

Thiol-Disulphide Balance: Could Be a New Marker for Thyroid Cancer?

Ayşe Özdemir^{1*}, Özcan Erel²

¹Department of Biochemistry, Uşak Training and Research Hospital, Uşak University, Uşak, Turkey

²Department of Biochemistry, Ankara Atatürk Training and Research Hospital, Yıldırım Beyazıt University, Ankara, Turkey

Email: *ayse.ozdemir@usak.edu.tr

How to cite this paper: Özdemir, A. and Erel, Ö. (2018) Thiol-Disulphide Balance: Could Be a New Marker for Thyroid Cancer? *Journal of Cancer Therapy*, 9, 598-604. <https://doi.org/10.4236/jct.2018.98051>

Received: June 7, 2018

Accepted: August 13, 2018

Published: August 16, 2018

Copyright © 2018 by author s and Scientific Research Publishing Inc.

This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).

<http://creativecommons.org/licenses/by/4.0/>

Open Access

Abstract

Objectives. Cancer is a very widespread disorder known in world wide since long, but its biochemical features remain unclear. Thyroid carcinomas are the most common endocrine cancer and its frequency continues to escalate. There is evidence that the serum concentration of TSH is an unreliable predictor for the diagnosis of thyroid cancer. The formation of the plasma thiol pool from low and large molecular weight proteins suggests that thiol/disulfide balance is important in cancerous cases. The aim of this study was to investigate an oxidative stress marker (thiol/disulphide homeostasis) and IMA (Ischemia modified albumin), Albumin, CEA (Carcinoembryonic antigen), TSH (Thyroid stimulate hormone), thyroxine (T_4), free thyroxine (FT_4), triiodothyronine (T_3) and free triiodothyronine (FT_3) in patients with thyroid cancer and compare the results with healthy controls for the first time in literature. **Materials-Methods:** A total of 43 participants including 23 patients with thyroid cancer and 20 healthy individuals were included in the study. Serum levels of TSH, T_4 , FT_4 , T_3 and FT_3 have been measured during treatment and follow-up of patients with thyroid carcinoma. Serum levels of TSH, T_4 , FT_4 , T_3 and FT_3 , IMA, Albumin, CEA, Native thiol (-SH), disulfide (-S-S) and total thiol (TT) as well as disulphide/native thiol and disulphide/total thiol ratios were compared between the groups. Native thiol, disulfide and total thiol concentrations were measured with a novel automated method (Roche, cobas 501, Mannheim, Germany). **Results and conclusion:** This paper discusses an oxidative stress marker (thiol/disulphide homeostasis) and tumor markers IMA, Albumin, CEA, TSH, T_4 , FT_4 , T_3 and FT_3 in patients with thyroid cancer and compares the results with healthy controls. Mean age at participant was 41.73 years for thyroid cancer patients (21 females/2 males). A control group of 20 participants was included the study (19 females/1 male, mean age 51.75).

Keywords

Disulphide, Thiol, Tumor Marker, Thyroid Cancer

1. Introduction

Many pathologies and diseases have been linked to oxidative stress (aging, cancer, cardiovascular disease, respiratory diseases such as asthma and obstructive sleep apnea; diabetes mellitus; rheumatic diseases such as rheumatoid arthritis; urological diseases such as prostate cancer and benign prostatic hyperplasia; neurological diseases such as Parkinson's and Alzheimer's) [1]. Thyroid carcinomas are very common and divided into papillary, follicular, medullary, and anaplastic carcinomas. Thyroid carcinomas are malign disease of the thyroid tissue, typically doesn't cause any symptoms early in the disease. But as thyroid cancer grows, may cause symptoms such as a lump in the neck, swelling in the neck, pain in the front of the neck, hoarseness or other voice changes that do not go away, trouble swallowing and breathing, a constant cough that is not due to a cold [2] [3].

Thiols are sulphur analogs of alcohols, taking the suffix “-thiol”. They are also called “mercaptans” due to their holding mercury. Sulfides are sulphuric analogs of ethers. Thiol is an organic component consisting sulfid which has a critical role in preventing the formation of any oxidative stress condition in cells [4]. Total thiol in the body is made up of free form of thiol tied to proteins or created by plummeting glutation. Albumin contributes to forming the large part of the thiol tied to proteins. Cells are protected against oxidative damage through thiol and sistein storage found in active parts of proteins such as catalase, superoxyde dismutase, tioredocsin and peroredocsin with thiol glutation at low molecule weight by activating glutation peroxidase and glutation S transferase enzymes. Cells turn into reversible disulfide bands by oxidizing ROS, causing oxidative damage, with thiol groups in the medium [4] [5]. Thiol and disulfid have roles in stabilization of protein structures (static), regulation of protein and enzyme functions, in receptors, carriers, Na-K channel and transcription [4] [6]. The dynamic balance between thiol and disulfid play a great role in antioxidant defence, detoxification, apoptosize, regulation of enzyme activities, transcription and in mechanism of cellular signal transmission. While a large part of plasmatic thiol pool is consisted of albümin and other proteins, a little part of it is made up of low molecule weight thiols such as cystein, cysteinly glycine, glutation, homocystein and γ -glutemilcystein. Abnormal thiol/disulfid balance levels are found in patogenesis of various diseases such as diabetes, mellitus, cardiovascular diseases, cancer, rheumatoid arthritis, chronic renal impairment, Parkinson, Alzheimer, multiple sclerosis and liver diseases [7]. Of the low molecule weight thiols, S-glutation (GSH) is searched as a potential biomarker of oxidative stress in some disecises such as renal cancer and diabete, and it is seen at increased level

in uremia of the patients with peritoneum dialysis in Type 1 and Type 2 diabetes [5] [8]. A study argued that thiol-disulfide balance may be a prognostic biomarker in lung cancer; moreover, an ongoing study also claimed that native thiol lowness may have a role in ischemic stroke pathogenesis [7]. Thiol-Disulfide homeostasis has an important role in many disorders. Oxidative stress has been one of the questioned factors in the pathogenesis of cancer in several studies, but its exact role is still unclear [1] [4] [5] [6] [7] [9] [10] [11] [12]. The incidence of thyroid cancer is thought to have increased in recent years (from 3.6/100,000 in 1973 to 8.7/100,000 in 2002). In this study show that in patients with thyroid cancer undergoing thyroid surgery were analysed retrospectively in 321 of total 2210 cases [13]. When compared to two consecutive time-frames, an increase in incidence of thyroid cancer was observed [14].

Previous studies researched thiol/disulfide homeostasis and oxidative damage in several diseases as a cancer [7] [15] [16] [17] [18] [19]. Until now, there has been no study researching thiol/disulfide homeostasis in thyroid cancer. In this study, we aimed to investigate this newly developed biomarker in thyroid cancer.

2. Materials and Methods

2.1. Study Population

This study was conducted in the General Surgery Clinic and between January 2018 and April 2018 in Turkey. All of the participants are over the age of 18. Patients that were diagnosed with thyroid cancer. The healthy control group consisted of healthy volunteers, who have without a chronic disease (kidney failure, diabetes mellitus, liver disease, cardiovascular and cerebrovascular disease) and drug use (smoking, alcohol consumption). Venous blood samples (For thiol/disulfide homeostasis tests) were obtained from all participants in the hospital. To separate serum from cells, collected blood samples were centrifuged at 1500 rpm for 10 min. Serum total IMA, Albumin, CEA, TSH, T_4 , fT_4 , T_3 and fT_3 were determined using an automated clinical biochemistry analyzer with original reagents. Remaining serum samples were stored at -80°C until all samples were collected. Native thiol and total thiol were measured by using a new and fully automatic system, disulfide and ratios of disulfide/native thiol, disulfide/total thiol and native thiol/total thiol were calculated (Erel Neselioglu) [6]. The study was conducted in accordance with the Declaration of Helsinki 2013 Brazil version and was approved by the Kütahya Ethics Research Committee. All participants provided written informed consent prior to participation in the study. tT_3 , tT_4 , fT_3 , fT_4 , TSH parameters of the participants were their routine parameters at the time they were included in the study and those were recorded from patient files.

2.2. Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) 17 program. Normality of distribution was evaluated using the

Shapiro-Wilk test. Normally distributed numerical variables were presented as mean \pm standard deviation. Intergroup comparisons of normally distributed numerical variables were done with The Mann-Whitney U test. $P < 0.05$ was considered indicative of statistical significance.

3. Results

Ninety-three patients (21 females and 2 males) with thyroid cancer and 20 healthy controls (19 females and 1 males) were included in the study. The mean age was 41.73 years in the thyroid cancer patient group and 51.75 years in the control group. Clinical characteristics of the patients were summarized in **Table 1**. The mean fT_4 level was higher in thyroid cancer patients when compared to the controls (1.22 mg/dL vs 0.98 mg/dL, $p = 0.011$). There were no differences for the levels of serum IMA, CEA, and TSH between the study and the control groups ($p > 0.05$). Native thiol (482.45 $\mu\text{mol/L}$ vs 493.98 $\mu\text{mol/L}$), total thiol (509.13 $\mu\text{mol/L}$ vs 518.15 $\mu\text{mol/L}$), and disulphide (13.33 $\mu\text{mol/L}$ vs 12.08 $\mu\text{mol/L}$) levels were lower in thyroid cancer patients when compared to the controls (**Table 2**). Mean disulphide/native thiol (2.82% vs 2.48%, $p = 0.394$) and mean disulphide/total thiol ratios (2.65% vs 2.35%) and TSH level (20.58% vs 2.00 mg/dL) were higher in patients with thyroid cancer patients (**Table 2**). There were no correlations between serum thiol/disulphide parameters and T_3 , T_4 and TSH hormone in patients with thyroid cancer. It could be said that

Table 1. Clinical characteristic of two groups.

Characteristic	Thyroid cancer patients (n = 23)	Control Goup [20]
Mean age	41.73	51.75
Male	8.69	5
Female	91.3	95

Table 2. Clinical parameters of the thyroid cancer patients and the control group.

Parameters	Thyroid cancer patients (n = 23)	Control Goup (n = 20)
Native thiol (-SH) $\mu\text{mol/L}$	471.31 \pm 78.65	493.99 \pm 86.18
Total thiol (-SH+-S-S) $\mu\text{mol/L}$	497.44 \pm 78.71	518.16 \pm 88.09
Disulphide (-S-S) $\mu\text{mol/L}$	13.07 \pm 5.10	12.09 \pm 4.46
-S-S/-SH, %	2.85 \pm 1.21	2.48 \pm 0.98
-S-S-/(-SH+-S-S), %	2.67 \pm 1.07	2.35 \pm 0.89
-SH/(-SH+-S-S), %	94.66 \pm 2.15	95.30 \pm 1.77
Albumin	4.42 \pm 0.64	4.44 \pm 0.32
IMA	0.72 \pm 0.09*	0.67 \pm 0.07
TSH	1.12 \pm 1.89	2.01 \pm 1.66
fT_3	2.81 \pm 0.45	N.R
fT_4	1.39 \pm 0.25	0.99 \pm 0.27
CEA	1.81 \pm 2.05	N.R.

*p value < 0.05 considered significant. Results are given as mean \pm SD.

changes in the thiol-disulphide homeostasis may not interact with thyroid hormone values. In this study, the evidence regarding the association between serum thiol/disulphide parameters and T₃, T₄, TSH hormone is discussed placing these new findings into context.

4. Discussion

Oxidative damage plays an important role in the development of age-dependent diseases such as cancer, atherosclerosis, hypertension, ischaemia-reperfusion injury, inflammation, diabetes, Parkinson disease and Alzheimer disease [18] [19] [20] [21] [22]. Thiols contain functional sulfhydryl group (-SH). Plasma thiol pool is comprised of cysteine, homocysteine, γ -glutamylcysteine, cysteinylglycine, glutathione, albumin and protein. The antioxidant defense system includes enzymatic (catalase, superoxide dismutase, and glutathione reductase/glutathione peroxidase) and non-enzymatic system (carotenoids, tocopherols, ascorbates and glutathione). Among these, the most important thiol-containing molecule is glutathione [15] [16]. If oxidative stress increases, formed disulphide bonds can be reduced to thiol groups. Therefore dynamic thiol/disulphide homeostasis is retained. The dynamic thiol-disulphide balance has a key role in antioxidant defense [15] [16] [17] [21] [22] [23]. Until the present time, dynamic thiol-disulphide balance could be measured single-sided, but recently developed method of Erel and Neselioglu made possible to measure the both sides [6] [23]. It not included a biomarker to guide treatment, to a decrease in complications and to indicate the change of prognosis in many patients with cancer. At the present time, prognosis and treatment protocols of patients are tried to be controlled with the examination of TSH and thyroid hormones in thyroid cancer patients. We have not obtained any study in the literature examining dynamic thiol-disulphide homeostasis in thyroid cancer disease. We believe that dynamic thiol-disulphide homeostasis may be a good biochemical marker in following a patient with thyroid cancer.

Our investigation indicated that although thiol/disulphide homeostasis is a relatively cheap, easily available and optionally manual spectrophotometric analysis, this test could not be biochemical marker in thyroid cancer patients. Our study involves some limitations such as a relatively small number (23 patients and 20 controls) of patients who admitted to a single center.

In this study, we investigated dynamic thiol-disulphide homeostasis status in patients with thyroid cancer for the first time. However, It is required further research on a larger patient population.

Acknowledgements

Thanks Dr Dalyan Özdemir for their contribution in the work.

Compliance with Ethical Standards Conflict of Interest

The authors report no declarations of interest.

Ethical Approval

This study was approved by the local ethics committee and the institutional review board.

References

- [1] Allen, R.G. (1998) Oxidative Stress and Superoxide Dismutase in Development, Aging and Gene Regulation, *Age*, **21**, 47-76.
<https://doi.org/10.1007/s11357-998-0007-7>
- [2] (2018) Thyroid Cancer.
<https://www.mayoclinic.org/diseases-conditions/thyroid-cancer/symptoms-causes/syc-20354161>
- [3] Yalçın, G.T. (2013) Flavonoidlerin kanser hücrelerine etkisi. (Effect of Flavonoids on the Cancer Cells). Selçuk Üniversitesi Sağlık Bilimleri Enstitüsü. Yüksek Lisans Tezi.
<http://acikerisim.selcuk.edu.tr:8080/xmlui/bitstream/handle/123456789/1190/329293.pdf?sequence=1&isAllowed=y>
- [4] Chianeh, Y.R. and Prabhu, K. (2014) Protein Thiols as an Indicator of Oxidative Stress. *Archives Medical Review Journal*, **23**, 443-456.
<http://dergipark.gov.tr/download/article-file/25261>
- [5] Cerutti, P.A. (1985) Prooxidant States and Tumor Promotion. *Science*, **227**, 375-381. <https://doi.org/10.1126/science.2981433>
- [6] Erel, O. and Neselioglu, S.A. (2014) Novel and Automated Assay for Thiol/Disulphide Homeostasis. *Clinical Biochemistry*, **47**, 326-332.
<https://doi.org/10.1016/j.clinbiochem.2014.09.026>
- [7] Kumar, G.R., Kumar, P.A., Shah, N., Kumar, C.A., Kant, J.U., Chandra, Y.U., Kumar, G.P. and Pakuwal, U. (2014) Oxidative Stress and Antioxidants in Disease and Cancer: A Review. *Asian Pacific Journal of Cancer Prevention*, **15**, 4405-4409.
<https://doi.org/10.7314/APJCP.2014.15.11.4405>
- [8] Bektaş, H., Vural, G., Gümüşyayla, Ş., Deniz, O., Alışık, M. and Erel, Ö. (2015) Akut İskemik İnmeli Hastalarda Tiyol-disülfid Dengesinin Araştırılması, *Türk Beyin Damar Hast Dergisi*. Cilt 21, Ek 15.
https://www.journalagent.com/tbdhd/pdfs/TBDHD_21_SUP_OKUL_OZEL_SAYIS_I_1_35.pdf
- [9] Dirican, N., Dirican, A., Şen, O., Aynalı, A., Atalay, Ş., Bircan, H.A., Öztürk, Ö., Erdoğan, S., Çakır, M. and Akkaya, A. (2016) Thiol/Disulfide Homeostasis: A Prognostic Biomarker for Patients with Advanced Non-Small Cell Lung Cancer? *Redox Report*, **21**, 197-203. <https://doi.org/10.1179/1351000215Y.0000000027>
- [10] Winther, J.R. and Thorpe, C. (2014) Quantification of Thiols and Disulfides. *Biochimica Biophysica Acta*, **1840**, 838-846.
<https://doi.org/10.1016/j.bbagen.2013.03.031>
- [11] Erel, Ö. (2005) A New Automated Colorimetric Method for Measuring Total Oxidant Status. *Clinical Biochemistry*, **38**, 1103-1111.
<https://doi.org/10.1016/j.clinbiochem.2005.08.008>
- [12] Adaş, G., Adaş, M., Özülker, F. and Akçakaya, A. (2012) Tiroid Kanseri, *Okmeydanı Tıp Dergisi* 28 (Ek sayı 1):26-34.
- [13] Makay, Ö., Yoldaş, T., İçöz, G., Akyıldız, M. and Yetkin, E. (2007) Tiroid kanserinde değişim süreci: 1995'den 2006'ya Yıl/2007 Cilt/23 Sayı/2 Nisan-Mayıs-Haziran ISSN 1300-0705 s. 58-61. e-ISSN: 2564-7032.

- <http://www.turkjsurg.com/full-text-pdf/32/tur>.
- [14] Ates, I., Ozkayar, N., Inan, B., *et al.* (2016) Dynamic Thiol/Disulphide Homeostasis in Patients with Newly Diagnosed Primary Hypertension. *Journal of the American Society of Hypertension*, **10**, 159-166. <https://doi.org/10.1016/j.jash.2015.12.008>
- [15] Ates, I., Kaplan, M., Yuksel, M., *et al.* (2016) Determination of Thiol/Disulphide Homeostasis in Type 1 Diabetes Mellitus and the Factors Associated with Thiol Oxidation. *Endocrine*, **51**, 47-51. <https://doi.org/10.1007/s12020-015-0784-6>
- [16] Kundi, H., Ates, I., Kızıltunc, E., *et al.* (2015) A Novel Oxidative Stress Marker in Acute Myocardial Infarction: Thiol/Disulphide Homeostasis. *American Journal of Emergency Medicine*, **33**, 1567-1571. <https://doi.org/10.1016/j.ajem.2015.06.016>
- [17] Özdemir, A. (2010) Investigation of the Effects of Mentha Spicata Lamiaceae Mentha Extracts Prepared in Different Solvents Given to Rats with Dry Powder on Blood, B-Carotene, A,C Vitamins, Catalase, Glutathione Peroxidase, Glutathione Reductase, Malondialdehyde, Superoxide Dismutase Enzymes and Total Anti-Oxidant Capacity. PhD Dissertation, No. 2010-003, Afyon Kocatepe University, Institute of Health Sciences.
<http://sagbilens.aku.edu.tr/wp-content/uploads/sites/16/2016/02/2003-2011-E%C4%9Fitim-%C3%96%C4%9Fretim-Y%C4%B1llar%C4%B1.pdf>
- [18] Özdemir, A. and Sözbilir, N.B. (2016) The Effect of *Mentha spicata* L. Dry Powder and Its Different Types Extracts on Certain Biochemical Parameters and Total Anti-Oxidant Capacity. *Afyon Kocatepe University Kocatepe Veterinary Journal*, **9**, 12-18.
- [19] Valko, M., Rhodes, C.J., Moncol, J., Izakovic, M. and Mazur, M. (2006) Free Radicals, Metals and Antioxidants in Oxidative Stress-Induced Cancer. *Chemico-Biological Interactions*, **160**, 1-40.
- [20] Vural, G., Gumusyayla, S., Bektas, H., Deniz, O., Ergin, M. and Erel, O. (2016) Dynamic Thiol-Disulphide Homeostasis in Patients with Multiple Sclerosis. *World Journal of Neuroscience*, **6**, 214-219. <https://doi.org/10.4236/wjns.2016.63026>
- [21] Benz, C.C. and Yau, C. (2008) Ageing, Oxidative Stress and Cancer: Paradigms in Parallax. *Nature Reviews Cancer*, **8**, 875.
- [22] Kilic, A., Yorulmaz, A., Erdogan, S., Kulcu Cakmak, S., Guney, E., Sen, O. and Erel, O. (2017) An Evaluation of Thiol/Disulphide Homeostasis in Patients with Psoriasis. *Advances in Dermatology and Allergology*, **5**, 464-467.
<https://doi.org/10.5114/ada.2017.71113>
- [23] Elman, G. and Lysko, H. (1979) A Precise Method for the Determination of Plasma Sulfhydryl Groups. *Analytical Biochemistry*, **93**, 98-102.
[https://doi.org/10.1016/S0003-2697\(79\)80122-0](https://doi.org/10.1016/S0003-2697(79)80122-0)