ORIGINAL ARTICLE

Serum HbA1C –a Marker for Lung Cancer?

Ashwin Mathur*, Om Prakash Nag**

ABSTRACT

Background :

Lung cancer is a leading cause of mortality in both developed and developing countries. Current focus in most of the researches especially regarding early and definitive diagnosis.

Serum HbA1C is a non invasive blood investigation, widely used in patients of Diabetes; it is freely available and is cost effective.

Aim :

To assess the association between serum HbA1C and lung cancer and to evaluate if it's increase is a risk factor for development of Lung Cancer.

Material And Method :

It is a hospital based observational case control study conducted on 100 patients, who were included as per the inclusion and exclusion criteria and undergone thorough clinical examination and laboratory investigations.

These patients were followed up for one year.

Conclusion :

- The study showed that there was statistically significant difference in mean serum HbA1C level (6.56% in lung cancer group and 5.56% in control group).
- The mean HbA1C level was higher in non small cell lung cancer group (6.78%) as compared to small cell carcinoma (5.99%), although it was not statistically significant

INTRODUCTION

Lung cancer is one of the most common and dreaded malignancy worldwide and is a leading cause of cancer-related deaths[1]. It is responsible for more cancer-related deaths than breast cancer, colon cancer and prostate cancer combined[2,3]. Predominantly a disease of the elderly[4] the average age of newly diagnosed lung cancer patients is around 60 years[5]. It is slightly more common in males than in females[6]. although the trend appears to be changing now The male and female ratio of >6:1 in 1973 has changed to 1.5:1 in 2008[7].

Although smoking remains the principal cause of lung cancer worldwide[8] only 10% of smokers develop lung cancer, thus genetic, occupational and dietary risk factors also appear to play an important role in its pathogenesis[9]. The other risk factors include, passive smoking, exposure to environmental pollutants, occupational exposure to chemicals and to the natural radioactive gas radon[10]. Genetic predisposition, especially polymorphisms of the tumor suppressor genes and the allelic variants of the genes involved in detoxification, are implicated in the susceptibility to the disease[11].

Despite advances in treatment, the prognosis remains poor, with only 15% of patients surviving > 5 yr from time of diagnosis. For patients with stage IV (metastatic) disease, the 5-yr overall survival rate is < 1%. Improving survival requires focusing attention on smoking cessation, early detection, and research into the genetic profile of lung tumors and developing novel forms of therapy[12].

Glycated hemoglobin (HbA1C) is formed by a post- translational, non- enzymatic, substrate-concentration dependent irreversible process of combination of aldehyde group of glucose and other hexoses with the amino-terminal valine of the α-chain of

*Professor, Department of Palliative Medicine, SMS Medical College & Hospital, Jaipur, Rajasthan

**Medicine Specialist, Netam Hospital Kondagaon, Distt. Kondagaon, Chattisgarh

Corresponding Author

Dr. Ashwin Mathur, Professor, Department of Palliative Medicine,

SMS Hospital, Jaipur, Rajasthan

Mob: 9829038756,

Email: drmathurashwin@gmail.com

hemoglobin[13] and reflects the 3 month average endogenous exposure to glucose including postprandial spikes in the blood glucose level, and has low intra individual variability, particularly in persons without diabetes. These characteristics contribute to the superiority of glycated hemoglobin over fasting glucose for long-term macrovascular risk stratification. The estimation of HbA1C has provided a dependable method of assessing glycemic control in diabetics. This method has been extensively validated in diabetics as a reliable, inexpensive and non-manipulable parameter[13].

A large number of kinetic studies have revealed that glycemia in the recent past influences the HbA1C values more than the remote past. Thus, mean blood glucose of past 1 month, 2 months and 3 months contributes 50%, 40% and 10% respectively to the final result[14].

There are only a very few relevant epidemiological studies regarding association of serum HbA1C and risk of development of lung cancers. In view of the above, this study was planned to assess serum HbA1C levels in lung cancer patients and to compare it with the levels of HbA1C in normal population.

MATERIAL AND METHOD

It is a hospital based observational case control study conducted on 100 patients (fifty cases of lung cancer and fifty healthy controls) who visited the department of medicine and medical oncology at SMS hospital and were included as per the inclusion and exclusion criteria and undergone thorough clinical examination and laboratory investigations.

These patients were followed up for one year.

INCLUSION CRITERIA

- Histopathologically proven new and on treatment patients of lung cancer.
- Patients of all age groups and both sexes.
- Lung cancer of any stage.
- Patients willing to provide informed consent.

EXCLUSION CRITERIA

- Patients suffering from other cancers along with lung cancer.
- Patients on treatment for diabetes.
- Patients taking drugs other than anti diabetic drugs which could affect the HbA1C levels:
  - Drugs causing falsely low levels of HbA1C: - Dapsone, Ribavirin, ART, Trimethoprime-Sulfamethoxazole, Hydroxyurea, low dose Aspirin
  - Drugs causing falsely high HbA1C levels- High dose Aspirin, chronic opioid abuse
- Patients with the following medical conditions were excluded:
  - Associated with falsely increased HbA1C levels : uremia, Iron DeficiencyAnemia, Vitamin B12 deficiency, Hyperbilirubinemia, Alcoholism
  - Associated with falsely decreased HbA1C levels: sickle cell disease, Thalassemia, Acute and chronic blood loss, Hypertriglyceridemia, Chronic Liver Disease.
- Patients unwilling or unable to give informed consent.

Statistical analysis

Statistical analysis was done using continues data, summarized in form of mean and SD. The difference in continuous data was analyzed using student's t` test.

Data was expressed in form of proportions. The difference in proportion was analyzed using chi square test. Odd's ratio for diabetes mellitus as a risk factor for lung carcinoma was found out by 2x2 table. 95% confidence interval of odd's ratio was also calculated. The level of significance was kept 95% for all statistical analysis.

RESULT

- The study showed that there was statistically significant difference in mean serum HbA1C level (6.56% in lung cancer group and 5.56% in control group)

TABLE 1: Comparison of mean HbA1C level in Lung cancer and control groups

Group	N	Mean HbA1C (%)	Std. Deviation
Lung Cancer Group	50	6.56	1.79
Control Group	50	5.56	0.61

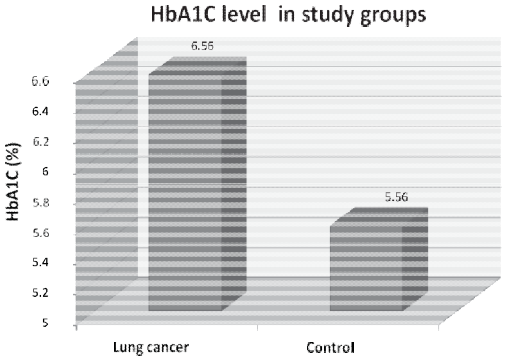

FIGURE 1 HbA1C levels in lung cancer patients and in control population

- Out of 50 cases in lung cancer group 20 (40%) cases had raised (≥ 6.56%) HbA1C and in control group only 2 (4%) subjects had raised HbA1C (6.5%)

Table 2: Distribution of study subjects according to their HbA1C status

HbA1C	Lung cancer group		Control group		Grand Total	
	N	%	N	%	N	%
< 6.5	30	60	48	96	78	78
⩾ 6.5	20	40	2	4	22	22
Grand Total	50	100	50	100	100	100

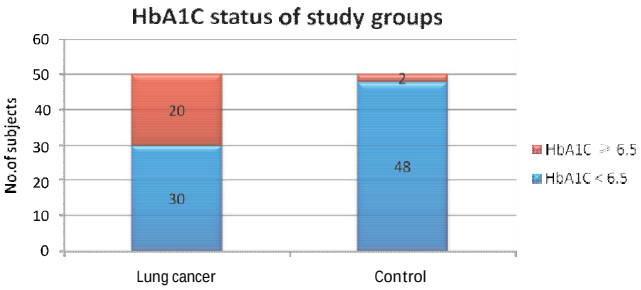

FIGURE 2: Number if patients having high HbA1C levels levels in lung cancer group and in control population

DISCUSSION

There are various studies showing association of cancers and serum glycosylated hemoglobin (HbA1C). However, the number of studies investigating the association between lung cancer and HbA1C are limited.

Our study indicates that there may be an increased cancer risk associated with HbA1C levels more than 6%, i.e.in those with moderately elevated HbA1C levels (6%–6.9%), -which is below the accepted guidelines for the diagnosis of diabetes.

It may be possible that hyperglycemia and hyperinsulinemia together may contribute to the association between type 2 diabetes and cancer through the following mechanisms:

Glucose, through its action on production of insulin and insulin-like growth factor (IGF)-I may enhance tumor development by stimulating cell proliferation and by inhibiting apoptosis[15,16].

Insulin enhances the stimulatory effects of growth hormone on IGF-I synthesis, and also increases IGF-I bioactivity by down-regulating the synthesis of IGF-binding proteins-1 and -2[17].

Both insulin and IGF-I are involved in the synthesis and circulating levels of sex steroids and sex hormone-binding globulin and thus may also specifically increase the risk of hormone-responsive cancers such as breast and endometrial cancers[17].

Several prospective studies support the role of IGF-I on the development of prostate[18,19] colorectal[20,21] and pre menopausal breast[22,23] cancers.

The significantly increased risk for respiratory cancers observed among the subjects having elevated glucose levels was slightly unexpected, since previous studies reporting results on diabetes and/or impaired glucose tolerance and lung cancer have indicated only non significant weakly positive associations[24-26] and even inverse associations[27,28]. Our findings are unlikely to be explained by tobacco smoking, as the analysis based on nonsmokers showed similar results. The increased risk observed may be due to elevated levels of IGF-I, as Yu et al.[29] has also previously reported a strong positive association between circulating IGF-I and lung cancer.

However, our study has the following limitations:

The main limitation of this study is the lack of anthropometric data. As being overweight is a known risk factor for both impaired glucose tolerance and diabetes as well as for several cancers, the increased risks observed for these cancers may be due to excess body weight or obesity rather than elevated glucose levels per se.

The short follow-up time is a second limitation of this study, because with such a short time interval between HbA1C estimation and diagnosis of malignancy, we could not restrict the analyses to the cases diagnosed at least 2 years after the HbA1C test to eliminate subjects with undetected disease at the time of the blood test. Therefore, we could not exclude the possibility that undiagnosed cancer at the time of the HbA1C test might have led to elevated glucose levels.

A study by ZHANG et al. noted considerable increase in HbA1C levels in lung cancer patient. The average serum HbA1C in their population was 6.11% in the control group and 7.00% in the lung cancer group. They also observed that serum HbA1C in lung cancer patients was higher compared to the cut-off HbA1C level of ≥ 6.5% in the American Diabetes Association Clinical Practice Recommendations for the diagnosis of diabetes.

Another study by Travier et al observed, that amongst the 634 cancer cases incidence was greater in persons with HbA1C levels of 6% or above than in persons with normal levels of HbA1C, and for lung cancers he found a significantly increased risk of 2.27 (95% Confidence Interval[CI]: 1.34–3.86) for the participants having moderately elevated(6-6.5%) HbA1C levels and a non significant increased risk of 1.58 (95% CI: 0.77–3.26) for the participants having highly elevated (≥ 7%) HbA1C

levels as compared with persons having normal (≤ 6%) HbA1C levels.

REFERENCES

1. Hitoshi Kitamura, Takuya, Koji, Hiroaki and Hanako Sato et al. The Open Pathology Journal, 2008, 2, 106-114 Molecular and Genetic Pathogenesis of Lung Cancer: Differences between Small-Cell and Non-Small-Cell Carcinomas.
2. https://www.iaslc.org/about-lung-cancer
3. Philip T. Cagle et al. - Etiology of Lung Cancer*:* Molecular Pathology of Lung Cancer*;* http://www.springer.com/978-1-4614-3196-1
4. Lung Cancer. http://www.medicinenet.com/lung_cancer/article.htm# toca Date Accessed: 18.05.2011
5. LUNG CANCER OVERVIEW*;* CHAPTER 3*;* 2005 Nucleus Medical Art www.nucleusinc.com
6. Boehringer Ingelheim*;* Lung Cancer Backgrounder*;* September 2016
7. National Collaborating Centre for Cancer 2011
8. KELLY M. LATIMER et al*;* Lung Cancer: Diagnosis, Treatment Principles, and Screening*;* American Academy of Family Physicians 2015;91(4):250-256.
9. T Sethi : Lung cancer Introduction; Thorax 2002;57:992–993
10. Siegel R et al; Cancer statistics, 2011: CACancer J Clin. 2011;61(4):212–36.2. Jemal A and Bray Fet al;. Global cancer statistics. CA Cancer J Clin2011; 61(2):69–90.
11. Sasho Z. Panov Radiol Oncol 2005; 39(3): 197-198. Molecular biology of the lung cancer.
12. Tumors of the Lungs; The Merck Manual of Diagnosis & Therapy, 19th Edition Chapter 204. Mediastinal & Pleural Disorders Chapter 205.
13. H. B. Chandalia, and P.R. Krishnaswamy Glycated hemoglobin current science, volume 83, no. 12,2002
14. Huisman TH, Martis EA, Dozy A. Chromatography of hemoglobin types on carboxymethylcellulose. J. Lab Clin Med 52 (2): 312-27
15. Kaaks R, Lukanova A. Energy balance and cancer: the role of insulin and insulin-like growth factor-I. Proc Nutr Soc 2001; 60: 91–106.
16. LeRoith D, Roberts CT Jr. The insulin-like growth factor system and cancer. Cancer Lett 2003; 195: 127–137.
17. Kaaks R. Nutrition, hormones, and breast cancer: is insulin the missing link? Cancer Causes and Control 1996; 7: 605–625.
18. Stattin P, Bylund A, Rinaldi S et al. Plasma insulin-like growth factor-I, insulin-like growth factor-binding proteins, and prostate cancer risk: a prospective study. J Natl Cancer Inst 2000; 92: 1910–1917.
19. Chan JM, Stampfer MJ, Giovannucci E et al. Plasma insulin-like growth factor-I and prostate cancer risk: a prospective study. Science 1998; 279: 563–566.
20. Kaaks R, Toniolo P, Akhmedkhanov A et al. Serum C-peptide, insulin-like growth factor (IGF)-I, IGF-binding proteins, and colorectal cancer risk in women. J Natl Cancer Inst 2000; 92: 1592–1600.
21. Palmqvist R, Hallmans G, Rinaldi S et al. Plasma insulin-like growth factor 1, insulin-like growth factor binding protein 3, and risk of colorectal cancer: a prospective study in northern Sweden. Gut 2002; 50: 642–646.
22. Hankinson SE, Willett WC, Colditz GA et al. Circulating concentrations of insulin-like growth factor-I and risk of breast cancer. Lancet 1998; 351:1393–1396.
23. Muti P, Quattrin T, Grant BJ et al. Fasting glucose is a risk factor for breast cancer: a prospective study. Cancer Epidemiol Biomarkers Prev 2002; 11:1361–1368.
24. Saydah SH, Loria CM, Eberhardt MS, Brancati FL. Abnormal glucose tolerance and the risk of cancer death in the United States. Am J Epidemiol 2003; 157: 1092–1100.
25. Coughlin SS, Calle EE, Teras LR et al. Diabetes mellitus as a predictor of cancer mortality in a large cohort of US adults. Am J Epidemiol 2004; 159: 1160–1167.
26. Jee SH, Ohrr H, Sull JW et al. Fasting serum glucose level and cancer risk in Korean men and women. JAMA 2005; 293: 194–202.
27. Batty GD, Shipley MJ, Marmot M, Smith GD. Diabetes status and post-load plasma glucose concentration in relation to site-specific cancer mortality: findings from the original Whitehall study. Cancer Causes Control 2004; 15:873–881.
28. Hall GC, Roberts CM, Boulis M et al. Diabetes and the risk of lung cancer. Diabetes Care 2005; 28: 590–594.
29. Yu H, Spitz MR, Mistry J et al. Plasma levels of insulin-like growth factor-I and lung cancer risk: a case-control analysis. J Natl Cancer Inst 1999; 91: 151–156.