Metallothionein and Malondialdehyde Correlation in Prostate Cancer Patients

Nendyah Roestijawati[1], Yudhi Wibowo[1], Diah Krisnansari[1], Dwi Arini Ernawati[1]

[1]Assistant Professor, Department of Community Medicine, Faculty of Medicine Universitas Jenderal Soedirman, Purwokerto, Indonesia

Abstract

Prostate cancer can be caused by heavy metals exposure that can be identified from increasing levels of metallothionein. Exposure to heavy metals is carcinogenic through the formation of ROS in the oxidative stress process. One of the markers of oxidative stress in prostate cancer is malondialdehyde. Purpose of study to determine the relationship between levels of metallothionein and malondialdehyde in prostate cancer. Research design was cross sectional with subjects were 30 patients with prostate cancer at district hospital at Purwokerto, Indonesia. Measurement levels of metallothionein and malondialdehyde used ELISA sandwich method. Data analysis used Spearman correlation test. There was a correlation between levels of metallothionein and malondialdehyde ($p < 0.05$, $r = 0.36$). The increase of metallothionein level cause enhancement malondialdehyde level. As a conclusion, study report that there was corelation between metallothionein and malondialdehyde levels illustrates the process of oxidative stress on prostate cancer due to heavy metals exposure.

Keywords*: metallothionein, malondialdehyde, prostate cancer*

Introduction

Prostate cancer is the most common visceral cancer in men. Prostate cancer ranks second as the most common cause of cancer-related deaths in men over 50 years of age. Risk factors for prostate cancer include age, endocrine status, genetic susceptibility, occupation, ethnicity, race and environmental factors. One of the environmental factors that are a risk factor for prostate cancer is exposure to heavy metals. Compared with non occupational exposure, high occupational Cd exposure may be associated with the increased risk of prostate cancer. Several studies find a positive correlation between cadmium and prostate cancer biomarker, prostate specific antigen (PSA)[1-3].

Exposure to cadmium induces metallothionein (MT) in some tissues, including the liver and kidneys. In acute toxicity, liver is the primary target, whereas in chronic toxicity, kidneys are major targets of Cd[4]. MT plays roles in the gastrointestinal absorption of Cd, Cd retention in tissues and decreases biliary excretion of Cd[5]. Reactive oxygen species (ROS) are often implicated in Cd toxicology. Cd generated superoxide anion, hydrogen peroxide, and hydroxyl radicals, which are often accompanied by activation of redox sensitive transcription factors (e.g., NF-κB, AP-1 and Nrf2) and alteration of ROS-related gene expression. It is agreed that oxidative stress plays important roles in acute Cd poisoning[6].

Oxidative stress is associated with several pathological conditions including inflammation and infection. Chronic increases in ROS are known to induce somatic mutations and neoplastic transformation, including prostate cancer[7]. The review by Oh and colleagues. suggested that oxidative stress biomarkers MDA may be potentially predictive biomarkers of prostate cancer[8]. The study aimed to determine correlation between metallothionein and malondialdehyde in prostate cancer.

Methods

The research was analytic observational with cross sectional design. Forty samples were patients with prostate cancer through biopsy. The number of samples was calculated based on the correlation formula with r = 0.5, α = 0.05 and β = 0.20. Measurement of metallothionein and malondialdehyde levels was carried out using the sandwich ELISA method. Data analysis was performed using the Spearman correlation test.

Result

According to table, the average of metallothionein levels was 32.35±26.50 ng/dL and malondialdehyde was 3.10±0.42 (µmol/L). There was correlation between levels of metallothionein and malondialdehyde ($p < 0.05$, $r = 0.36$).

Table 1. The Characteristics of Metallothionein (MT) and Malondialdehyde (MDA) from Patients

Subject characteristics	Value
Age (yr)	68.25 ± 8.30
Metallothionein (ng/dL)	32.35 ± 26.50
Malondialdehyde (µmol/L)	3.10 ± 0.42

Table 2. Correlation between Metallothionein (MT) and Malondialdehyde (MDA

Variable	p	r
MT – MDA	0.026	0.36

Discussion

Metallothionein levels increase in some tumors include breast, colon, kidney, prostate, ovarian, nasopharyngeal, bladder, salivary gland, testicular and thyroid tumors. Expression of metallothionein cannot be universally ascertained for all types of tumors, but the expression of metallothionein correlates closely with the proliferative capacity of tumor cells and also depends on differentiation status, growth factors and gene mutations. Study found the levels of metallothionein was higher than normal levels. These unique proteins are involved in diverse intracellular functions, but their role in the detoxification of heavy metals and in the maintaining of essential metal ion homeostasis, which is due to their high affinity for these metals, is mostly investigated[9].

Results of study observed MT in prostate cancer were contradictory. While one study showed significantly lower MT in the tumorous tissue, the other identified a significantly increased MT level. In addtition, a study based on radioimmunoanalysis revealed a non-significantly decreased MT level in the tumorous tissue. Although prostate cancer is unique regarding the MT metabolism, no conclusive findings were provided by this meta-analysis and more studies are therefore needed[10].

Metallothionein expression can be stimulated by heavy metals, cytokines and growth factors. Increased concentrations of heavy metals in the body trigger the formation of free radicals and ROS that cause oxidative damage. Oxidative damage is responded by cells by synthesizing proteins and antioxidants. One of the synthesized proteins is metallothionein. Metallothionein functions as an antioxidant in non-enzymatic oxidant defense systems to overcome oxidative damage. Oxidative damage induces Mt genes in many cell types. In metallothionein expression the intracellular level acts as an essential metal store, the take of ROS and the transcription activity regulator. Meanwhile, the emergence of metallothionein at the extracellular level, gives a very important role, namely as a sign of danger to damage that can be inflicted at the cellular level. In the process of controlling stress conditions, metallothionein is found in the blood with increased concentration [9].

Oxidative stress is known to be one of the mechanisms that trigger the prostate development and progression of prostate hyperplasia. Oxidative stress is a cellular level condition that occurs when there is an imbalance between ROS production and the ability of a biological system to repair oxidative damage or neutralize the effects of reactive intermediates including peroxide and free radicals. High ROS production leads to a significant reduction of antioxidants, protein defense mechanisms, lipids and DNA damage and other cellular functional disorders. Oxidative damage can be exacerbated by a decrease in antioxidant efficiency . Oxidative stress has been linked to the development of Benign Prostate Hyperplasia and prostate cancer progression. ROS can indirectly cause random DNA formation by triggering autocatalytic lipid peroxidation, which produces a variety of genotoxic potential substances for breakdown products, including alkoxyl radicals, peroxyl radicals, and aldehydes, such as malondialdehyde [11].

Lipid peroxidation or reaction of oxygen with unsaturated lipids produces a wide variety of oxidation products. The main primary products of lipid peroxidation are lipid hydroperoxides (LOOH). Among the many different aldehydes which can be formed as secondary products during lipid peroxidation, malondialdehyde (MDA), propanal, hexanal, and 4-hydroxynonenal (4-HNE). MDA appears to be the most mutagenic product of lipid peroxidation, whereas 4-HNE is the most toxic (11). In this study MDA levels was higher than normal. several studies have found an increase of malondialdehyde in prostate cancer patients [7,12,13].

Increased levels of malondialdehyde and metalotionein in prostate cancer patients may be caused by exposure to heavy metals, especially cadmium. Study by Pizzino et al revealde that adolescents with elevated Cd levels had a significant increase in MDA and MT-1A compared to the control group [14].

Conclusion

The correlation between malondialdehyde and metallothionein levels illustrates the process of oxidative stress on prostate cancer due to heavy metals exposure. Metallothionein can be considered as a biomarker of cadmium or other heavy metal exposure in prostate cancer screening, especially for cadmium exposed worker.

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Ethical Clearance: The research has been reviewed by Ethical Committee of Health Research, Faculty of Medicine, Universitas Jenderal Soedirman.

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