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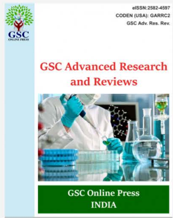

(Research Article)

Clinical impact of serum hemoglobin A1c and insulin levels in terms of postoperative complications in the nondiabetic patients with non-small cell lung cancer

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Abstract

Background: Hemoglobin A1c and insulin levels are important parameters to indicate glucometabolic status of the patients. It is important to understand major changes in glycometabolic status so as to predict postoperative complications. In this study, we aim to assess the impact of serum hemoglobin A1c and insulin levels on postoperative morbidity in lung cancer patients.

Materials and Methods: Between 2018 and 2019, 100 consecutive nondiabetic patients who underwent lung resection via thoracotomy with the indication of NSCLC were included in the study. Preoperatively all patients routinely underwent computed tomography and positron emission tomography (PET/CT), cranial magnetic resonance imaging (MRI) and pulmonary function and DLCO (Diffusing Capacity for Carbon Monoxide) tests. Preoperatively blood HbA1c, and fasting insulin levels of all patients were measured. Age, gender, BMI, insulin, HbA1c levels and postoperative complications were evaluated.

Results: The higher incidence of postoperative complications was found to be related to patients with higher insulin (46.8 mIU/L vs 16.9 mIU/L, p=0.001) and HbA1c (6.22% vs 5.46%; p=0.001) levels compared with those with normal levels In patients who underwent redo surgery to treat hemorrhagic complications, higher insulin and HbA1c levels were observed (61 mIU/L, and 6.54 %, respectively , p=0.001). HbA1c and insulin levels were also higher in cases with prolonged air leak (44.7 mIU/L, and 6.25%, respectively; p=0.001). Bronchopleural fistula was observed in three patients with high insulin and HbA1c levels (60.3 mIU/L, and 6.23%, respectively; p=0.001).

Conclusion: Preoperative HbA1c and fasting insulin levels are important parameters to predict postoperative morbidity in lung cancer patients.

Keywords: Serum hemoglobin A1c; Insulin Levels; Postoperative Complications; Nondiabetic Patients Lung cancer

1. Introduction

Surgical interventions lead to the emergence of Systemic Inflammatory Response Syndrome consisting of a chain of reactions such as the release of stress hormones and inflammatory mediators where glycogen, fat, and protein are catabolized with resultant release of glucose, free fatty acids and amino acids into the circulation (1,2).

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Firstly, in 1877 Claude Bernard reported a case of hyperglycemia in association with hemorrhagic complications, and drew attention to a stress-induced disturbance in glucose homeostasis (3). Patient-related factors such as age, gender and preoperative insulin sensitivity and surgical factors have an impact on the extent of insulin resistance (4). Postoperative insulin resistance is a characteristic feature of the catabolic response to surgical injury (5). Moreover, in cases of more complex or prolonged surgery with higher complexity, tissue trauma, and/or blood loss, insulin resistance becomes more resistant to treatment (6).

In many species via insulin resistance the body responds to stress and injury (7). Insulin resistance/hyperinsulinemia starts to increase in nondiabetic overweight/obese individuals. The Third National Health and Nutrition Examination Survey has demonstrated an overall 35.1% increase in the prevalence of hyperinsulinemia in these patients (8).

In nondiabetic individuals HbA1c is a predictive biomarker for future cardiovascular events, and cases with HbA1c levels in the upper normal range should trigger a search for other cardiometabolic risk factors (9, 10). Assessment of preoperative HbA1c levels is suggested as a presumptive diagnostic tool for detecting patients at risk for hyperglycemia (11).

Although insulin- resistant subjects can be identified by measuring serum insulin levels, this method is not used as often as needed (12). Fasting serum insulin can be used as a surrogate of insulin resistance particularly among nondiabetic subjects (13).

However up to now HbA1c and insulin levels have not been compared in terms of their effects on postoperative complications of thoracic surgery In this study, we aimed to evaluate the relationship (if any) between serum levels of hemoglobin A1c, insulin and postoperative morbidity in lung cancer patients .

2. Material and methods

These patients received treatment, and were evaluated during follow-up period between November 1, 2018, and July 1, 2019. Some important clinico-histopathological, and demographic characteristics of the patients were recorded, and their BMIs were calculated. The patients histologically diagnosed as primary NSCLC and staged according to the TNM staging criteria of The International Association for the Study of Lung Cancer (IASLC 8th edition) were included in this study. Eligible patients for this study had stage I-IIIA NSCLC disease based on the results of clinical assessments, cardiopulmonary function tests, contrast-enhanced thoracic computed tomography (CT) scan, positron-emitted tomography-CT (PET-CT) scan, magnetic resonance imaging (MRI) of the brain and selective mediastinal staging with endobronchial ultrasonography (EBUS), and/or endoscopic ultrasonography (EUS). The diagnosis was confirmed by histopathological examination and the cases were classified as those with squamous cell carcinoma (n=59) or adenocarcinoma (n=41). Patients who had synchronous lung tumors, clinical evidence of active infection or inflammation, metastatic disease, history of R1 or R2 resection, diabetes mellitus, cardiac insufficiency, VATS resection or pneumonectomy and those scheduled for sub lobar resection or individuals without detailed clinical data were excluded from the study.

2.1. Complications

Postoperative pulmonary complications included clinically diagnosed wound infection, pneumonia, respiratory insufficiency, bronchopleural fistula, postoperative hemorrhage, and Acute Respiratory Disease Syndrome (ARDS).

2.2. Sample Collection

Preoperatively blood samples (2 ml) were collected from fasting subjects early in the morning for the evaluation of biochemical parameters such as HbA1c and insulin levels. Following centrifugation at 3000 rpm for 10 min, under sterile conditions, serum samples were stored in clean and dry Eppendorf tubes in the freezer at -20 °C until analyzed.

2.3. Laboratory methods used to measure insulin and HbA1c levels.

HbA1c levels in venous blood samples were measured using Roche Integra Tina Quant analyzer, version 2.0 (Roche Diagnostics, Indianapolis, USA). According to our laboratory reference values normal HbA1c levels ranged between 4.8% and 5.9%. ELISA method (Alpha Diagnostic, Human Insulin ELISA kit) was used for the determination of serum insulin levels. Values between 5-35 µU\ml were considered normal for fasting serum insulin levels.

2.4. Anesthesia

The patients were administered prophylactic antibiotics 30 to 60 minutes before the first incision. A single dose of first or second-generation cephalosporin was given by i.e., route, Intravenous fluids were not administered to any of the groups preoperatively. Anesthesia induction was performed through intravenous route with midazolam 2 mg, fentanyl (3–4 mcg/kg) and thiopental (4–6 mg/kg). Pancuronium (0.1 mg/kg) or atracurium (0.5 mg/kg) was used for muscular relaxation. General anesthesia was maintained with continual propofol and intermittent bolus doses of fentanyl.

2.5. Statistical analysis

Descriptive statistics were given as the mean and standard deviation of minimum, and maximum values for the normally distributed, and median 25th and 75th percentiles for non-normally distributed quantitative variables, while as numbers and percentages for qualitative variables. Logistic regression analysis was applied to determine the risk factors. Chi-square analysis was used to show the relationship between demographic variables, HbA1c, insulin levels, clinical and categorical data of the patients with descriptive statistical data. Student's t- test, Mann- Whitney U test, and Krusal –Wallis analysis were used to analyze continuous variables. For the statistically significant factors, binary logistic regression analysis was performed. The findings were evaluated within 95% confidence interval and at the significance level of 5%. All statistical analyzes were performed using IBM SPSS 22.0 software.

3. Results

3.1. Patient Characteristics

Our study included 83 male and 17 female patients with NSCLC. The median age of the patients was 62.6 years (range: 59-67.8 years). The patients were initially diagnosed as having stage 1-2 (n=98; 98%) and stage IIIA (n=2; 2%) NSCLC. Clinical and laboratory factors according to histopathologic features and type of resections used are presented in **Table 1**.

The increased incidence of postoperative complications was found to be related to patients with higher insulin (46.8 vs 16.9 mIU/L), p=0.001) and HbA1c (6.22% vs 5.46%, p=0.001) levels relative to those with normal values. The patients who underwent revision surgery for hemorrhagic complications had comparatively higher mean insulin and HbA1c levels (61 mIU/L and 6.54 %, respectively; p=0.001).

Average HbA1c and insulin levels were higher in cases with prolonged air leak (44.7 mIU/L, and 6.25%, respectively; p=0.001). Bronchopleural fistula was observed in three patients with higher insulin and HbA1c levels (60.3 mIU/L, and 6.23 %, respectively; *p*=0.001) (**Table 1**).

Table 1 Average HbA1c and insulin levels of clinical and laboratory factors according to histopathologic features and type of resections used

Variables	n	HbA1c % (mean ± SD)	Insulin levels mIU/L (mean ± SD)
Gender			
Male	83		
Female	17		
Age (mean±SD)	62.6±8.2		
Smoking (pack-years;mean±SD)	28±13.4		
BMI (mean±SD)	25.2±4.2		
Histologic Type			
Adenocarcinoma	59		
Squamous cell carcinoma	41		
Surgical procedures			

Right upper lobectomy	28	5.8±0.9	29.8±24.9
Left pneumonectomy	8	5.7±0.6	42.6±53.3
Left upper lobectomy	16	5.8±1.2	33.7±21.9
Right lower lobectomy	13	6.0±1.5	131.3±28.0
Left lower lobectomy	12	6.0±1.2	32.2±33.5
Right pneumonectomy	9	5.9±1.0	39.2±22.5
Bilobectomy superior	4	5.6±0.5	25.3±21.1
Middle lobectomy	4	5.4±2.9	27.9±11.3
Pathological stage			
IA	9	5.5±0.4	22.8±17.0
IB	35	5.8±1.4	30.8±24.3
IIA	36	5.8±0.9	29.4±31.7
IIB	18	5.7±1.3	27.9±26.6
IIIA	2	5±0	12.5±3.5
Postoperative complications			
Hemorrage (2 RUL, 3 RP)	5	6.5±0.9	61.0±16.1
Prolonged air leak	33	6.3±1.6	44.7±22.4
Bronchopleural fistula (2 RP, 1 LP)	3	6.2±1.5	60.3±21.0
Postoperative complication			
Yes	38	6.2±1.5	46.9±22.1
No	62	5.4±0.5	16.9±13.2
Operative mortality	0		

4. Discussion

In our study, complication rates were found to be higher in nondiabetic patients with higher insulin and HbA1c levels after lung resections for NSCLC. Especially in insulin-resistant individuals hyperinsulinemia plays a critically higher clinical, and pathophysiological role in the development of abnormalities. All tissues are not equally resistant to the adverse effects of insulin. As a compensatory mechanism, in insulin-resistant individuals hyperinsulinemia tries both to maintain normal glucose uptake by muscles and to normalize adipose tissue lipolysis with resultant deleterious effects on tissues such as kidney, ovary, and sympathetic nerve system and liver that sustains normal insulin sensitivity. Therefore, assessing the temporal changes in fasting insulin concentrations conveys importance in predicting both the increasing prevalence of insulin resistance and its potential clinical consequences (8). In the RISC (Relationship between Insulin Sensitivity and Cardiovascular disease) study patients with insulin hypersecretion reportedly tended to be older, had higher percent fat mass, worse lipid profiles, and higher liver insulin resistance indices compared with the rest of the cohort. Mean BMI, and age of our patients were (25.2±4.2 kg/m^2 and 62,6±8,2 years, respectively. Consistent with these data, our study population consisted of slightly overweight elderly patients (16).

There are many methods of measuring fasting insulin levels with their relevant advantages and disadvantages. In this study, we preferred to measure insulin levels after 12 hours of fasting. We observed a significant increase in postoperative complications in correlation with HbA1c levels. Based on relevant literature data, we can easily hypothesize that hyperinsulinemia is mechanistically related to the increased risk of asthma or other lung diseases (17). However, pathogenic mechanism of pulmonary damage caused by hyperinsulinemia has not been precisely defined.

Sato et al. found an important relationship between insulin resistance and major complications, especially infectious complications. In their study, patients had a 50% decrease in postoperative insulin sensitivity, a 5-6-fold increase in the risk of major complications, and a 10-fold increased risk of severe infection (18). In our study, median insulin values of the patients with, and without complications were 46.8 mIU/L and 16.9 mIU/L, respectively (p <0.001). According to these results, insulin levels were significantly higher in patients with prolonged air leakage, and hemorrhagic complications. Irrespective of the average blood glucose concentrations, increased glycemic variability has been shown as an etiologic factor in cases of increased oxidative stress and endothelial dysfunction (19).

Saravia and et al indicated the usability of insulin as a more informative diagnostic biomarker for the development of cardiovascular risk compared to glucose levels. In otherwise-healthy overweight but not morbidly obese population, insulin levels seem to predict an earlier stage of cardiometabolic disorders than HbA1c and glucose. Insulin appears to be an early-stage diagnostic marker of metabolic disorders (20).

Hyperglycemia may be encountered in critically ill nondiabetic patients scheduled for surgical interventions (21). Although relatively more reliable information may be obtained on the glycometabolic status through multiple daily glucose measurements or continuous blood glucose monitoring, they are not applicable to a general population (22). In addition to glucose measurements, a variety of different approaches have been proposed over time to evaluate and monitor lycometabolic status (23). Average blood glucose levels over the last 8-12 week may be determined by measuring hemoglobin A1c concentrations, as is known long-term high blood sugar levels may cause immunoregulatory T-cell dysfunction and disturb T-lymphocyte ratios. HbA1c reflects postprandial spikes in the blood glucose levels, and has lower intraindividual variability, particularly in nondiabetic patients. When the HbA1c levels were examined in our study, the median value of HbA1c levels were 6.2% in 22 patients with complications and 5.46% in patients without complications. HbA1c levels were slightly higher in patients undergoing thoracic surgery among nondiabetic patients with complications. There are very few studies in the literature investigating the relationship between glycemic changes and complications after pulmonary resections (24). Patients without diabetes with suboptimal HbA1c levels may have a level of dysglycemia that may not meet the criteria for a diagnosis of diabetes mellitus, but may still contribute to an adverse postoperative outcome (25).

In 17.7% of nondiabetic patients with suboptimal HbA1c levels (HbA1c: 6–7%) impaired fasting glucose criteria defined by American Diabetes Association have been observed. Impaired glucose tolerance has been reported in 13.7% of nondiabetics with optimal HbA1c levels (HbA1c: %6) (11). In our patients, HbA1c levels and fasting insulin levels sub optimally elevated by 28 percent.

Corpus et al. reported abnormal HbA1c levels (i.e.>6%) in 32% of their nondiabetic patients undergoing percutaneous coronary revascularization, This finding was explained by many characteristic features of the insulin-resistant state which are also risk factors for atherosclerosis such as obesity, dyslipidemia, and hypertension (26).

5. Conclusion

As reported in the literature, surgery is an important etiologic factor for impaired metabolism. In addition, patients have a metabolic response that is impaired to varying degrees due to cancer, anxiety-related stress, malnutrition, or various systemic diseases. Glycemic change which is one of the parameters showing metabolic response should be well defined in the preoperative period while preparing the patients for the surgical process. Preoperative HbA1c and fasting insulin levels are important parameters to predict postoperative morbidity in lung cancer patients.

Compliance with ethical standards

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Disclosure of conflict of interest

There is no conflict of interest in the manuscript.

Statement of ethical approval

Ethical approval was obtained for the study.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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