

Clinical Significance of Serum Dikkopf-1 Concentration in Lung Cancer Patients

Thesis

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BY

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List of Contents

	Page
Acknowledgement	I
List of Abbreviations	II
List of Tables	V
List of Figures	VII
Introduction	1
Aim of the Work	4
Review of Literature	5
I. LUNG CANCER.....	5
(A) Definition.....	5
(B) Epidemiology.....	5
(C) Risk Factors.....	8
(D) Classification of Lung Cancer.....	13
(E) Staging of Lung Cancer.....	18
(F) Diagnosis of Lung Cancer	20
(G) Prognosis.....	42
II.WNT PROTEINS.....	44
(A) Introduction.....	44
(B) Structure.....	44
(C) Receptors, Agonist and Antagonist.....	45
(D) Wnt Pathway.....	47
(E) Role of Wnt Signals.....	50

Contents *(Cont..)*

	Page
III-DIKKOPF RELATED PROTEIN1.....	55
(A) Introduction.....	55
(B) Chemistry and Genetics.....	55
(C) Distribution.....	57
(D) Mechanism of Action.....	57
(E) Function.....	58
(F) Clinical Significance of Dikkopf-1.....	61
(G) Potential Therapeutic Uses of Dikkopf.....	65
(H) Methods of Assay of Dikkopf-1.....	66
Subjects and Methods	76
Results	88
Discussion	99
Summary and Conclusion	109
Recommendations	113
References	114
Arabic Summary	



منسّق: الخط: ٣٦ نقطة، خط اللغة العربية
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خط اللغة العربية وغيرها: ٢٤ نقطة

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وغيرها: ٢٤ نقطة

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وغيرها: ١٧ نقطة

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ
قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا
عَلَّمْتَنَا إِنَّكَ أَنْتَ الْعَلِيمُ الْحَكِيمُ
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List of Abbreviations

Aa	: Amino acids
APC	: Adenomatous polyposis coli
AUC	: Area under curve
BN	: Bombesin
Ca	: Calcium
CamKII	: Calmodulin dependent kinase II
CEA	: Carcinoembryonic antigen
CKIα	: Casein kinase I α
CNS	: Central nervous system
COPD	: Chronic obstructive pulmonary disease
CpG	: Cytosine phosphate guanosine
CRD	: Cysteine-rich domain
CSF	: Cerebrospinal fluid
CT scan	: Computerized topography scan
CYFRA21-1	: Cytokeratin 19 fragment
DAP	: Death associated protein
DE	: Diagnostic efficacy
Dkk-1	: Dkkopf related protein 1
DNA	: Deoxyribonucleic acid
Dvl	: Dishevelled
EFF	: Efficacy
ELISA	: Enzyme linked immunosorbent assay
ER_/PR_	: Estrogen and progesterone receptor-negative
ESCC	: Esophageal cancer cell lines
FAP	: Familial adenomatous polyposis
FEVR	: Familial exudative vitreopathy

List of Abbreviations (Cont.)

FITC	: Fluorescein isothiocyanate
FN	: False negative
FP	: False positive
Fz	: Frizzled
GRP	: Gastrin releasing peptide
GSK	: Glycogen synthase kinase
G-to-T	: Guanine-to-Thymine
HSCs	: Hematopoietic stem cells
IASLC	: International Association for the Study of Lung Cancer
IQR	: Inter-Quartile range
KDa	: Kilo dalton
Lef	: Lymphoid enhancer-binding factor
LOH	: Loss of herterozygosity
LRP	: Low density lipoprotein related protrein
MRI	: Magnetic resonance imaging
MSC	: Mesenchymal stem cells
MW	: Molecular weight
NCP	: Nitrocellulose paper
NFAT	: Nuclear factor associated with T cells
NPV	: Negative predictive value
NSCLC	: Non-small cell lung cancer
NSE	: Neuron-specific enolase
O6-MGMT	: O(6)-Methylguanine-DNA Methyltransferse
OPG	: Osteoprotegerin
OPPG	: Osteoperosis- pseudoglioma syndrome

List of Abbreviations (Cont.)

PCP	: Planar cell polarity pathways
PCR	: Polymerase chain reaction
PKC	: Proteins kinase C
PPV	: Positive predictive value
ProGRP	: Progastrin-releasing peptide
RASSF1A	: Ras association domain family 1 A promotor
RB	: Retinoblastoma gene
RIA	: Radioimmunoassay
ROC	: Receiver operating characteristic curve
ROCK	: Rho-associated kinase
r_s	: Spearman's rank correlation
RT-PCR	: Reverse transcriptase polymerase chain reaction
SCC	: Squamous cell lung cancer
SCC –Ag	: Squamous cell carcinoma antigen
SD	: Standard deviation
SDS-PAGE	: Sodium dodecyl sulfate-polyacrylamide gel electrophoresis
SFRPs	: Secreted Fz-related proteins
Sgy	: Soggy
TA	: Tumor antigen
TCF	: T Cell-specific transcription factor
TIMP	: Tissue inhibitor of metalloprotease
TN	: True negative
TP	: True positive
TSG	: Tumor suppressor gene
TTNA	: Transthoracic needle aspiration
UV	: Ultraviolet
VEGF	: Vascular endothelial growth factor

List of Tables

	<u>Page</u>
Table 1: The most common diagnosed cancer worldwide.....	6
Table 2: The most common causes of cancer death worldwide	7
Table 3: Histological classification of lung cancer.....	18
Table 4: The International Association for the Study of Lung Cancer (IASLC) staging system for non-small cell lung carcinoma	19
Table 5: Common lung cancer manifestations	22
Table 6: Methods for the tissue diagnosis of lung cancer	23
Table 7: Prognosis of non-small cell lung cancer.....	43
Table 8: Members of Wnt family proteins	45
Table 9: Descriptive and comparative statistical between control group II and patients' group I regarding Dkk-1 serum level using Wilcoxon Rank Sum test.....	92
Table 10: Descriptive and comparative statistical between control subgroup IIa and control subgroup IIb regarding age and Dkk-1 level using Wilcoxon Rank Sum test	92
Table 11: Descriptive and comparative statistics between patients' subgroup Ia (lung cancer patients with metastasis) and patients' subgroup Ib (lung cancer patients without metastasis) concerning age and Dkk-1 level using Wilcoxon Rank Sum test	93
Table 12: Descriptive and comparative statistics between histopathological types among group I patients concerning age and Dkk-1 level using Kruskal Wallis test	93
Table 13: Descriptive and comparative statistics between non smokers and smokers of patients' group I according to age and Dkk-1 level using Wilcoxon Rank Sum test	94
Table 14: Descriptive and comparative statistics between females and males of patients' group I according to age and Dkk-1 level using Wilcoxon Rank Sum test	94

List of Tables (Cont.)

	<u>Page</u>
Table 15: Correlation statistics between Dkk-1 and age in patients' group I, control subgroup IIa and control subgroup IIb using Ranked Sperman correlation test	95
Table 16: Diagnostic performance for serum Dkk-1 to discriminate lung cancer patients (group I) from control (group II)	95
Table 17: Sensitivity of Dkk-1 for detection of different histological types of lung carcinoma	96
Table 18: Diagnostic performance for serum Dkk-1 to discriminate lung cancer with metastasis (subgroup Ia) from lung cancer without metastasis (subgroup Ib).....	96

List of Figures

	<u>Page</u>
Figure 1: Percentage of cancer worldwide	6
Figure 2: Percentage of cancer deaths worldwide	7
Figure 3: Small cell lung carcinoma	16
Figure 4: Squamous cell carcinoma	16
Figure 5: Adenocarcinoma.....	17
Figure 6: Large cell lung carcinoma	17
Figure 7: Carcinoid tumour of lung	17
Figure 8: Canonical Wnt signals pathway	48
Figure 9: Structure of Dkk Family	56
Figure 10: Dkk-1 mechanism of action	58
Figure 11: The role of Dkk-1 in Wnt signals pathway.....	59
Figure 12: The role of Dkk-1 in bone metabolism.....	61
Figure13: Principle of sandwich enzyme linked immunosorbant assay	67
Figure14: Immunohistochemical staining of lung cancer tissues and normal lung	68
Figure 15: Western blot method	70
Figure 16: RT- PCR	73
Figure 17: Northern blot assay	75
Figure 18: Diagram showing preparation of dilution series of Dkk1 standards for ELISA.....	80
Figure 19: ROC curve analysis showing the diagnostic performance of Dkk1 for discriminating patients' group I (patients with lung cancer) from the control group II (patients with benign lung diseases and healthy subjects).	97
Figure 20: Comparison between patients' group I (all patients with lung cancer) and the control group II (patients with benign lung diseases and healthy subjects) as regard median values of Dkk-1.....	98
Figure 21: Comparison between lung cancer patients' subgroups and control subgroups as regards median values of Dkk-1.....	999898

INTRODUCTION

Lung cancer is a major health problem worldwide. It is the most frequent leading cause of death in men and the third among women (*Jemal et al., 2009*). In Egypt, lung cancer is the second most common cause of death in men and the fourth most common cancer (*Curado et al., 2007*).

Around 90% of lung cancers are related to cigarette smoking. The increased incidence from smoking is proportional to the length and intensity of smoking history. On average, a lifetime smoker has a 20-fold increase in the risk of developing lung cancer compared with a lifetime non-smoker. Lung cancer is more common in men than in women, closely following past patterns of smoking prevalence, and 80% of cases are diagnosed in people aged over 60 (*Persons et al., 2010*).

Lung cancer is classified into four major histological types; adenocarcinoma (30% to 40% of lung cancers), squamous cell carcinoma (25% to 30%), small cell lung carcinoma (15% to 20%) and large cell lung carcinoma (less than 10%) (*Hammerschmidt and Wirtz, 2009*).

Only 16% of lung cancers are diagnosed when the disease is still localized with a five year survival 49.5% while the rest

of patients who are diagnosed when already having metastases have a five year survival 20.6% (*Enewold et al., 2009*).

Bronchoscopy is the only minimally invasive procedure for lung cancer diagnosis, however it is not sensitive and only can reach the central lesions (*Collins et al., 2007*). Tumor markers that are currently available for lung cancer, such as carcinoembryonic antigen, cytokeratin 19 fragment, neuron-specific enolase and progastrin-releasing peptide, are not satisfactory for diagnosis at an early stage or for monitoring the disease because of their relatively low sensitivity and specificity in detecting the presence of cancer cells. Thus, there is an urgent need for a sensitive non invasive method for early detection of lung cancer (*Sheng et al., 2009*).

Dickkopf-1 (Dkk1) is known as a negative regulator of the Wnt signaling pathway, which plays an important role in development and in regulating adult stem cell systems. A variety of cellular processes are mediated by Wnt signaling, including proliferation, differentiation, survival, apoptosis, and cell motility (*Sheng et al., 2009*).

Wnt proteins bind to a membrane receptor complex composed of a Frizzled (Fz) G protein-coupled receptor and a low density lipoprotein receptor-related protein (LRP). Binding of Wnt proteins to this receptor complex leads to activation of Wnt/ β -catenin pathway with activation of disheveled (Dvl) and leads to inhibition of glycogen synthase

kinase-3 β and subsequent stabilization of β -catenin. This protein then translocates to the nucleus, where it binds to and activates lymphoid-enhancer binding factor/T-cell transcription factors. Loss of regulation of this pathway can lead to tumorigenesis (*Voorzanger et al., 2009*).

The change in Dkk-1(Dkk-1) expression has been reported in several types of cancers including multiple myeloma and cancers of the colon, breast, prostate as well as lung cancer (*Pinzone et al., 2009*).

In lung cancer, the change in Dkk-1 expression suggests that it could be a potentially useful biomarker for diagnosis and/or prognosis of this disease. This might allow early intervention and would have its impact on therapeutic regimens (*Yamabuki et al., 2007*).



AIM OF THE WORK

The aim of the present study was to evaluate the clinical utility of serum Dikkopf-1 (Dkk-1) protein as a biomarker for lung cancer by ELISA technique.