) I, II, III, cervical, anal, oropharyngeal, and vulval cancers using the rates of the all-cause mortality, cancer-specific mortality and morbidities[11].

IV. Conclusion

Community based cervical screening programs could detect high grade cervical intra-epithelial neoplasms (CIN), which are the obligate precursors to invasive cancer. The increasing incidence of other HPV-related cancers among both men and women is because these are not amenable to screening. HPV vaccination coverage for males improves population-level control of HPV infection and prevents related diseases such as anogenital warts and anal cancers. Monitoring such a Program faces challenges given the long time-frame for cancer as an outcome and genital specimens among men not being routinely collected for estimating HPV prevalence. Surveillance measures should be directed towards specific targeted

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populations with high risk for HPV infection such as MSM and HIV infected men.

There is a compelling need to quantify the impact of HPV vaccination, and in this regard we need to monitor the cost-effectiveness, conduct operational research, and focus on vaccine development in the future. Unlike the cervical screening programs for females, measuring the effectiveness of a male vaccination program is challenging. Sentinel surveillance programs should compare baseline geno-prevalence with post-vaccine geno-prevalence, and disease end-points need to be monitored through disease registries.

The burden of disease among men needs to be factored in cost-effective models, apart from other inputs such as vaccine price, coverage, and other factors influencing vaccination among males. Gender-neutral vaccination would result in herd immunity, which in-turn could rapidly reduce the viral load in the population. Our failure to implement the male vaccination program will result in a missed public health opportunity.

As HPV sero-prevalence is higher in women than among men and decreases to a greater extent with increasing age respectively, there is a need for different models to understand the whole disease pathway. This in-turn, could channelize various approaches for prevention and treatment. In this regard, male vaccination is a safe and effective option for preventing HPV infection and its consequences.

Since out-of-pocket payment has a negative impact on the intent for HPV vaccination, its inclusion in the Indian Universal immunization program would aid in the higher uptake. Tailored messages need be targeted for Parents, adolescent boys, and Providers to address the multi-level influences. Screening services for non-cervical HPV associated cancers may not be feasible, and its incidence (chiefly among men) is likely to increase.

HPV related cancers are largely preventable, and an aggressive immunization stance and screening schedules are essential in India. Vaccination will reduce transmission rates and increase herd immunity, which will prevent not just cervical cancers but also other HPV-associated malignancies among men and women.

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Effect of Cigarette Smoking on Trace Elements among Residents in Khartoum State, Sudan

By Sara Khalafalla Abdalgader, Salman Taha Ahmed Elmukashfi, Abubakr Hassan Khougali & Rashid Eltayeb Abdalla

Shendi University

Abstract- *Background:* Hundreds of thousands around the world die from a disease caused by smoking cigarettes. A number of researches indicated that smoking has numerous immediate health effects on the respiratory, cardiovascular, gastrointestinal, immune, and metabolic systems. Lung cancer, other cancer, heart disease, and stroke typically do not occur until years after Persons first cigarette. Epidemiological studies have consistently shown an association between the toxin in the cigarette and coronary heart disease (CHD). Cigarette smoking had a dangerous effect on the essential biochemical mechanisms on the human body.

Objective: This research were conducted to determine the direct effects of cigarette smoking on some minerals (Mg^{2+}, Fe^{2+} & Zn^{2+}) and to bridge the gap of information.

Material and Methods: Study design is a Prospective, laboratory-based analytical study, which was used to measure Mg^{2+}, Fe^{2+} & Zn^{2+} in cigarette smokers in the period from March to June 2019. This study was conducted in Khartoum state at Bahry and Alkalakla localities.

Keywords: *cigarette smoking, magnesium, iron, zinc, Sudanese.*

GJMR-F Classification: *NLMC Code: QW 504.5*



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Effect of Cigarette Smoking on Trace Elements among Residents in Khartoum State, Sudan

Sara Khalafalla Abdalgader [α], Salman Taha Ahmed Elmukashfi [σ], Abubakr Hassan Khougali [ρ], & Rashid Eltayeb Abdalla [ω]

Abstract- Background: Hundreds of thousands around the world die from a disease caused by smoking cigarettes. A number of researches indicated that smoking has numerous immediate health effects on the respiratory, cardiovascular, gastrointestinal, immune, and metabolic systems. Lung cancer, other cancer, heart disease, and stroke typically do not occur until years after Persons first cigarette. Epidemiological studies have consistently shown an association between the toxin in the cigarette and coronary heart disease (CHD). Cigarette smoking had a dangerous effect on the essential biochemical mechanisms on the human body.

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Results: The study showed that there was significant decrease in the serum levels of magnesium (mean =15.0 mg/dl) when compared with normal range [17-27 mg/dl]. Also there was significant increase of serum iron (mean=3.1mg/dl) compared with normal range (0.5-1.5mg/dl), and significant decrease in serum level of zinc (mean 0.4mg/dl) compared with normal range (0.5-1.2mg/dl).

The study revealed that age of the smokers, duration of the smoking, marital status, economic, their education, and that the number of cigarettes smoked per day do not affect the serum level of magnesium, iron, and zinc, but in marital status the zinc level which has significance difference.

Conclusion: The study concluded that the serum level of magnesium, iron, and zinc was affected by smoking, the serum level of magnesium and zinc are decrease, and iron increased in smoking. The age, duration, number of cigarettes, social status, economic status, job, and education of smokers do not affect the serum level of magnesium, iron, and zinc.

Keywords: *cigarette smoking, magnesium, iron, zinc, Sudanese.*

Author α ρ: Department of Clinical Chemistry, Faculty of Medical Laboratory Sciences, Shendi University, Sudan.
Author σ: Department of Clinical Chemistry, Medical Laboratory Science Program, Al-Yarmouk College, Sudan.
e-mail: salmantahamls@gmail.com
Author ω: Department of Biochemistry, Faculty of Medicine, Shendi University, Sudan.

I. Introduction

Smoking is a practice in which a substance, most commonly tobacco or cannabis smoke, tasted or inhaled. The most common method of smoking today is through tobacco Use Leads Most Commonly to diseases affecting the heart and lungs, with smoking being a risk factor for heart attacks, strokes, chronic obstructive pulmonary disease (COPD), Emphysema, and cancer. It also causes peripheral vascular disease and hypertension. All developed due to the exposure time and the level of dosage of tobacco [1, 2]. Minerals are essential substances involved as catalysts in most cellular enzymatic reactions and assume a role in metabolism [3].

Fe^{2+}, Zn^{2+}, and Mg^{2+} are examples of these essential minerals. Functions of Fe^{2+} include involvement in energy metabolism, gene regulation, cell growth, and differentiation [4, 5], etc. Mg^{2+} is a critical cation and cofactor in numerous intracellular processes. It is involved in more than 300 essential metabolic reactions, some of which are: energy production, synthesis of essential molecules, structural roles, ion transport across cell membranes, cell signaling, and cell migration [6].

Zn^{2+} is second only to iron in importance as an essential trace element. The biochemical role of Zn^{2+} is its influence on the activity of more than 300 enzymes. Zn^{2+} can be essential for the structure, regulation, and catalytic action of an enzyme. Zn^{2+} occurs in enzymes that realize the synthesis and metabolism of DNA and RNA. Zn^{2+} influences the synthesis and metabolism of proteins, participates in glycolysis and cholesterol metabolism, maintains membrane structures, effects functions of insulin, and affects growth factor [7, 8].

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Literature survey showed that no sufficient work had been conducted to study the effect of cigarette smoking on serum minerals alterations, so this study were carried out to determine the influence of cigarette smoking on serum Fe^{2+}, Zn^{2+}, and Mg^{2+} levels among Sudanese smokers and to determine the relationship between the levels of serum Fe^{2+}, Zn^{2+}, and Mg^{2+} with age, a number of cigarettes per day, and duration of smoking cigarette smoking causes minerals disturbances which lead to serious consequences, smoking leads to tissue hypoxia which leads to inadequate oxygenation of blood circulation that results in erythropoiesis [9, 10] which enhances erythropoiesis and increases red cell mass above normal level [11], this leads to an increase in the number of destroyed red cells in the normal turnover process, which subsequently increases iron overload, which causes hepatocellular damage. Chronic oxidative stress may modulate iron uptake and storage, leading to a self-sustained and ever-increasing spiral of cytotoxic and mutagenic events [12, 13]. Smoking causes Mg^{2+} deficiency due to decreased supply (lesser appetite) and reduced absorption caused by disturbances in the digestive system functions [14]. Nicotine-addicts usually have the risk of depletion/deficiency in nutrients and minerals, including zinc [15]. Minerals disturbances may lead to life-threatening metabolic abnormalities such as coronary heart disease, liver disease, lung infection, kidney failure, and disorders of endocrine system [16].

II. Material and Methods

The study design is a Prospective, laboratory-based analytical study, which was used to measure Mg^{2+}, Fe^{2+} & Zn^{2+} in cigarette smokers in the period from March to June 2019. This study was conducted in Khartoum state at Bahry and Alkalakla localities. They included 30 Blood samples was collected from cigarette smokers, the restriction of the sample size to 30 subjects is due to lack of financial support. Data was collected using a questionnaire. After disinfected by using alcohol, about (2.5ml) of venous blood were collected from each volunteer by venipuncture technique, and were placed in anticoagulant containers, and then centrifuged at (3000 rpm) for (5 minutes) to obtain plasma which kept in Eppendorf tubes for measurements of Fe^{2+}, Zn^{2+}, and Mg^{2+}. And the plasma levels of magnesium, iron, and zinc were determined by the use of the atomic absorption spectrophotometer (OPERATOR'S MANUAL January 2003 VER 3.94 C), and the results was analyzed by SPSS.

a) Ethical Consideration

Permission to carry out the study were taken from health administration, Shendi University committee, and the smokers was informed before the collection of samples, and verbal consent was take.

b) Data Collection

Data were collected using a structural interviewing questionnaire. Which was designed to collect and maintain all valuable information concerned each case examined.

c) Sampling Collection

The forearm was disinfected by using alcohol, about (2.5ml) of venous blood were collected from each volunteer by venipuncture technique, and were placed in anticoagulant containers, and then centrifuged at (3000 rpm) for (5 minutes) to obtain plasma which kept in Eppendorf tubes for measurements of Fe^{2+}, Zn^{2+}, and Mg^{2+}.

d) Quality Control

The precision and accuracy of all methods used in this study were checked at each batch.

e) Data analysis

The data were analyzed by using the application of SPSS (statistical package for social sciences), version 21.

III. Results

The direct effect of cigarette smoking on Mg^{2+} /Fe^{2+} and Zn^{2+} concentration among the Sudanese population In Khartoum State. The result of Fe^{2+} denoted high concentration with mean (3.1mg/L) compared with normal range (0.5-1.5mg/L). But the result of Mg^{2+} indicated mean (15 mg/L), which was low concentration compared with normal range (17-28mg/L), also the result of Zn^{2+} showed low concentration with a mean (0.4 mg/L) compared with normal range 0.5-1.2mg/L.

Table 1: Mean and Std. Deviation of Fe^{2+}, Mg^{2+}, and Zn^{2+}

	Fe^{2+}	Mg^{2+}	Zn^{2+}
Mean	3.1mg/L	15.0mg/L	0.4mg/L
Std. Deviation	0.8	1.7	0.1

Table (1) revealed that high Mg^{2+} and low Fe^{2+} & Zn^{2} levels.

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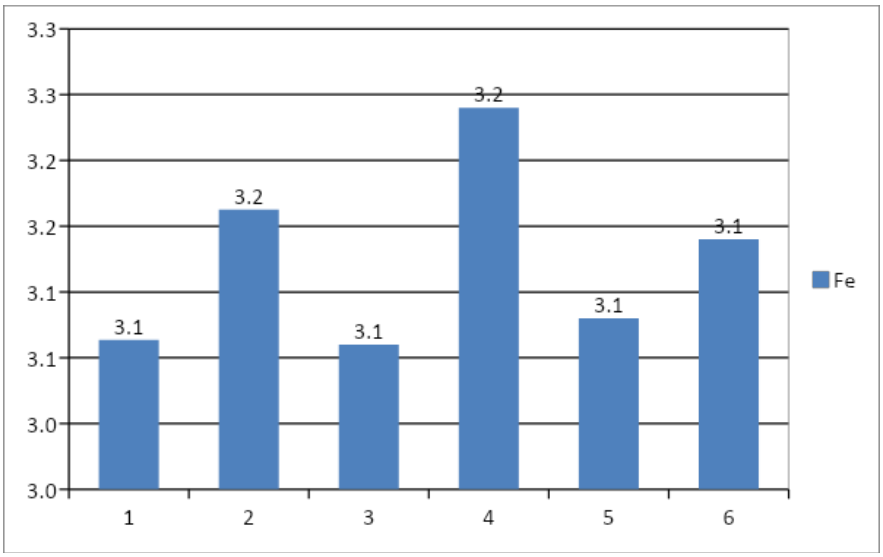


Figure 1: Mean of Fe^{2+}, with age (p-value =0.70), duration (p-value= 0.60) and number of cigarette (p-value =0.80), revealed insignificance difference in compare with normal p-value (0.05)

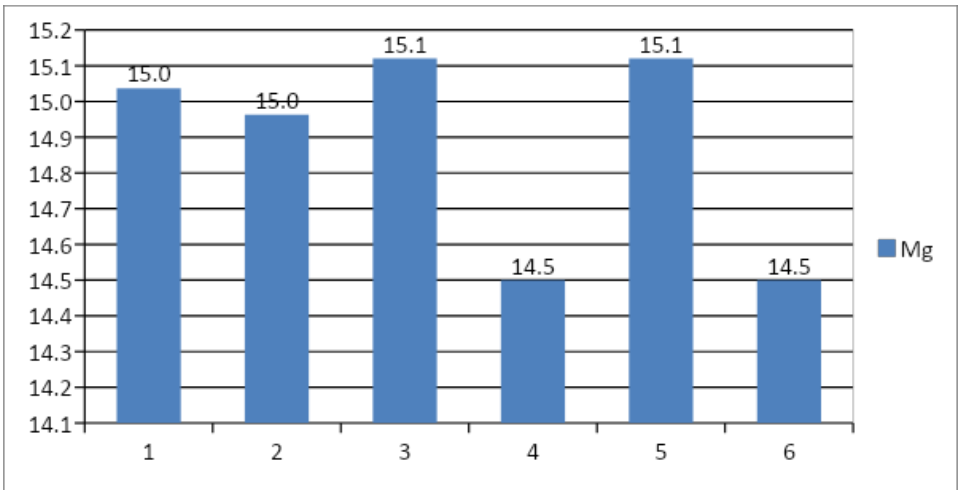


Figure 2: Mean of Mg^{2+} with age (p-value=0.90), duration (p-value=0.40) and number of cigarette (p-value=0.40), revealed insignificance difference in compare with normal p-value (0.05)

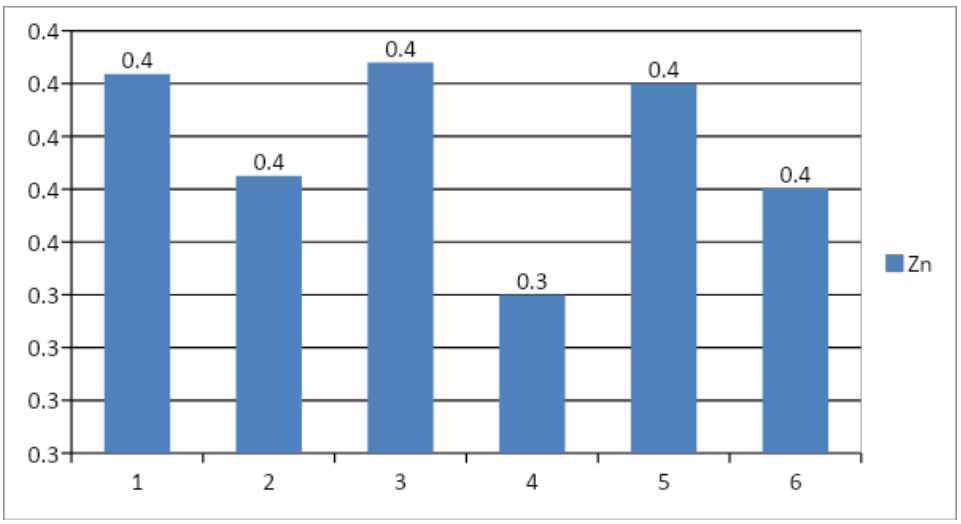


Figure 3: Mean of Zn^{2+} with age (p-value= 0.60), duration (p-value =0.30) and number of cigarette (p-value =0.60), revealed insignificance difference in compare with normal p-value (0.05)

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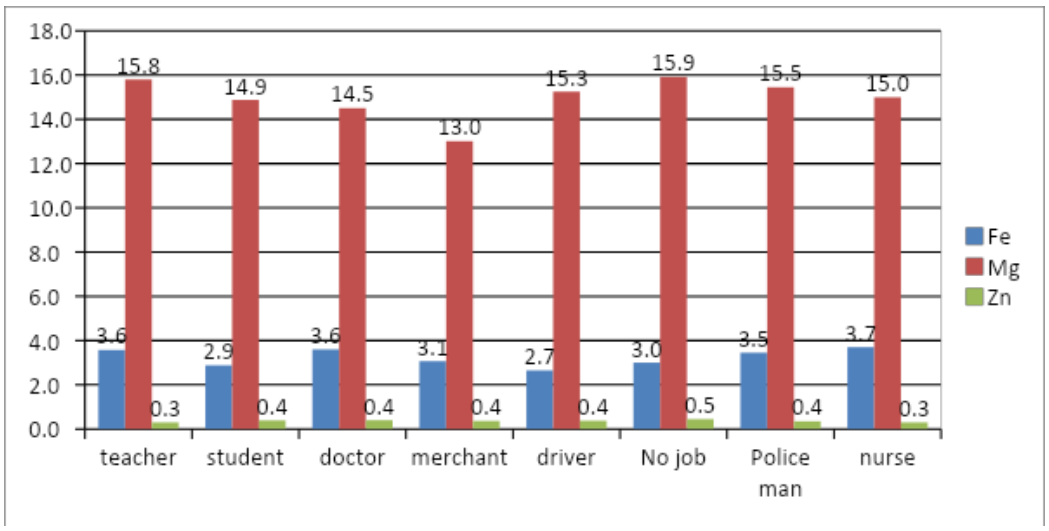


Figure 4: Mean of Fe^{2+} (p-value =0.40), Mg^{2+} (p-value= 0.50), Zn^{2+} (p-value= 0.80) with job, revealed insignificance difference in compare with normal p-value (0.05)

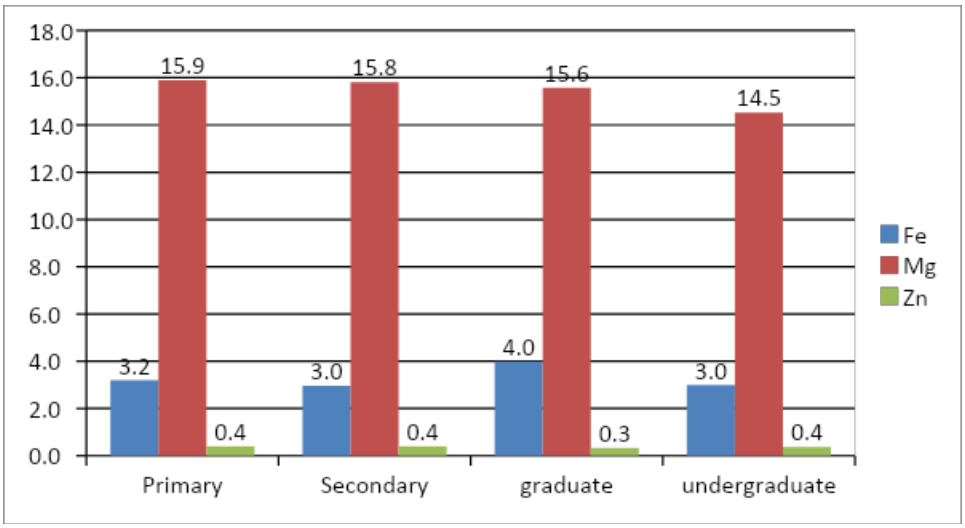


Figure 5: Mean of Fe^{2+} (p-value=0.70). Mg^{2+} (p-value=0.50), and Zn^{2+} (p-value =0.30) with education revealed insignificance difference in compare with normal p-value (0.05)

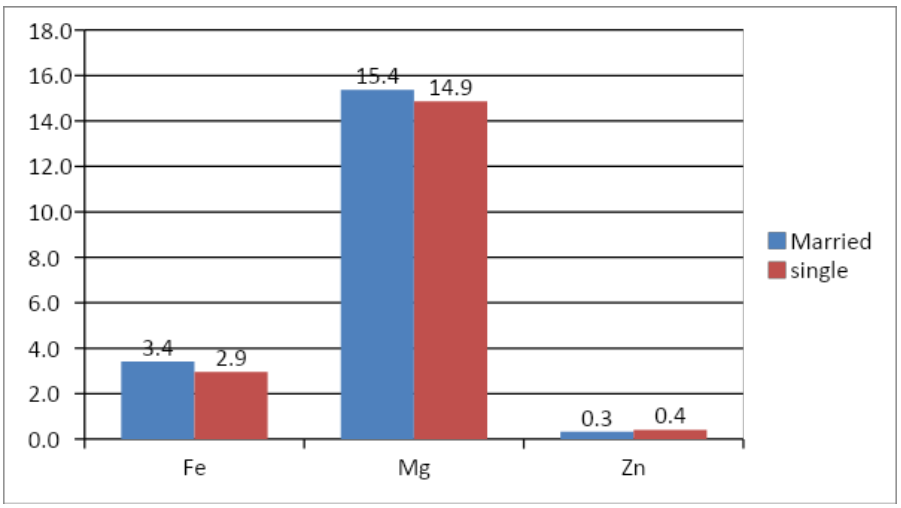


Figure 6: Mean of Fe^{2+}, (p-value= 0.10) Mg^{2+} (p-value=0.40) with marital status revealed insignificant difference. Zn^{2+}show significance difference (p-value=0.02).in compare with normal p-value (0.05)

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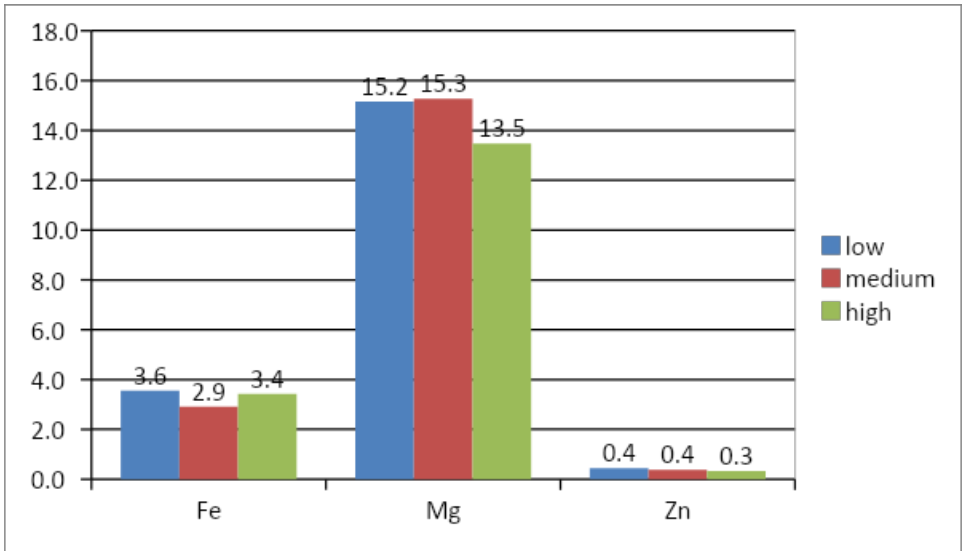


Figure 7: Mean of Fe^{2+}, (p-value=0.50), Mg^{2+} (p-value =0.40) & Zn^{2+} (p-value=0.20) with economic status, revealed insignificant difference in compare with normal p-value (0.05)

IV. Discussion

The present study were carried out to investigate the trace element (magnesium, iron, and zinc) among Sudanese people of cigarette smokers in Bahry and Alkalakla cities/ in Khartoum state in Sudan during the period from March to June 2018; 30 blood samples was collected from Sudanese male smokers.

The present study showed that a high concentration of Fe^{2+} with a mean (3.1mg/dl) compared with the normal range (0.5-1.5mg/dl). The serum level of Mg^{2+} is low mean (15 mg/L), when compared with the normal range (17-28mg/L), and also resulted of Zn^{2+} showed low concentration with a mean (0.4 mg/L) compared with the normal range 0.5-1.2mg/L, this agreed with (Sulafa Ali and Samia Mahdi et al. 2013) who was reported statistically significant changes in the serum levels of Mg^{2+} and Fe^{2+} between test and control group, the level of Mg^{2+} was high and was Fe^{2+} low in smokers compared to nonsmokers.

The findings of this study also prevailed a non-significant difference between the serum levels of Mg^{2+}, Fe^{2+}, and Zn^{2+} of the test group according to the duration (P-value = 0.4/0.6/0.3), and to the age (P-value = 0.9/0.7/0.6) respectively. The number of cigarettes smoked per day have no effect on the level of serum Mg^{2+}, Fe^{2+} and Zn^{2+} (P-value =0.4/0.8/0.6), this agreed with (Sulafa Ali and Samia Mahdi et al. 2013) who was reported that there was statistically no significant influence of age, duration and number of cigarette per day on Mg^{2+}, Fe^{2+} levels, when compared with serum Mg^{2+}, Fe^{2+} with age, duration, and number of cigarette per day with a study group.

The results of the recent study presented the non-significant difference between the serum levels of, Mg^{2+}, Fe^{2+} and Zn^{2+} of the test group according to the job (P-value =0.5/0.4/0.8) respectively, and non-significance difference to the education (P 0.5/0.7/0.3) subsequently, also to social status (p 0.4/0.1) in which Zn^{2+} has a significant difference with (p 0.02) and showed a non-significant difference between the serum level of Mg^{2+}, Fe^{2+}, and Zn^{2+} according to economic status (p 0.4/0.5/0.2) respectively.

V. Conclusion

From this study can be concluded that the serum level of magnesium iron and zinc was affected by smoking, the serum level of magnesium and zinc are decrease, and iron increased in smoking. The age, duration, number of cigarettes, social status, economic status, job, and education of smokers do not affect the serum level of magnesium, iron, and zinc.

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Simulation model for breast cancer management in India

By Vinod K Ramani & Radheshyam Naik

Abstract- The natural history of cancer in a patient can be simulated in a flexible broad-based disease model. Such models describe events and outcomes at the person level, the results of which can be aggregated to estimate the population morbidity. With minimal assumptions regarding the natural history of disease, models could project outcomes of interventions for cancer screening and treatment.

The same could be used for testing conventional treatment protocols and assess the reasons for failure of a particular strategy. Leads from the analysis can be utilized for proposing improvisations for the treatment protocol such as combinatorial strategies, which enables better suppression of tumor despite the resistant cells.

This commentary describes relevant concepts associated with simulation modeling of tumor growth and tumor-host interactions, and summarizes some of the prominent approaches.

Keywords: *breast cancer, simulation model, estimation.*

GJMR-F Classification: *NLMC Code: QZ 20.5*

SIMULATIONMODELFORBREASTCANCERMANAGEMENTININDIA

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Simulation model for breast cancer management in India

Vinod K Ramani [α] & Radheshyam Naik [σ]

Abstract- The natural history of cancer in a patient can be simulated in a flexible broad-based disease model. Such models describe events and outcomes at the person level, the results of which can be aggregated to estimate the population morbidity. With minimal assumptions regarding the natural history of disease, models could project outcomes of interventions for cancer screening and treatment.

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This commentary describes relevant concepts associated with simulation modeling of tumor growth and tumor-host interactions, and summarizes some of the prominent approaches.

Keywords: breast cancer, simulation model, estimation.

I. Introduction

Mathematical models could potentially simulate the dynamic nature of biological processes. These models are the product of research in the interface between mathematics and biology. Such quantitative approaches benefit research in the field of cancer. Computational techniques should be applied to various aspects of tumor growth with an intent to understand the response of cancer cells to therapeutic interventions. Models could tally outcomes across individuals and gain insight into the underlying dynamics in risk factors and cancer interventions.

The life history of an individual might include events such as his current age, accumulation of risk factors for cancer since birth, age at which preclinical cancer develops, age's at which cancer landmarks progress and their metastatic spread, diagnosis of cancer (through screening or symptomatic presentation), treatment of cancer and death from cancer or other co-incident causes. The onset and progression rates of adenomas could be modified by risk factors, screening could detect pre-cancerous lesions and pre-clinical cancer, and treatment can alter post-diagnosis survival rates.

Models use indirect evidence for making assumptions about the process of carcinogenesis based on data from biopsy studies, prevention, screening and treatment trials, research studies, cancer registries and other types of studies. Such models account that tumor progression is a statistically distributed characteristic of cells influencing their global behavior. The parameters of the model are estimated using empirical data inputs initially and later through statistical algorithms. Such parameters will be predicted initially using observed data on cancer outcomes, and subsequently the impact of interventions could be studied. Outputs can include the full range of benefits and costs of the interventions.

In-silico trials will facilitate optimization of patient care by predicting patient-specific responses to various treatment combinations or dosage schedules.

The National Cancer Institute's (NCI) Cancer Intervention and Surveillance modeling network (CISNET)[1] model relies on assumptions regarding the natural history of the disease and is utilized for recommending mammography as a screening method in the USA. The research concept in this short report is to model the adenoma-carcinoma natural history sequence of breast cancer (BC) suitable to the Indian context.

II. Content

65% of BC related deaths are estimated to occur in low and middle income (LMIC) countries, by 2025[1]. Simulation models of BC progression, detection, and outcome usually include the natural history of the disease. Few other transparent models focus on observable events in disease progression, thus requiring fewer inputs from users and rendering portability across applications.

CISNET[2] Breast working group conducts collaborative modeling research to address critical early detection and clinical management issues in breast cancer. The aim is to evaluate improvised screening strategies such as using polygenic risk and emerging imaging technologies for their impact on the population. It also evaluates clinical management strategies with targeted treatment paradigms in the adjuvant setting and at recurrence. Such modeling leads to synthesizing research information for estimating future mortality trends in the United States. The common inputs are from observational studies from sources such as: National health interview survey (NHIS), Surveillance, Epidemiology and End Results (SEER), Breast cancer surveillance consortium (BCSC) and National center for health statistics (NCHS).

Author α σ: Preventive Oncology unit', Healthcare Global Enterprise Ltd., KR Road, Bangalore. e-mails: drvinod.r@hcgel.com, radheshyam_n@yahoo.com

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Guidelines should enable good practices in modeling, which includes designing the approach, selecting a technique, implementing and validating the model, parameterizing the inputs and assessing uncertainty, and using the resulting tool to enable decision making[3].

We can summarize the six components of a model[3] as:

1. Conceptualization of model,
2. Estimation of model parameters and handling uncertainty,
3. Validation of models and concerns for transparency,
4. State transition modeling,
5. Discrete event simulation,
6. Dynamic transmission model,

We can consider several types of models[3] for problems with decision making:

i. If the conceptualization involves representing the disease or treatment process as a series of health states, 'the State transition model' could be appropriate.
ii. When disease or treatment process includes interaction between individuals, the modeling methods should evaluate those interactions ('Dynamic transmission models'; 'Discrete event simulations'; 'Agent-based models'),
iii. When individual pathways through the model are influenced by multiple characteristics of the entity, a 'Discrete event simulation' is recommended,
iv. 'Dynamic transmission model' could evaluate an infectious disease intervention which can impact disease transmission in the population, and the frequency distribution of agent strains is altered (e.g. genotypes or serotypes),
v. Uncertainty estimation can be either deterministic or probabilistic. The link to the underlying evidence should be clear whether employing deterministic sensitivity analysis methods (point estimate and range) or probabilistic sensitivity analysis (parametrized distribution),
vi. Documentation of the model will enable evaluation and potential reproduction. Such process includes terms such as type of model and intended applications, funding sources, the structure of model, inputs, outputs, other components that determine model's function and their relationships, data sources, validation methods, results and limitations.

We can capture the dynamics of sub-cellular interaction of a tumor in the model. We need to develop simulation tools for visualizing the same, with the possibility of interventions to control the action of tumor cells. Treatment as an outcome is defined either as induction of cell death among proliferating cancer cells or reduction of tumor support such as by decreasing the carrying capacity. We can define the strategies for tumor treatment in a differential equation model (DEM)[4], which captures the tumor cell differentiation (proliferation/death) based on the considered time difference.

The total number of cancer cells in the patient's body is not the only determinant of the health outcome. Among cancer patients, the local invasion of tissues and metastasis to distant sites of the body are the main causes of death as an outcome. The DEM does not capture such spatial processes, which however can be simulated in a partial differential equation model[4] (PEM).

PEM models could also examine the interplay between cancer cells, degrading enzymes, and the tissue, thus further improvising equations towards a reaction-diffusion-taxis model. Such models explain 'haptotaxis'; which describes determinants of cancer cell migration, such as extracellular matrix density and gradients of adhesive molecules in the matrix[4].

The Surgeons tend to visualize the visible margin of the cancerous tissue, however individual cancer cells have the potential to migrate beyond the same. Discrete models of tumor growth could explore the context of stochastic events and their probability of invasion[4].

The immune system recognizes the tumor cells, and tries to compete and deplete them. When the tumor cells win, they start condensing into a solid form. Such tumor cells diffuse signals to the outer environment, which in-turn are the means of communication for cellular interaction. The sequential evolution of steps in such a system could be summarized as[5]:

a) changes in the genetic make-up, cell cycle distortions and lack of apoptosis,
b) regulation of cell activities (both immune and environmental) through the emission of cytokine signals,
c) tumor cell condensation into solid forms, angiogenesis, and diffusion of macroscopes,
d) dissemination of metastatic cells,

In order to develop a valid model in India, we need to utilize the existing data which represents the epidemiology of BC. Contextually, clinical breast examination (CBE) has the potential to improve the stage at diagnosis as the same is delayed to Stage 3 & 4[6] in India.

The Microsimulation Screening ANalysis (MISCAN) model used in Koning[6] et al.'s study estimates the effectiveness and cost-effectiveness of CBE and mammography in India. This model simulates and compares individual life histories in a population, whether a cancer screening program is present or absent. The model incorporates demographic and epidemiological characteristics of the population to provide reliable predictions of BC morbidity.

In Western countries, the preferred method of screening is mammography. However, such facilities

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may not be cost-effective, and its availability in rural India is a concern. The peak incidence of BC in India is among pre-menopausal women who are relatively young for using mammography as a screening tool. Hence, the analysis in the model[5] includes screening with CBE among varying eligible age groups and screening intervals.

The differences in natural history of breast cancer in India when compared with other developed countries, includes the fact that beneficiaries are not subjected to effective screening procedures regularly, and access to care is delayed due to late presentation of symptoms. The assumption of the model[5] is that when an early stage is detected, it leads to improved survival of the patient.

This Model[6] finds that given the young demographics of the Indian population, it is cost-effective to screen the 40 to 60 years age group, when compared with 50 to 70 years group. The younger age group strata chosen for screening in this model, is influenced by determinants such as low life expectancy (62 years) and peak incidence among younger ages. The frequency of screening could be either every-5 year intervals or biennial or annual CBEs, all of which considerably reduce the mortality and increase the gain in the number of life years.

The concept that screening service is a privilege that needs to be sought, is reinforced by the estimates of the screening costs for CBE and mammography in the model[6]. These were 10% and 28% respectively, of the routine BC management strategies. The model[6] shows that the cost-effectiveness ratio gained is Int $1341 per life-year, which is 50% of the GNI per capita. Thus screening with CBE is a very cost-effective measure in India, as the WHO commission on Macroeconomics and health proposes a guideline of cost-effectiveness ratio being less than the per-capita GDP[6].

The microenvironment of a tumor comprises of the immune cells and cytokines, which act as the 'soil' nourishing the development of the tumor. The formation of tumor triggers the production of cytokines from the immune system. The core of tumor comprises of the following cells[7],

a) Cancer stem cells (S),
b) Cancer cells (C),
c) Resistant stem cells (SR),
d) Resistant cancer cells (CR),

Differentiation of S leads to the evolution of heterogenous sub-population of tumor cells, which is the 'seed' component. The interactions between the soil and seed determine the development of drug resistance and treatment failure in cancers.

The model can virtually depict the seed-soil interaction in the development of a tumor. 'S' numbers are low in the initial stages of tumor and due to their slow replication rate are resistant to radiotherapy and are partially sensitive to chemotherapy. The models can thus analyze treatment failures due to conventional chemotherapy and radiotherapy, which probably could be due to SR and CR within the tumor. Since S have an immunosuppressive effect on the soil, treatment protocols should additionally include immunotherapy. Models could simulate the temporal evolution dynamics of such tumor-immune interaction.

The efficacy of the treatment protocol is an outcome measure in this model[7]. This concept should be defined in terms of reduction in tumor size, and recovery from immune-suppression induced by the tumor. The parameters which should be included are the fold change of tumor mass and the TH1/TH2 (T helper cells) ratio. Mathematical strategies could be combined in the model to encompass the effect of molecular events (viz.. angiogenesis), chemokines and exosomes as mediators of cellular interactions, and the influence of miRNA in the pathways. Such models could enable optimizing drug dosage and advanced protocols for cancer treatment.

Advanced models could further shed light on cancer prognosis through studying the role of M2 macrophages in regulating tumor proliferation through feedback loops, differentiation of S from symmetric to asymmetric pattern rendering refractoriness for treatment, IL10 (Interleukin) feedback influence on TH1/TH2 ratio, and TH1 derived IFN-v (Interferon) differential elimination of S.

It is imperative to develop modeling tools because the impact of indicators on benefits (eg.: mortality reduction) and harm (e.g.: over-diagnosis) cannot be observed directly. It is not possible to immediately measure the outcomes among population, who either did or did not undergo screening procedures. Changes in screening programs are inevitable, and they tend to accumulate over time. The impact of one change can be entangled with another, and it is difficult to assess them discretely.

Randomized controlled trials (RCT) usually provide the required data to build the models. The results of RCT are from diverse centers, and usually depict post-hoc meta-analysis of the research studies. However, comparative modeling could facilitate the synthesis of evidence and relevant comparisons.

III. Conclusion

This commentary builds on existing evidence regarding the development of quantitative models and their comparison with experimental data. Models combine clinical and epidemiologic risk factors with new biologic and genetic data for accurately assessing the risk of cancer. They can function as virtual laboratories conducting synthetic experiments such as comparison of various interventions (in varied conditions) and

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estimating their population-level impact. Valid models enable inference on the natural history of cancer from partially observed processes, including the impact of interventions (prevention, screening, treatment). Such models find utility as risk assessment tools during screening activities, which in-turn could enable devising either targeted high risk or population-based interventions. Novel models which focus on complex biological processes such as tumor-immune interactions and the effect of microenvironment, will enable improvising cancer treatment protocols. Model simplicity ensures transparency, description, and ease of validation. Simultaneously, models should preserve face validity for clinical experts. Such models provide a framework to support evidence-based policy decisions in India.

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Human Papilloma Virus: An Oncogene

By Digjeet Kaur

Abstract- Human papilloma virus (HPV) is an extremely common group of viruses universally out of which 14 are, cancer causing. HPV is transferred from one person to another during direct skin to skin contact or via sexual transmission being the most common mode. This virus commonly causes warts. It can also infect the normal cells, transforming them into precancerous lesions or various types of cancer. In this article, we will discuss about HPV, its association with various types of cancer, treatment protocol and HPV vaccine.

Keywords: human papilloma virus, cancer epidemic, HPV vaccine, treatment of HPV infection.

GJMR-F Classification: NLMC Code: QW 165.5.P2



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Keywords: human papilloma virus, cancer epidemic, HPV vaccine, treatment of HPV infection.

I. Introduction

90% of HPV infections are symptomless, and resolve within a span of two years approximately[1]. If HPV infection still persists, it results in either warts or precancerous lesions. These lesions, depending on the site affected, increase the risk of cancer of the cervix, vulva, vagina, penis, anus, mouth, or throat. Majorly cervical cancer is due to HPV; mainly two types, HPV16 and HPV18 (most common oncogenic virus) [1]. HPV6 and HPV11 leads to genital warts and laryngeal papillomatosis[1].Uterine cervical cancer, being the third most common cancer in women all around the world and the second most common cancer in Indian women, is caused by infection via these oncogenes[2]. HPV is associated with more than 90% of anal and cervical cancers, about 70% of vaginal and vulvar cancers, 70% of oropharyngeal cancers and more than 60% of penile cancers[2].

HPV has an infectious intra-epithelial cycle and infecting, both cutaneous and mucosal squamous epithelium[2]. The HPVs belongs to the family Papillomaviridae that consists of small, non-enveloped deoxyribonucleic acid (DNA) viruses. The genome of HPV consists of double-stranded cDNA and encodes DNA sequences for six early (E1, E2, E4, E5, E6, and E7) and two late proteins (L1 and L2).[2] The E1 and E2 proteins are the early viral proteins required for replication and translation of virus, E2 also regulates the expression of E6 and E7, E4, and E5 helps in viral assembly and growth stimulation, whereas late proteins L1 and L2 forms minor and major capsid proteins.[2]These viruses can be classified into high risk and low-risk HPV types depending on their oncogenic potential. HPV 16 has the highest ability to cause cancer.

The HPV infects squamous epithelial cells, which has proliferating capacity, and get to the basal cell during trauma. In these cells, HPV causes the expression of viral genes that helps in the viral replication. The interaction of HPV with the host cells occurs via surface receptors such as heparin sulphate proteoglycans and alpha 6 integrin. The early proteins E1 and E2 are required for the initiation of replication. The protein E2, being the transcriptional repressor of E6 and E7, controls the expression of E6 and E7. The mode of replication is the rolling circle mechanism during which the virus gets integrated into the human genome. The integration disturbs the E2 gene thereby resulting in a higher expression of E6 and E7 oncoproteins and leading to cell transformation. After the viral replication, the L1 and L2 gene products form the virus capsid and the mature virus is produced. Finally, the virus is released with the help of E4 protein.

II. Associated Cancer with HPV

1. Cervical cancer

Main type of cancer caused by HPV infection. But, cervical cancer is quite uncommon. In 2018, approximately 311 000 women died from cervical cancer; more than 85% of these deaths occurring in low- and middle-income countries.[3]Although most HPV infections clear up on their own and most pre-cancerous lesions resolve spontaneously, there is a risk for all women that HPV infection may become chronic and pre-cancerous lesions leading to cervical cancer in certain years.HPV infection can spread from a mother to baby during pregnancy.

It takes period of 15 - 20 years for cervical cancer to develop in a healthy women. It can take only 5 to 10 years in women with weakened immune systems (such as those with untreated HIV). Women with HIV/AIDS, are at a 22-fold increased risk of cervical cancer. Because the transformation of normal cervical cells into cancerous ones is slow, cancer occurs in people having been infected with HPV for a long time, usually over a decade or more (persistent infection).

2. Anal cancer

Sexually transmitted HPVs are the reason for anal cancers. The risk for anal cancer is 17 to 31 times higher in HIV-positive individuals which also had HPV infection.

3. Penile cancer

Approximately 50% of penile cancers are associated with HPV. HPV16 being the most common type. The risk of penile cancer increases 2- to 3-fold for patients infected with HIV and HPV.

Author: e-mail: digjeetkaurmonga@gmail.com

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4. Head & neck cancer

Oral infection with high-risk carcinogenic HPV (most commonly HPV 16) is associated with head and neck cancers. This association has no relation with tobacco and alcohol use. Sexually transmitted HPV is the reason for 25% of cancers of the mouth and upper throat (the oropharynx) universally.

This type of cancer is more commonly seen in men than in women.

5. Lung cancer

Certain studies links HPV to benign and malignant tumours of the respiratory tract. People with lung cancer were more likely to have several high-risk forms of HPV antibodies compared to those who did not have lung cancer.

6. Skin cancer

In very rare cases, HPV may cause epidermodysplasia verruciformis (EV) in individuals with a weakened immune system. The virus, unchecked by the immune system, causes the overproduction of keratin by skin cells, resulting in lesions resembling warts or cutaneous horns which could transform into skin cancer. The types of HPV is associated with it are HPV5, HPV8, and HPV14.

7. Head and neck cancer

Due to a remarkable shift in the epidemiology of head and neck cancer in this country there has been drastic increase in its cases. While exposure to mutagens like tobacco and alcohol remains the most common risk factor for squamous cell cancers, a rapidly expanding subset of head and neck cancers are acquired through human papillomavirus (HPV) infection. Most head and neck cancers caused by HPV form in the part of the throat that includes the base of the tongue and the tonsils. Symptoms of oropharyngeal cancer includes a long-lasting sore throat, earaches, hoarseness, swollen lymph nodes, pain when swallowing, and unexplained weight loss. Some people have no symptoms.

The vaccine protects against the types of HPV that can cause oropharyngeal cancers, so it may also prevent oropharyngeal cancers.

Other infections caused by HPV[4]

Genital warts: These ate flat lesions, small cauliflower-like bumps or tiny stem like protrusions. In women, genital warts appear mostly on the vulva but can also occur near the anus, on the cervix or in the vagina. In men, genital warts appear on the penis and scrotum or around the anus. Genital warts rarely cause discomfort or pain, though they may itch or feel tender.

Common warts: Common warts appear as rough, raised bumps and usually occur on the hands and fingers. They can be painful.

Plantar warts: Plantar warts are hard grainy growths appearing on the heels or balls of your feet. They may cause discomfort.

Flat warts: Flat warts are flat-topped, slightly raised lesions. They can appear anywhere, but children usually get them on the face and men tend to get them in the beard area. Women tend to get them on the legs.

III. HPV Vaccine[3]

At present, there are 3 vaccines that protect against both HPV 16 and 18, which are the reason for 70% of cervical cancers. The third vaccine protects against other three HPV types, which are responsible for 20% of cervical cancers. Given that the vaccines which are only protecting against HPV 16 and 18 also have some cross-protection against other less common HPV types which cause cervical cancer, WHO considers the three vaccines equally protective against cervical cancer. Two of the vaccines also protect against HPV types 6 and 11, which cause anogenital warts.HPV vaccines work best if administered prior to exposure to HPV.

IV. Treatment Protocol[5]

There is no cure for HPV, but doctors can often treat the warts and precancerous lesions caused by the infection through:

- A loop electrosurgical excision procedure(electric current to remove abnormal tissue)
- Freezing techniques
- Surgery
- Medicated creams for direct application to the skin for genital warts.

Treatment depends on the stage of the disease and options include surgery, radiotherapy and chemotherapy. Palliative care is also an essential for cancer management to relive pain and suffering.

Diagnosis of cervical cancer must be made by histopathologic examination. Staging is done based on tumour size and spread of the disease to distant organs.

V. Conclusion

With the increasing cases of cancer, especially in women, awareness should be created worldwide focussing on prevention rather than cure. The discovery of HPV vaccine prevents infection by certain strains of HPV. But for the vaccine to be effective, it should be given before the activation of the respective virus. Hence, prevention is better than cure. Measures should be taken to lower the chances of being getting infected. An HPV test combined with PAP test can be used as preventive measure by women older than 30 years.

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Tips for writing a good quality Medical Research Paper

1. Choosing the topic: In most cases, the topic is selected by the interests of the author, but it can also be suggested by the guides. You can have several topics, and then judge which you are most comfortable with. This may be done by asking several questions of yourself, like "Will I be able to carry out a search in this area? Will I find all necessary resources to accomplish the search? Will I be able to find all information in this field area?" If the answer to this type of question is "yes," then you ought to choose that topic. In most cases, you may have to conduct surveys and visit several places. Also, you might have to do a lot of work to find all the rises and falls of the various data on that subject. Sometimes, detailed information plays a vital role, instead of short information. Evaluators are human: The first thing to remember is that evaluators are also human beings. They are not only meant for rejecting a paper. They are here to evaluate your paper. So present your best aspect.

2. Think like evaluators: If you are in confusion or getting demotivated because your paper may not be accepted by the evaluators, then think, and try to evaluate your paper like an evaluator. Try to understand what an evaluator wants in your research paper, and you will automatically have your answer. Make blueprints of paper: The outline is the plan or framework that will help you to arrange your thoughts. It will make your paper logical. But remember that all points of your outline must be related to the topic you have chosen.

3. Ask your guides: If you are having any difficulty with your research, then do not hesitate to share your difficulty with your guide (if you have one). They will surely help you out and resolve your doubts. If you can't clarify what exactly you require for your work, then ask your supervisor to help you with an alternative. He or she might also provide you with a list of essential readings.

4. Use of computer is recommended: As you are doing research in the field of medical research then this point is quite obvious. Use right software: Always use good quality software packages. If you are not capable of judging good software, then you can lose the quality of your paper unknowingly. There are various programs available to help you which you can get through the internet.

5. Use the internet for help: An excellent start for your paper is using Google. It is a wondrous search engine, where you can have your doubts resolved. You may also read some answers for the frequent question of how to write your research paper or find a model research paper. You can download books from the internet. If you have all the required books, place importance on reading, selecting, and analyzing the specified information. Then sketch out your research paper. Use big pictures: You may use encyclopedias like Wikipedia to get pictures with the best resolution. At Global Journals, you should strictly follow here.



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6. Bookmarks are useful: When you read any book or magazine, you generally use bookmarks, right? It is a good habit which helps to not lose your continuity. You should always use bookmarks while searching on the internet also, which will make your search easier.

7. Revise what you wrote: When you write anything, always read it, summarize it, and then finalize it.

8. Make every effort: Make every effort to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in the introduction—what is the need for a particular research paper. Polish your work with good writing skills and always give an evaluator what he wants. Make backups: When you are going to do any important thing like making a research paper, you should always have backup copies of it either on your computer or on paper. This protects you from losing any portion of your important data.

9. Produce good diagrams of your own: Always try to include good charts or diagrams in your paper to improve quality. Using several unnecessary diagrams will degrade the quality of your paper by creating a hodgepodge. So always try to include diagrams which were made by you to improve the readability of your paper. Use of direct quotes: When you do research relevant to literature, history, or current affairs, then use of quotes becomes essential, but if the study is relevant to science, use of quotes is not preferable.

10. Use proper verb tense: Use proper verb tenses in your paper. Use past tense to present those events that have happened. Use present tense to indicate events that are going on. Use future tense to indicate events that will happen in the future. Use of wrong tenses will confuse the evaluator. Avoid sentences that are incomplete.

11. Pick a good study spot: Always try to pick a spot for your research which is quiet. Not every spot is good for studying.

12. Know what you know: Always try to know what you know by making objectives, otherwise you will be confused and unable to achieve your target.

13. Use good grammar: Always use good grammar and words that will have a positive impact on the evaluator; use of good vocabulary does not mean using tough words which the evaluator has to find in a dictionary. Do not fragment sentences. Eliminate one-word sentences. Do not ever use a big word when a smaller one would suffice.

Verbs have to be in agreement with their subjects. In a research paper, do not start sentences with conjunctions or finish them with prepositions. When writing formally, it is advisable to never split an infinitive because someone will (wrongly) complain. Avoid clichés like a disease. Always shun irritating alliteration. Use language which is simple and straightforward. Put together a neat summary.

14. Arrangement of information: Each section of the main body should start with an opening sentence, and there should be a changeover at the end of the section. Give only valid and powerful arguments for your topic. You may also maintain your arguments with records.

15. Never start at the last minute: Always allow enough time for research work. Leaving everything to the last minute will degrade your paper and spoil your work.

16. Multitasking in research is not good: Doing several things at the same time is a bad habit in the case of research activity. Research is an area where everything has a particular time slot. Divide your research work into parts, and do a particular part in a particular time slot.

17. Never copy others' work: Never copy others' work and give it your name because if the evaluator has seen it anywhere, you will be in trouble. Take proper rest and food: No matter how many hours you spend on your research activity, if you are not taking care of your health, then all your efforts will have been in vain. For quality research, take proper rest and food.

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

19. Refresh your mind after intervals: Try to give your mind a rest by listening to soft music or sleeping in intervals. This will also improve your memory. Acquire colleagues: Always try to acquire colleagues. No matter how sharp you are, if you acquire colleagues, they can give you ideas which will be helpful to your research.

20. Think technically: Always think technically. If anything happens, search for its reasons, benefits, and demerits. Think and then print: When you go to print your paper, check that tables are not split, headings are not detached from their descriptions, and page sequence is maintained.

21. Adding unnecessary information: Do not add unnecessary information like "I have used MS Excel to draw graphs." Irrelevant and inappropriate material is superfluous. Foreign terminology and phrases are not apropos. One should never take a broad view. Analogy is like feathers on a snake. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Never oversimplify: When adding material to your research paper, never go for oversimplification; this will definitely irritate the evaluator. Be specific. Never use rhythmic redundancies. Contractions shouldn't be used in a research paper. Comparisons are as terrible as clichés. Give up ampersands, abbreviations, and so on. Remove commas that are not necessary. Parenthetical words should be between brackets or commas. Understatement is always the best way to put forward earth-shaking thoughts. Give a detailed literary review.

22. Report concluded results: Use concluded results. From raw data, filter the results, and then conclude your studies based on measurements and observations taken. An appropriate number of decimal places should be used. Parenthetical remarks are prohibited here. Proofread carefully at the final stage. At the end, give an outline to your arguments. Spot perspectives of further study of the subject. Justify your conclusion at the bottom sufficiently, which will probably include examples.

23. Upon 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 for 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 of your research.

Informal Guidelines of Research Paper Writing

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 criteria peer reviewers will use for grading the final paper.

Final points:

One purpose of organizing a research paper is to let people interpret your efforts selectively. The journal requires the following sections, submitted in the order listed, with each section starting on a new page:

The introduction: This will be compiled from reference matter and reflect the design processes or outline of basis that directed you to make a study. As you carry out the process of study, the method and process section will be constructed like that. The results segment will show related statistics in nearly sequential order and direct reviewers to similar intellectual paths throughout the data that you gathered to carry out your study.

The discussion section:

This will provide understanding of the data and projections as to the implications of the results. The use of good quality references throughout the paper will give the effort trustworthiness by representing an alertness to prior workings.

Writing a research paper is not an easy job, no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record-keeping are the only means to make straightforward progression.

General style:

Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

To make a paper clear: Adhere to recommended page limits.



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Mistakes to avoid:

- Insertion of a title at the foot of a page with subsequent text on the next page.
- Separating a table, chart, or figure—confine each to a single page.
- Submitting a manuscript with pages out of sequence.
- In every section of your document, use standard writing style, including articles ("a" and "the").
- Keep paying attention to the topic of the paper.
- Use paragraphs to split each significant point (excluding the abstract).
- Align the primary line of each section.
- Present your points in sound order.
- Use present tense to report well-accepted matters.
- Use past tense to describe specific results.
- Do not use familiar wording; don't address the reviewer directly. Don't use slang or superlatives.
- Avoid use of extra pictures—include only those figures essential to presenting results.

Title page:

Choose a revealing title. It should be short and include the name(s) and address(es) of all authors. It should not have acronyms or abbreviations or exceed two printed lines.

Abstract: This summary should be two hundred words or less. It should clearly and briefly explain the key findings reported in the manuscript and must have precise statistics. It should not have acronyms or abbreviations. It should be logical in itself. Do not cite references at this point.

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 approaches to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Use comprehensive sentences, and do not sacrifice readability for brevity; you can maintain it succinctly by phrasing sentences so that they provide more than a lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study with the subsequent elements in any summary. Try to limit the initial two items to no more than one line each.

Reason for writing the article—theory, overall issue, purpose.

- Fundamental goal.
- To-the-point depiction of the research.
- Consequences, including definite statistics—if the consequences are quantitative in nature, account for this; results of any numerical analysis should be reported. Significant conclusions or questions that emerge from the research.

Approach:

- Single section and succinct.
- An outline of the job done is always written in past tense.
- Concentrate on shortening results—limit background information to a verdict or two.
- Exact spelling, clarity 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.

Introduction:

The introduction should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable of comprehending and calculating the purpose of your study without having to refer to other works. The basis for the study should be offered. Give the most important references, but avoid making a comprehensive appraisal of the topic. Describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will give no attention to your results. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here.

The following approach can create a valuable beginning:

- Explain the value (significance) of the study.
- Defend the model—why did you employ this particular system or method? What is its compensation? Remark upon its appropriateness from an abstract point of view as well as pointing out sensible reasons for using it.
- Present a justification. State your particular theory(-ies) or aim(s), and describe the logic that led you to choose them.
- Briefly explain the study's tentative purpose and how it meets the declared objectives.

Approach:

Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done. Sort out your thoughts; manufacture one key point for every section. If you make the four points listed above, you will need at least four paragraphs. Present surrounding information only when it is necessary to support a situation. The reviewer does not desire to read everything you know about a topic. Shape the theory specifically—do not take a broad view.

As always, give awareness to spelling, simplicity, and correctness of sentences and phrases.

Procedures (methods and materials):

This part is supposed to be the easiest to carve if you have good skills. A soundly written procedures segment allows a capable scientist to replicate your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order, but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt to give the least amount of information that would permit another capable scientist to replicate your outcome, but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section.

When a technique is used that has been well-described in another section, mention the specific item describing the way, but draw the basic principle while stating the situation. The purpose is to show all particular resources and broad procedures so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step-by-step report of the whole thing you did, nor is a methods section a set of orders.

Materials:

Materials may be reported in part of a section or else they may be recognized along with your measures.

Methods:

- Report the method and not the particulars of each process that engaged the same methodology.
- Describe the method entirely.
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures.
- Simplify—detail how procedures were completed, not how they were performed on a particular day.
- If well-known procedures were used, account for the procedure by name, possibly with a reference, and that's all.

Approach:

It is embarrassing to use vigorous voice when documenting methods without using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result, when writing up the methods, most authors use third person passive voice.

Use standard style in this and every other part of the paper—avoid familiar lists, and use full sentences.

What to keep away from:

- 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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Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part as entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Use statistics and tables, if suitable, to present consequences most efficiently.

You must clearly differentiate material which would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matters should not be submitted at all except if requested by the instructor.

Content:

- Sum up your conclusions in text and demonstrate them, if suitable, with figures and tables.
- In the manuscript, explain each of your consequences, and point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation of an exacting study.
- Explain results of control experiments and give 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 manuscript.

What to stay away from:

- Do not discuss or infer your outcome, report surrounding information, or try to explain anything.
- Do not include raw data or intermediate calculations in a research manuscript.
- Do not present similar data more than once.
- A manuscript should complement any figures or tables, not duplicate information.
- Never confuse figures with tables—there is a difference.

Approach:

As always, use past tense when you submit your results, and put the whole thing in a reasonable order.

Put figures and tables, appropriately numbered, in order at the end of the report.

If you desire, you may place your figures and tables properly within the text of your results section.

Figures and tables:

If you put figures and tables at the end of some details, make certain that they are visibly distinguished from any attached appendix materials, such as raw facts. Whatever the position, each table must be titled, numbered one after the other, and include a heading. All figures and tables must be divided from the text.

Discussion:

The discussion is expected to be the trickiest segment to write. A lot of papers submitted to the journal are discarded based on problems with the discussion. There is no rule for how long an argument should be.

Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implications of the study. The purpose here is to offer an understanding of your results and support all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of results should be fully described.

Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact, you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved the prospect, and let it drop at that. Make a decision as to whether each premise is supported or discarded or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."

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.

- You may propose future guidelines, such as how an experiment might be personalized to accomplish a new idea.
- Give details of all of your remarks as much as possible, focusing on mechanisms.
- Make a decision as to whether the tentative design sufficiently addressed the theory and whether or not it was correctly restricted. Try to present substitute explanations if they are sensible alternatives.
- One piece of 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 other available information. Present work done by specific persons (including you) in past tense.

Describe generally acknowledged facts and main beliefs in present tense.

The Administration Rules

Administration Rules to Be Strictly Followed before Submitting Your Research Paper to Global Journals Inc.

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Segment draft and final research paper: You have to strictly follow the template of a research paper, failing which your paper may get rejected. You are expected to write each part of the paper wholly on your own. The peer reviewers need to identify your own perspective of the concepts in your own terms. Please do not extract straight from any other source, and do not rephrase someone else's analysis. Do not allow anyone else to proofread your manuscript.

Written material: You may discuss this with your guides and key sources. Do not copy anyone else's paper, even if this is only imitation, otherwise it will be rejected on the grounds of plagiarism, which is illegal. Various methods to avoid plagiarism are strictly applied by us to every paper, and, if found guilty, you may be blacklisted, which could affect your career adversely. To guard yourself and others from possible illegal use, please do not permit anyone to use or even read your paper and file.

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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

INDEX

A

Arrhythmia · 2

C

Carcinoma · 12, 25, 28
Catalytic · 20
Consortium · 28

D

Diastolic · 1, 2, 3, 4, 6, 7, 9

E

Endocardium · 1
Endocrine · 22
Epithelial · 16, 17, 32

I

Improvisations · 27
Ischemia · 1, 4

M

Malignancies · 12, 15, 18
Malignant · 2, 34
Metastatic · 27, 29

O

Oropharyngeal · 12, 13, 14, 16, 17, 32, 34

P

Papilloma · 32
Prophylactic · 13, 15, 16
Protrusions · 34

R

Regurgitation · 4

S

Squamous · 12, 32, 34





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