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# Role of Insulin Like Growth Factor (IGF) in Lung Cancer with Underlying Diabetes Melitus

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**Abstract**

Lung cancer is one of the diseases which the highest incidence and mortality in the world. Lung cancer consists of small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) with various subtypes. Diabetes mellitus is one of the comorbidities that is often found in lung cancer patients, which is around 6% - 18% in lung cancer patients. Diabetes is a comorbidity factor that has a serious effect in increasing cancer cell progressivity through the activity of insulin growth factor (IGF) which consists of receptors (IGF-R) and binding proteins (IGFP). The role of IGF produces oncogenic mutations at the DNA level with the process of lung cancer immunity stimulates mitogenesis initiated by insulin and initiates neoplasm cells. IGF receptor mechanism has antineoplastic properties, to fulfill glycemia control that will reduce lung cancer progressivity and prevent clinical worsening so that it can help reduce lung cancer mortality with oral hypoglycemia drugs along with lung cancer therapy modalities such as cytotoxic agents, radiotherapy, immunotherapy, and surgery. The role of IGF is to amplify insulin levels in glucose, lipid, and protein metabolism. IGF can induce cell differentiation and initiation of neoplasm. Diabetes mellitus as a comorbidity can poor clinical outcomes and promote progression through IGF receptor activation in the tumorigenesis process.

Keywords: lung cancer, diabetes mellitus, insulin growth factor

## 1. Introduction

Lung cancer (LC) is a type of malignancy with the highest incidence and mortality in the world, LC incidence is about 2 million new cases (11.4%), compared to overall cancer incidence approximately 19.3 million cases. Incidence of LC (14.3%) and mortality (21.5%) is higher toward male rather than female. Global Burden of Cancer (GLOBOCAN) (2020) based from an epidemiology survey by International Agency for Research on Cancer (IAFC), LC is the major leading cause of death for approximately 1.8 million death (18%) in both male and female population. From epidemiological data there is a significant increase in the incidence of LC with diabetes mellitus. From various studies also say that DM as a risk factor and risk marker for developing LC (Sung dkk., 2020; Fuentes dkk., 2021).

Incidence of LC in female is approximately 8.4% with mortality is about 13.7%. The cause of the high incidence of LC is due to tobacco smoking, occupational pollution exposure and air pollution. Estrogen hormone is a protective chemical of female from free radical in air pollution is related to lower case of among female population (Sung dkk., 2020; Fuentes dkk., 2021).

Diabetes mellitus (DM) is one of the common comorbidities in LC, both DM and LC belong to multifactorial disease, chronic high potent to be fatal and a patient could be suffered from DM and LC. Epidemiological study showed the increasing case of LC patient with DM and obesity. Several cohort and meta-analysis showed that diabetes and insulin resistance (in metabolic

syndrome) is an independent risk factor to the growth of several malignancy. In other hand, insulin resistance and hyperinsulinemia could be a marker of cancer risk. The relation between hyperinsulinemia and obesity increases the carcinogenesis toward the circulated factor-1 (IGF-1) (Gristina dkk., 2015).

DM is the comorbidity of LC which lead worsening and increasing LC progressivity by enhancing IGF. The role of OHA in patients with LC and DM is not fully understood, however several meta-analyses showed, the ability of metformin in lowering blood glucose could prevent the tumorigenesis while the IGF is mostly produced in liver. Synergy between oral hypoglycaemic agents of LC patient with DM could lower the progressivity of cancer cell even though the cancer therapy is followed in accordance to the stage (Danila dkk., 2020).

Insulin Growth Factor (IGF) consists of two ligands, namely IGF-1 and IGF-2 with receptor IGF-1R and IGF-2R, respectively. The role is to aid the entry of IGF molecule and induce tumorigenesis. Patients with DM with hyperglycaemic state significantly increase IGF-1 and IGF-2 level thus enhancing cellular progressivity. While IGF get into the cell through the cellular membrane, the receptors (IGF-1R and IGF-2R) engaged to binding protein (IGFBP 1-6), tumour immunity molecules actively prevent inflammation process induced by host innate and adaptive immunity. Clinical approach of LC patient with DM is involving the role of IGF-1R inhibitor agent to prevent the binding and decrease overall progressivity. The efficacy of cytotoxic agents and radiotherapy synergized to the strategy, cancer cell become more sensible and eradicated (Zhao dkk., 2020; Fariz dkk., 2016).

Increasing number of anticancer targeted therapy disrupt the pathway between IGF-1 and insulin receptor, resulting in negative effect on glucose metabolism. DM could be prevented by lifestyle modification and pharmacotherapy, the cancer risk also decreased. Metformin (biguanide) is first line drug and commonly prescribed in clinical practice due to the anti-neoplastic activity. Recent meta-analysis showed that metformin could decrease cancer risk up to 39%, compared to the combination of antidiabetic drugs (Gristina dkk., 2015).

## 2. Discussion

### 2.1. Lung Cancer and IGF-1

LC is a formation of cellular neoplasia which originated from lung and airway tissue with high incidence and mortality. Data from GLOBOCAN 2020 showed Worldwide, the incidence rate for all cancers combined was 19% higher in men (222.0 per 100,000) than in women (186 per 100,000) in 2020, although rates varied widely across regions. The ratio between male and female is 1:15 vs 1:17. Patient with LC commonly hospitalized in severe stage due to diagnostic process was not initiated earlier, especially older age of 70 years with several comorbidities, such as DM, chronic obstructive pulmonary disease (COPD) and geriatric problems with degenerative diseases. Increasing case In Indonesian were found as much as 1.4‰ in 2013, while in 2018 was approximately 1.49‰. These data were collected through epidemiological survey by Riset Kesehatan Dasar (Riskesdas). Data by gender, incidence of LC in male is fewer (0.74‰) than female (2.85‰). Report of overall case of cancer showed that lung cancer is highest incidence in GLOBOCAN 2020 (Petrek and Yu, 2019).

LC diagnosis is guided by National Comprehensive Cancer Network (NCCN) 2020. History and physical examination should be done as early identification and guiding physician to several differential diagnosis, so that the symptoms are related to LC or non carcinoma respiratory

system problem. History taking include the tobacco smoking, occupational exposure (radon, asbestos, etc.) and household pollutions. LC patients had chronic recurrent cough without resolution even with medication. The symptoms could be aggravated by haemoptysis, anorexia, weight loss and breathlessness. Diagnostic confirmation could be done by several invasive and non-invasive procedure at first visit. Radiography of thorax with x-ray, computed tomography and magnetic resonance imaging (MRI) or invasive procedure by fine needle aspiration (FNA), pleural fluid cytology, bronchoscopy and mediastinoscopy could assist the confirmation by pulmonologists (Kim dkk., 2021; NCCN, 2020).

LC consists of two types SCLC) and NSCLC. Higher incidence is in NSCLC (85%) with several subtypes, adenocarcinoma,squamous cell carcinoma and giant cell carcinoma, however even the SCLC is only 15%, the symptoms and progressivity are severe. Adenocarcinoma is the common subtype of NSCLC which originated from alveoli, squamous cell carcinoma is from airway epithelium (bronchus) and giant cell is from peripheral tissue of lung tissue. The subtypes are illustrated as followed (Fig.1) (Petrek and Yu, 2019; Andayani and Julisafrida, 2020).

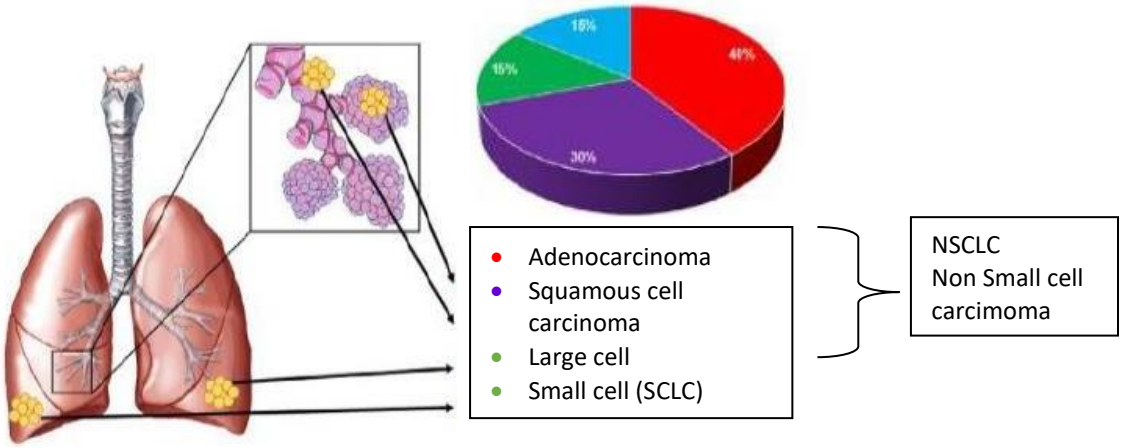


**Figure 1**. Lung cancer cell locations (Petrek and Yu, 2019)

### 2.2. Mechanism of IGF-1 on Lung Cancer

Insulin growth factor (IGF) is one of growth factor produced by liver and response to hypophysis hormone and give the feedback up to the hypothalamus. The role of IGF is to help insulin in glucose, lipid and protein metabolism, however, IGF is involved in cellular differentiation and induce the neoplasia forming. Ligand of IGF (IGF-1, IGF-2 and insulin) with each receptors (IGF-1R, IGF-2R and IR). Ligand of IGF-1 had been reported in malignancy publication and significantly signalling cellular component and induce cellular neoplasia, such as in airway, lung tissue, smooth muscle, fibroblasts and macrophage alveoli and triggering IGF activity toinitiate the lung cancer formation (Fig. 2) (Wang dkk., 2018).

Involvement of IGF1R in epithelial tomesenchymal transition (EMT) in LC is a differentiation process characterized by cell-to-cell detachment and apicobasolateral attenuation, resulting in invasively migrating mesenchyme. Increasing evidence suggests that IGF1R plays a key role in metastatic LC. The role of IGF1R as a prognostic factor in LC is controversial. In one study, no difference was observed in terms of survival between the group expressing IGF1R and the group not expressing IGF1R in stage I-IIIA, NSCLC patients undergoing surgery. However, Nakagawa dkk. found that IGF1R expression resulted in reduced disease-free survival (Wang dkk.,2018).

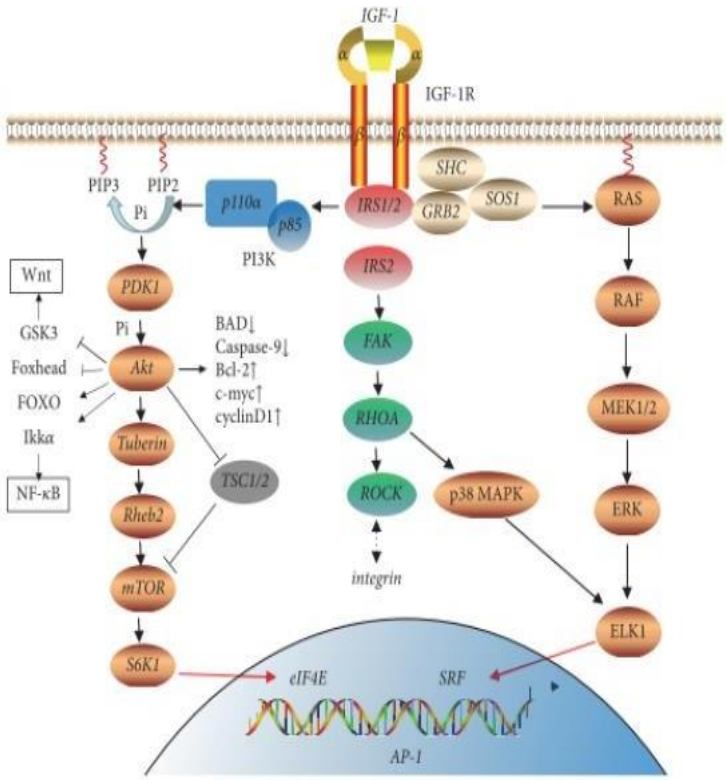


**Figure 2**. Process IGF-1 and IGF-1R signallingintracellular kinase activity (Wang dkk.,2018).

### 2.3. IGF-1R (Insulin like growth factor 1 receptor) and Lung Cancer Biology

One of the growth factors known as insulin growth factor (IGF) is a factor that is mostly produced from the liver and responds to pituitary hormones and provides feedback to the hypothalamus. The role of IGF is to help insulin function for glucose, lipid and protein metabolism, but IGF also provides a role in the process of cellular differentiation to potentially increase the risk of neoplasia. Ligands of IGF consist of IGF-1, IGF-2 and insulin with each receptor (IGF1R, IGF2R, IR). IGF-1 ligand has been studied in cases of malignancy and is stated to be significant in signaling cellular components that can cause differentiation of airway cells, lung parenchyma, smooth muscle cells, lung fibroblasts and alveolus macrophages so that IGF factor activity triggers the incidence of LC (Wang dkk.,2018).

The role of IGF-1R as prognostic factor in lung cancer still debated. In research, there was no difference between life survivals in patients with IGF-1R expression in LC stage I to IIIA. However, Nakagawa dkk., showed that expression of IGF-1R correlated to lower disease-free survivals (DFS), also correlated to post-operative relapse in lung adenocarcinoma (Sung dkk., 2020; Fuentes dkk., 2021).

Meta-analysis was done to confirm the prognostic value of IGF-1R expression showedthat IGF-1R correlated to DFS in NSCLC patients. Besides, measurement of IGF-1R withimmunohistochemistry had been used clinically toward patients with NSCLC (NCCN, 2020).

**2.4. Relation of Lung Cancer to DM**

In industry countries, 78% of overall cancer incidence were diagnosed after patients aged 55 years. Diabetes also common in patients witholder age (increasing prevalence to 23.8% after the age 60 years). Several cancer case with gender specific (including cervix, uterus, testis and prostate). Overall, cancer is common in malewith higher DM incidence. Besides, another factor such as genetic, socioeconomic background, lifestyle and environmental factors could be involved in variability of cancers. However, DM is not proportionally affecting the cancer population. Obesity and overweight population had higher risk of cancer due to insulin resistance, worse than normal body mass index (BMI) from 18.5 - <25 kg/$m^2$. Most of research exhibit that low red meat intake and high fibre from vegetables, fruits and seeds correlated to lower risk of cancer due to the higher insulin sensitivity and improved glycaemic control (Sung dkk., 2020; Fuentes dkk., 2021).

LC with Comorbidities DM is the condition which could lead exacerbation of previous disease, decreasing cure rate and recurrence rate. Diabetes could worsen the disease including the malignancies. Lung cancer could be worsened by diabetes mellitus. Diabetes could worsen the prognosis of lung cancer with several cardiovascular events, post-operativecomplication and late resolution from unsolved infections. Diabetes is a negative prognostic factor toLC patients and affecting to LC progressivity in male (hazard ratio; HR0.87) and female (HR 0.92). Hyperglycaemic control by diabetes medication aimed to antineoplastic effect and improve life expectancy (Danila dkk., 2020).

Oxidative stress increases the cancer cell invasion through the EMT and correlated to local or distant metastasion. Signalling pathway of IGF molecule by P13K/Akt enhance the regulation of oxidative stress, induce proliferation and fibroblast growth factor. The effect is endothelium changes followed by cell membrane modification until the differentiation initiated by time. Patients with DM had hyperglycaemia, hyperinsulin and susceptible to infection and affected to progressive carcinogenesis and metastasion. Male population with LC is higher due to tobacco smoking carcinogenic pollutant, and DM as comorbidity than female" Well controlled DM by oral antidiabetic could improve hyperglycemic state and significantly decrease progressivity of LC. in some studies, could improve hyperglycaemic state and significantly decreasing of lung cancer progressivity. Metformin, one of first line oral antidiabetic in new onset diabetes, could aid gluconeogenesis inhibition, decrease insulin resistance and inflammation process. Its effect in blood glucose circulation do not increase and delay the tumorigenesis (Danila E dkk., 2020).

Different cases of LC and DM management showed insulin use routinely. Antidiabetic drugs could lower IGF-1R production and prevent tumorigenesis, in contrast insulin use routinely increased blood insulin level which enhanced advance cancercell invasion. Mast cell modification by insulin elevated the inflammation response and recurrent bronchoconstriction. The role of insulin in LC mechanism is to induce chronic recurrent inflammation of airway and abnormal cell growth and neoplasm, especially in population with familial history or several respiratory comorbidities (COPD and asthma) (Khateeb dkk., 2019).

Microangiopathy as complication of DM affected the pulmonary circulation withreticular alveolar capillary structure and interstitial fibrosis. It would decrease perform of diffusion process, lung physiology changes and compensatory state. Inflammation by neoplasia is followed by lung physiology changing and patients with LC had higher mortality. The mechanism was induced by receptor advanced glycation end product (RAGE).The effect is vascular injury due to inflammation accumulation, mostly by interleukin (IL-6) (Khateeb dkk., 2019; Kurishima dkk., 2019).

### 2.5. Activation of IGF Receptor in Lung Cancer

Molecular markers LC is the nature of tumour cell and distinguished to normalcell. Higher markers in surface cell, while its role is initiating tumorigenesis, progressivity and metastasis. IGF-1 is one of the common molecular markers besides the binding protein IGF(IGFBP-3), vascular endothelial growth factor (VEGF), type 4 chemokine (CXCR4) and CD44. Transmembrane tyrosine kinase enzyme is one of the IGF-1 receptors (IGF-1R) with two subunits, namely extracellular α and transmembrane β, binding to IGF ligand and induce neoplasm cell biologic transduction. The binding of IGF-1R and IGF ligand induce the autophosphorilation which constantly initiate the tumorigenesis transduction (Xu dkk., 2019).

IGF-1R (Figure 3) was important to malignancy transformation through proliferative, adhesive, transformative mechanisms and cellular apoptosis. The research was followed by complete formulation about IGF. IGF axis had two ligands (IGF-1 and IGF-2), receptors (IGF-1R and IGF-2R) and binding protein IGFBP 1-6, correlated to progressivity. The mechanism in IGF-1R activation induces the P13/Akt and MEK/ERK signaling pathways to promote tumor growth through an inflammatory response and eventually the lesion turns into a tumor. Inhibition of the P13/Akt signaling pathway can increase the sensitivity of cancer cells to cytotoxic agents and therapy with chemotherapy provides results (Zhao dkk., 2020).

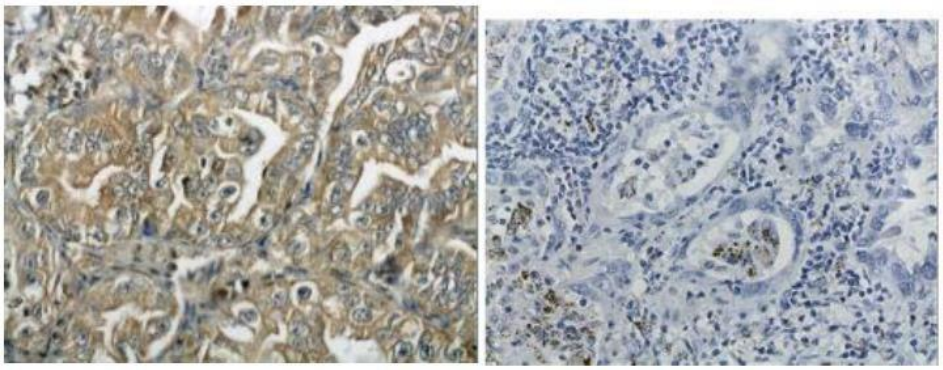

Figure 3. Increasing activity of lung tissue IGF-1R with inflammation by CD8A (Zhao dkk., 2020).

### 3. Conclusion

LC has highest incidence and mortality among cancer types. The appropriate therapy could eradicate LC. IGF receptor inhibition, mainly IGF-1R aimed to decrease cancer cell progressivity and improve cancer cell sensitivity to cytotoxic agents and radiotherapy. The role of IGF produces oncogenic mutations at the DNA level with the process of LC immunity stimulating mitogenesis initiated by insulin and initiating neoplasm cells. IGF receptor mechanism has antineoplastic properties, to fulfill glycemia control that will reduce LC progressivity and prevent clinical worsening so that it can help reduce LC mortality with oral hypoglycemia drugs along with LC therapeutic modalities such as cytotoxic agents, radiotherapy, immunotherapy, and surgical procedures. The role of IGF is to amplify insulin levels in glucose, lipid and protein metabolism. IGF can induce cell differentiation and initiation as neoplasm. Obesity patient had higher incidence in several cancers due to strong relationship with insulin resistance and DM rather than normal BMI. DM as a comorbidity can worsen clinical outcomes and increase progression through IGF receptor activation in the tumorigenesis process.

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