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Myeloperoxidase and Trace Elements Imbalance in Papillary Thyroid Carcinoma

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This research sought to analyze discrepancies in zinc, copper, iron, and magnesium levels and to examine the connections between trace elements, myeloperoxidase (MPO), and C-reactive protein (CRP) to explore their possible functions in individuals with papillary thyroid cancer (PTC).

This study included thirty-four patients with papillary thyroid cancer and thirty-one healthy subjects. Myeloperoxidase concentrations were assessed with an ELISA kit, while CRP was evaluated employing a Cobas c 311 automated analyzer from Roche Diagnostics. The measurement of Zn, Cu, Mg, and Fe was conducted utilizing standard calibration curves for atomic absorption spectrophotometry.

The findings suggest that PTC patients show increased levels of MPO, C-RP, and Cu, while levels of Zn, Fe, and Mg are reduced. These changes may be linked to inflammation and shortages of trace elements. They might also indicate a link between inflammatory processes, oxidative stress, and metabolic alterations in the tumor microenvironment.

However, this study did not determine the causal link between MPO and the trace elements, nor their clinical significance. Further research is needed to clarify the mechanisms involved and potential clinical consequences of these findings.

Keywords: Papillary Thyroid Cancer, Trace Elements, Myeloperoxidase, Oxidative Stress, Inflammation.

Abstract

Specific trace elements like iron, zinc, magnesium, and copper have been thoroughly researched regarding their effects on thyroid health. Deficiencies or imbalances of these elements can disrupt thyroid activity and result in thyroid-related problems.

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Introduction

Thyroid cancer (TC) ranks among the most common endocrine cancers (1), and its occurrence has increased in the last ten years (2). Papillary thyroid carcinoma (PTC) represents around 80–85% of all thyroid cancers (3). The World Health Organization (WHO) classifies tumors that are less than 1 cm in their largest dimension as papillary thyroid microcarcinoma (PTMC) (4). The synthesis of myeloperoxidase (MPO) is associated with the maturation of neutrophils in the bone marrow, where it is kept in azurophilic granules until neutrophil activation (5). Usually, during immune reactions, MPO is secreted by neutrophils at infection locations to fight off pathogens. In chronic inflammation or cancer-related processes, MPO is released, leading to tissue injury and fostering an inflammatory environment that aids cancer advancement (6).

MPO belongs to the heme peroxidase-cyclooxygenase superfamily. The mature MPO consists of a homodimer made up of two glycosylated protomers, with each protomer having a light chain of 14.5 kDa, a heavy chain of 58.5 kDa, and a heme group. Every protomer, referred to as hemi-MPO, operates independently. However, certain pro-MPO might avoid granule targeting and be released into the extracellular space in a monomeric form (7). MPO has been suggested to convey signaling proteins to neighboring cells and to take part in extracellular vesicles, which serve as a different method of intercellular communication (8).

Trace elements are crucial for proper thyroid function and are involved in thyroid conditions, such as autoimmune diseases and tumors. Among these trace elements, iron (Fe), zinc (Zn), and Magnesium (Mg) is widely researched because of their essential function in thyroid wellness. An imbalance or lack of these elements can disrupt thyroid function (9).

Zinc functions as an antioxidant and serves as a cofactor for the Cu/Zn-SOD enzyme, which transforms the superoxide radical ($O_2^{\bullet-}$) into O_2 and H_2O_2. CAT and GPx subsequently eliminate the resulting H_2O_2. Additionally, zinc inhibits NADPH oxidase function, which leads to decreased ROS generation. Moreover, zinc stimulates the creation of metallothioneins, cysteine-heavy proteins that are effective at scavenging ROS (10).

Magnesium (Mg), a vital mineral commonly found in the human body, participates in various biochemical processes that uphold physiological balance. It acts as a cofactor for over 300 enzymatic reactions, aiding in the transformation of adenosine triphosphate (ATP) into adenosine diphosphate (ADP) for energy generation (11). A deficiency in magnesium promotes baseline inflammation, which is strongly associated with oxidative stress and may result in several complications. Significantly, numerous studies in clinical oncology have indicated that Mg levels are related to tumors (12).

Copper balance is closely controlled in living organisms. Disruptions in copper homeostasis are linked to several pathological conditions. Copper serves as a vital trace element within the human body. In biological systems, copper exists in two redox forms: oxidized (Cu^{2+}) and reduced (Cu^{+}). Copper is mainly sourced from food consumption, predominantly in the form of Cu^{2+} (13).

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Extracellular copper as Cu2+ is directly moved by the divalent metal transport.
Porter 1 (DMT1), known as solute carrier family 11 member 2 (SLC11A2), is not directly usable by cells (14,15).
This study aimed to explore the relationship between selected trace elements Zn, Mg, Cu, and Fe and inflammatory activation in papillary thyroid carcinoma.

Materials &Methods

Study design and Sample collection:

The research is a case-control examination of imbalances in iron, magnesium, copper, and zinc. It also explores the relationships between trace elements, myeloperoxidase (MPO), and C-RP (an inflammatory marker) in patients with papillary thyroid cancer to evaluate their possible involvement in papillary thyroid carcinoma. Thirty-four patients diagnosed with papillary thyroid cancer and thirty-one healthy individuals took part in this study. Peripheral blood samples were gathered, and serum was isolated after permitting clotting for 2 hours at ambient temperature. The samples were subsequently centrifuged at 1000 x g for 20 minutes and kept at -20°C until needed. Samples were collected from Medi-cal City Hospital located in Baghdad, Iraq.

All samples were gathered prior to thyroidectomy. No participants were using medication or had a chronic disease history, and some disclosed a family history of different cancers, including breast and prostate cancers.

Experimental methods: Myeloperoxidase concentrations were assessed using ELISA, while CRP levels were evaluated on the Cobas c 311 automated analyzer (Roche Diagnostics).

Determination of Zinc and Copper (Zn & Cu): Standard calibration curves were developed using working solutions of zinc and copper at concentrations of 0, 50, 100, 150, and 200 µg/dL. Subsequently, 500 µL of the sample was diluted 12 times with deionized distilled water. Zinc and copper levels were measured using atomic absorption spectrophotometry at 213.9 nm for zinc and 324.7 nm for copper.

Determination of magnesium (Mg):

A 25 µL sample was diluted roughly 50 times with lanthanum chloride (LaCl2 · 7H2O), and the resulting diluted solution was examined using standard working solutions of magnesium. Absorbance was recorded at 285.2 nm (16).

Determination of Iron (Fe):

Ferric ions bound to transferrin in the samples were released using guanidinium and subsequently reduced to ferrous ions with ascorbic acid. The produced ferrous ions interacted with ferrozine to create a colored complex that was quantified spectrophotometrically (17).

Statistical Analysis

All data were examined using SPSS version 26 through t-tests, Pearson correlations, and multiple linear regression analysis. A P value of 0.05 was deemed significant.

Results:

Table 1 presents the overall count and age distribution for all 34 patients with papillary thyroid cancer (44% male, 56% female), whereas the control group consisted of 31 participants (42% male, 58% female).Table 2 highlights significant distinctions between the PTC and control groups regarding MPO, CRP, Fe, Mg, Zn, and Cu.

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Table (1). The mean and standard deviation of all participants' age and gender

Group	N	% Sex	Age
Control	31	42% males 58% females	39.193 ± 10.964
PTC	34	44% males 56% females	42.64 7± 9.101

Table (2). Myeloperoxidase and Trace Element Profiles Among the Study Groups Using Student's t-test.

	Control **Mean ± Std. Deviation**	**PTC** **Mean ± Std. Deviation**	**Sig.**
MPO nglmL	0.7311 ±0.1263	2.426 ± 0.558	P<0.001
CRP mg/L	3.2516 ±1.20274	7.616±1.124	P<0.001
Mg µg/dL	1.273±0.244	1.477±0.177	P<0.001
Zn µg/dL	100.548±12.126	73.323±12.741	P<0.001
Fe µg/dL	113.871±29.112	69.411±8.403	P<0.001
Cu µg/dL	118.612±12.88	152.942±10.92	P<0.001

**Significant at the 0.05 level (2-tailed).*

The findings showed a statistically significant rise in both MPO and C-RP (P < 0.001) in the PTC group relative to the control group. Additionally, the findings indicated that the concentrations of Zn, Fe, and Mg were markedly reduced in the PTC group compared to the control group (P < 0.001; Table 2).

Furthermore, the results showed a notable connection between MPO and CRP (P = 0.031). Additionally, the results showed a notable negative correlation between Zn and MPO (P = 0.047; Table 3)

Table (3) Pearson correlation between all parameters in the PTC group

	MPO	**Fe**	**Cu**	**Zn**	**CRP**
MPO		R=-0.075 P=0.686	R=-0.075 P=0.762	*R= -0.473** **P =0.047**	*R=435** **P=0.031**
Fe	R=-0.075 P=0.686		R=-0.084 P =0.765	R=0.310 P=0.072	R=-0.054 P=0.763
Cu	R=-0.075 P=0.762	R=-0.084 P =0.765		R=-0.365* **P=0.034**	R=0.063 P =0.722
Zn	*R= -0.473** **P =0.047**	R=0.310 P=0.072	*R=-0.365** **P=0.034**		R=-0.054 P=0.767

**Significant at the 0.05 level (2-tailed).*

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Table (4) Multiple linear regression analysis predicting MPO levels

Predictor	B	SE	β	95%	T-Test	P value
Constant	0.07	0.812	---	-1.556-1.696	0.086	0.932
Group (PTC & Control)	1.684	0.29	0.895	1.104-2.265	5.809	**0.001**
Zn	-0.006	0.004	-0.122	-0.015-0.002	-1.442	0.155
Fe	-0.002	0.003	-0.058	-0.007-0.003	-0.679	0.500
Mg	0.272	0.260	0.067	-0.248-0.792	1.048	0.299
Cu	-0.003	0.005	-0.107	-0.012-0.006	-0.923	0.455
CRP	0.042	0.045	-0.075	--0.132-0.006	0.752	0.360

N=65, R=0.908, R^2 =0.825, adjusted R^2= 0.810, P<0.001

Multiple regression analysis indicated that disease status was the main independent predictor, with MPO significantly linked to malignant conditions instead of alterations in trace elements (Table 4)

Discussion:

The results showed a statistically significant increase in both MPO and CRP (P < 0.001) in the PTC group relative to the control group. Additionally, the Pearson correlation analysis revealed a notable positive correlation between CRP and MPO (P = 0.031) and a significant negative correlation between Zn and MPO (P = 0.031).

The simultaneous increase in MPO and CRP suggests that enhanced neutrophil activation may intensify inflammatory signaling pathways, resulting in greater hepatic CRP synthesis and, consequently, heightened oxidative stress. These results correspond with previous studies emphasizing a beneficial link between MPO levels, inflammatory indicators, and disease severity (18). MPO is an enzyme that contains heme and is released by activated neutrophils in response to inflammation.

replies. It has an important function in the generation of reactive oxygen species (ROS), especially hypochlorous acid, which leads to oxidative stress and harm to tissues (19). Consequently, the heightened MPO levels found in PTC patients might indicate a more inflammatory and oxidative setting linked to tumor progression.

Additionally, the findings indicated that Zn, Fe, and Mg concentrations were markedly reduced in the PTC group compared to the control group (P < 0.001). Moreover, the findings showed a significant negative correlation between Zn and MPO (P = 0.047). Zn is essential for the immune response, and maintaining its balance is a key factor in a healthy immune system (19).

As a result, the decrease in Zn levels may adversely impact thyroid function, possibly playing a role in carcinogenesis (20). Zn plays a role in initiating the pro-inflammatory response, especially via the Nuclear Factor Kappa B (NF-κB) pathway. It might also relate to controlling

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oxidative stress and modulating inflammatory cytokines (20,21).

The decline in magnesium levels within the PTC group is well recognized and backed by various studies. Clinical data indicate a link between low serum magnesium levels and thyroid cancer (22). Unlike our study, there is no relationship between Mg and MPO. Mg may play a role through mechanisms related to oxidative stress, ongoing inflammation, and alterations of the tumor microenvironment (TME).

Multiple studies have shown that a lack of Zn and Mg leads to an inflammatory condition. Oxidative stress and inflammation are closely associated with dysfunctional mitochondrial activity. Elevated ROS can stimulate nuclear factor kappa B (NF-κB) and trigger the production of pro-inflammatory cytokines, such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α). Zn additionally promotes the creation of metallothioneins, which are protective proteins that sequester reactive oxygen species (ROS) and shield against hydroxyl radicals (23-25).

Overall, iron levels were notably reduced ($P < 0.001$) in the PTC group relative to the control group. Moreover, there is no correlation between MPO and Fe, despite the fact that Fe deficiency is influenced by extended inflammation. Specifically, increased production of interleukin-6 (IL-6), which is involved in regulating iron levels, is noted. IL-6 specifically boosts the production of hepatic hepcidin, the main regulator of iron metabolism. As a result, elevated hepcidin reduces intestinal iron absorption and inhibits iron release from macrophages and hepatocytes through ferroportin degradation, leading to functional iron deficiency.

In conclusion, inflammation limits iron access and reduces erythropoiesis and its effectiveness, leading to a decreased lifespan of red blood cells (26,27). Moreover, MPO produces highly reactive oxidants, including hypochlorous acid, which can oxidize hemoglobin and harm erythrocyte membranes. Moreover, oxidants derived from MPO might indirectly affect iron metabolism by stimulating inflammatory signaling pathways that boost the expression of IL-6 and hepcidin, thus strengthening iron sequestration (28).

The significant rise in Cu levels in the PTC group ($P < 0.001$) could be linked to an inflammation-induced acute-phase reaction. Interleukin-6 signaling prompts the liver to generate ceruloplasmin; in cancer-related inflammation, serum copper concentrations increase together with ceruloplasmin. Furthermore, increased copper requirements for proliferation, angiogenesis, and the development of cancerous cells may interfere with the function of copper transport and trafficking proteins like CTR1 and ATP7A/ATP7B, resulting in alterations in copper levels (27, 29).

Multiple regression analysis suggests that malignancy is the primary independent predictor of elevated MPO levels, instead of mere changes in trace element concentrations. Even though trace elements (like Cu or Zn) are often found at higher levels in cancer patients, they are generally considered as indicators of modified metabolism or nutritional health instead of direct contributors to MPO secretion (30,31).

Conclusion

The findings discussed here show various changes, including notable increases in MPO, C-RP, and Cu levels that are statistically significant. Conversely, lower concentrations of Zn,

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Fe, and Mg might be associated with inflammation and impaired trace element balance in PTC patients. These changes might illustrate a linked connection between inflammatory activation, oxidative stress, and metabolic reprogramming within the tumor microenvironment. Significantly, in this research, the causation and directionality of the relationship between MPO and trace elements remain unverified.

Recommendations:

Further research is necessary to elucidate the mechanistic pathway and clinical significance of these findings

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Ethical statement

Approval for this study's ethics was received from the Ethics Committee at the College of Medicine, Al-Iraqia University (FM.SA/77, dated 9/4/2026).

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Conflicts of interest: Non.

Author contributions

All authors contributed to sample collection and the preparation of the original draft, and read and approved the final version of the manuscript.

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