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ORIGINAL ARTICLE

Circulating Microrna-22 As a Biomarker Related to Oxidative Stress in Hyperthyroid Women Patient

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Abstract

Background Recent studies have connected microribonucleic acid (miRNA) to several illnesses as a stimulant or inhibitor. Oxidative stress and thyroid diseases are connected to miRNA-22. The underlying processes remain unknown. In this study, hyperthyroid women's miRNA-22 expression is linked to oxidative stress.

Materials and Methods 40 women suffering from hyperthyroidism and 40 in this study, healthy volunteers who served as controls were included. The levels of serum thyroid-stimulating hormone (TSH) were measured by sandwich assay, While the competitive binding immunoenzymatic assay was used to determine the levels of free triiodothyronine (FT3) and thyroxine (T4). To assess lipid profiles, an automated analyzer was employed. By enzyme-linked immunosorbent assay (ELISA), Interleukin 6 (IL-6) levels were measured. Activity of superoxide dismutase (SOD), catalase activity (CAT), (MDA) malondialdehyde, and levels of advanced oxidation protein products (AOPPs) assessed using a colorimetric technique. The quantitative polymerase chain reaction was used to evaluate the expression of serum miRNA-22.

Results Non-significantly increase SOD and significantly increase CAT activity were identified in patient groups than in the control group ($P<0.05$), also the patient group's AOPP and MDA concentrations were discovered to significantly rise from those of the control group. ($P< 0.05$). IL-6 levels were significantly higher in the patient group than in ($P<0.05$) the control group. The level of miRNA-22 was higher in the sick group as compared to the control groups ($P<0.05$).

Conclusion The pathophysiology of oxidative stress brought on by hyperthyroidism involves miRNA-22 expression, Oxidative stress increases and miRNA-22 gene expression increase in a reciprocal manner, which results in the disease's development.

Keywords: Hyperthyroid; Oxidative Stress; miRNA-22.

1 Introduction

The most widespread endocrine condition in the world is thyroid dysfunction, which comes in second place to diabetes. Men are less likely than women to be affected by this condition, and the percentage rises with age [1]. Hyperthyroidism occurs when there is excessive production of thyroid hormones [2]. Grave's disease is the most typical cause of thyrotoxicosis in the United States. Grave's disease is an autoimmune condition resulting in excessive T3 and T4 synthesis because of antibodies generated against the thyroid gland's TSH receptors. Grave's disease is more common in women and has a modest prevalence rate in the general population (0.3–0.6%) [3]. The manufacturing of thyroid hormones depends on hydrogen peroxide. Two isoform enzymes generate it in the thyroid gland. Dual oxidase 1 (DUOX1) and 2(DUOX2) belong to the NOX fam-

ily, with the most convincing experimental evidence for DUOX2. At each stage of the thyroid hormone production, including the oxidation of iodide and the subsequent creation of the hormone as well as the coupling reaction involving iodothyronine, hydrogen peroxide serves as an electron acceptor. It is necessary for the function of thyroperoxidase (TPO), the principal enzyme in the manufacture of thyroid hormones [4].

Oxidative stress happens when pro-oxidants and antioxidants are not in equilibrium; Free radicals also contribute to an increase in the severity of the disease for many diseases, including cases of infertility, neuropathy, and retinopathy [5].

Antioxidants are chemicals that can provide hydrogen atoms to free radicals produced by cellular metabolism or outside sources. This can damage DNA, lipids, and amino acids, eventually resulting in cell death [6]. The body's first line of defense against ROS is the family of superoxide dismutases (SOD). They function by oxidizing very reactive superoxide radicals and turning them into hydrogen peroxide (H2O2). It is then broken down by the enzymes peroxiredoxin (PRDX), Catalase (CAT), and glutathione peroxidase (GPX) [7]. The antioxidant system of the cell is supported by the antioxidant enzyme CAT, which is found in peroxisomes and plasma [8].

One of the suggested possible markers for oxidative damage is advanced oxidation protein products (AOPPs), which result from oxidative and carbonyl stress and increase overall inflammatory activity [9]. Malondialdehyde (MDA) is a good biomarker of oxidative stress and damage caused by free radicals in biological samples. MDA is primarily produced through the peroxidation of polyunsaturated fatty acids [10].

Interleukin (IL-6), a pleiotropic cytokine with different impacts on cells and tissues, is created by numerous distinctive cell sorts, counting safe cells, fibroblasts, endothelial cells, and tumor cells [11].

Numerous studies have demonstrated the importance of miRNAs for thyroid gland growth, differentiation, and hormone production. MiRNAs are noncoding, single-stranded RNAs with 19–25 nucleotides. They have a role in the regulation of transcriptional and post-transcriptional gene expression through specific interactions with target genes [12]. Physiological and pathological processes that miRNAs regulate include oxidative stress, adipocyte differentiation, metabolism, and appetite control [13]. MiR-22 is a 22-nucleotide protein that is found in a wide range of tissues and cell types. Its expression was first discovered in HeLa cells. However, it was later discovered to be highly conserved across many vertebrate species [14]. The purpose of this study was to summarize the regulation of miRNA-22-driven molecular gene expression, its connection to oxidative stress and hyperthyroid women development, and to review recent developments in this area.

2 Experimental Part

2.1 Sample collection and storage

Eighty participants in the current study were divided into two groups: women with hyperthyroid and normal control groups. We acquired all patient data, including age and sickness duration. The participants in the control group were carefully chosen to ensure that none of them had thyroid problems or any other disorders.

The average age of the participants in the current study ranged from (19 - 45) years old. For routine check-ups, patients visit the Al-Diwaniyah Teaching Hospital. A specialized physician identified all research participants, and clinical characteristics and biochemical tests supported the diagnosis, such as Thyroid Stimulating Hormone (TSH), Thyroxine (T4), and Triodothyronine (T3). Patients' details such as age, gender, BMI, smoking status, family history, and duration of illness are also documented. The Nabu Scientific Foundation in (Baghdad, Iraq), does every laboratory test analysis. Were used in the current investigation Al-Diwaniyah Teaching Hospital, Baghdad Lab, and Laboratory for Biochemistry at the College of Science at Al-Qadisiyah University are all in Al-Diwaniyah, Iraq.

Exclusion criteria: Women with autoimmune disease, COVID-19, cancer, diabetes, or hypothyroidism were not included in the study. Five milliliters of each subject's blood were taken and separated into serum. The blood serum was separated from the gel tube by centrifuging it at 4000 rpm for 10 to 15 minutes. Four sections of the isolated serum were separated using Eppendorf tubes. One component of the miRNA-22 research was maintained at -40°C, whereas the rest were preserved at -20°C during biological investigation.

3 Method

The Serum Thyroid-Stimulating Hormone (TSH) levels were measured by sandwich assay (Thyroid-Stimulating Hormone (CLIA) Kit, Mindray, China), while Free Triiodothyronine (FT3), and Thyroxine (T4) levels were measured competitive binding immunoenzymatic assay (Free Triiodothyronine (CLIA) Kit, Mindray, China) and (Total Thyroxine (CLIA) Kit, Mindray, China) respectively. Total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) measures were made as part of lipid profiles, utilizing standard procedures and an automated analyzer (Abbott, USA) from Al-Diwaniyah

Teaching Hospital. Human Interleukin 6 (IL-6) levels were measured by Enzyme-Linked Immunosorbent Assay (ELISA) (Human IL-6(Interleukin 6) ELISA Kit, Elabscience®, and USA). Spectrophotometer was used to measure the serum's activity (SOD) [15]. UV spectrometry was used to determine (CAT) [16]. The concentrations of (MDA) were measured using a spectrophotometer [17]. UV spectroscopy was used to assess the concentration of (AOPP) [9]. The expression of miRNA-22 in serum was evaluated using quantitative polymerase chain reaction (qPCR). In order to extract RNA, TRIzolTM Reagent from Invitrogen, USA, was used with (0.3 mL) of serum. The cDNA was made by miRNA with miR-22-RT by use (ProtoScript® First Strand cDNA Synthesis Kit, NEB, UK). The PCR (NEB, UK) utilized Luna Universal qPCR Master Mix. The resultant cDNA was mixed with miR-22-specific forward reverse universal primers (Table 1) and cDNA Bright Green master mix. The U6 gene was used as an internal control. The proportional miR-22 levels and (2 $-^{\Delta}\Delta Ct$) were calculated by threshold cycle (Ct), and the results showed an expression fold change.

4 Statistical Analysis

The Statistical Package for Social Sciences (SPSS) version 28 is used to conduct the statistical analysis. The data are presented as a mean and a standard deviation. Independent-sample t-test or a nonparametric ranking (Mann–Whitney U test) were used to evaluate various groups for normal and non-normal distribution data. A ($P > 0.05$) was considered significant throughout the investigation. The relationship between two continuous variables was found using the correlation coefficient (r).

5 Results

In this study, 40 patients and 40 healthy controls participated. Table 2 displays the characteristics of the patients as well as the outcomes of the biochemical tests. The body mass index (BMI) values in hyperthyroid patients were decreased than those in the control group. In Table 3, The T3 and T4 levels increased in the hyperthyroid group, but TSH levels were noticeably decreased than in the control group. While HDL-C was substantially greater in the control group, TC, TG, and LDL levels in the hyperthyroid group were significantly lower than those in the control ($P < 0.05$).

Table 1: Primers used for qPCR experiments.

Primers	Sequence	Size	Product Size (bp)
miR-22_RT	GTCGTATCCAGTGCGTGTCGTGGAGTCGGCAATTGCACTGGATACGACTAAAGC	47	——
miR-22For	GAGCTGCACTGACCAGTAGG	20	
			99
miR-22Rev	GTGCTGGCAGATGGATCACT	20	
U6 For	GAGAAGATTAGCATGGCCCCT	21	
			60
U6 Rev	ATATGGAACGCTTCACGAATTTGC	24	

Table 2: Demographic characteristics of the control group and patients.

Characteristic	Control	Hyperthyroid	p-value
Number	40	40	
Age (years)			
Range	19-45	20-45	0.75
Mean ± SD	34.56 ± 7.90	33.875 ± 8.16	
BMI (Kg/m2)			
Range	20 - 25.8	20.4 - 34.6	<0.0001
Mean ± SD	23.03 ± 1.349	27.14 ± 3.541	

Table 3: The clinical and lab characteristics of the study groups.

Parameters	Control	Hyperthyroid	p-value
Number	40	40	
TSH (µIU/mL)			
Range	0.65-4.94	0.08 -0.29	0.001
Mean ± SD	3.30675±1.139	0.18435± 0.0538 *	
T3 (ng/ml)			
Range	0.59-1.57	0.75 -11.63	0.001
Mean ± SD	1.105±0.2984	3.0037± 2.327 *	
T4 (µg/dL)			
Range	4.1-13.81	12.62-20.96	0.001
Mean ± SD	9.4135±2.5489	17.066 ± 2.2050 *	
TC (mg/dl)			
Range	111 - 168	96 - 137	0.001
Mean ± SD	144.35±21.68	101.25±38.69 *	
TG (mg/dl)			
Range	54 - 156	43 - 111	0.001
Mean ± SD	106.075±30.08	74.275±16.39 *	
HDL-C (mg/dl)			
Range	35 - 72	33 - 89	0.027
Mean ± SD	51.175±10.27	46.35±8.804 *	
LDL-C (mg/dl)			
Range	43.4 - 149.2	24.4 - 107.4	0.001
Mean ± SD	85.98±26.336	51.135±15.36 *	
SOD activity U/ml			
Range	7.437 - 14.47	6.935 - 18.49	0.334
Mean ± SD	10.62 ± 2.372	11.26 ± 3.453*	
CAT activity U/ml			
Range	0.7225 - 3.096	2.064 - 5.264	<0.0001
Mean ± SD	1.632 ± 0.7139	3.272 ± 0.8608*	
MDA Concentration (µmole/L)			
Range	0.05519 - 0.6596	0.1629 - 0.4712	0.003
Mean ± SD	0.2102 = 0.1159	0.2788 = 0.08165	
AOPP Concentration (µmole/L)			
Range	13.5 - 41	21 - 48.5	0.0009
Mean ± SD	26.63 - 8.411	33.05 ± 8.191*	
Comparison of IL-6 level pg/mL			
Range	2.879 - 11.22	15.69 - 23.7	<0.0001
Mean ± SD	5.635 ± 2.253	20.2 ± 2.766*	
MicroRNA-22 relative expression			
Range	1–1	1.009 - 3.238	<0.0001
Mean ± SD	1 ± 0	1.808 ± 0.612*	

* The mean statistically significant variations between the sick groups and the control group ($P < 0.05$) Body mass index (BMI). TSH stands for thyroid stimulating hormone, T3 for triiodothyronine, and T4 for thyroxine. TC for total cholesterol, and TG for triglyceride. LDL stands for low-density lipoprotein, and HDL-C stands for high-density lipoprotein.

SOD activity in comparison to the control group was non-significant increased ($P < 0.05$) in the hyperthyroid group (Figure 1). In contrast, CAT activity in comparison to the control group was significantly increased ($P < 0.05$) in the hyperthyroid group (Figure 2). MDA levels were greater in the hyperthyroid group than in the control group ($P < 0.05$) (Figure 3). The hyperthyroid group's AOPP levels did not significantly rise ($P < 0.05$) (Figure 4). IL-6 level was increased in hyperthyroid group when compared to control group ($P < 0.05$) (Figure 5). miRNA-22 expression levels in serum were significantly greater in the hyperthyroid group, according to qPCR miRNA analysis (Figure 6).

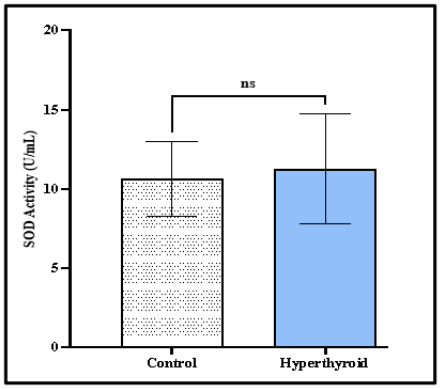

Figure 1: SOD activity U/ml comparison between the hyperthyroid and control groups P-value = 0.355.

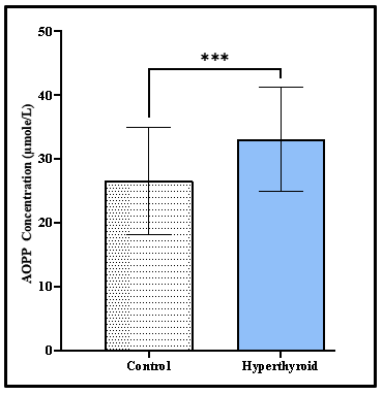

Figure 4: AOPP levels in µmol/L are compared between the hyperthyroid and control groups (P-value = 0.314).

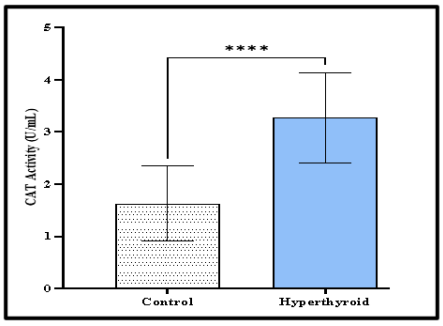

Figure 2: CAT activity U/ml comparison between the hyperthyroid and control groups (P-value < 0.001). The patient groups and the control group's statistically significant differences are marked by different letters ($P < 0.05$).

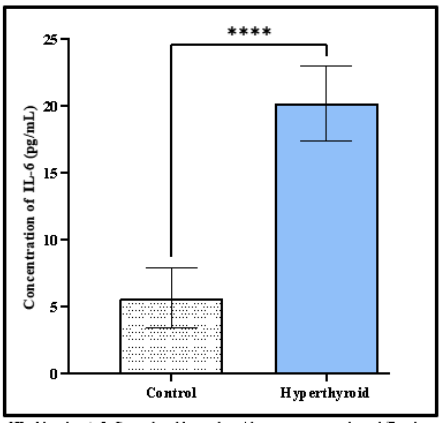

Figure 5: Comparison of IL-6 level pg/mL Control and hyperthyroid groups were evaluated (P-value < 0.001). The patient groups' and the control group's differences that are statistically significant are marked by different letters ($P < 0.05$).

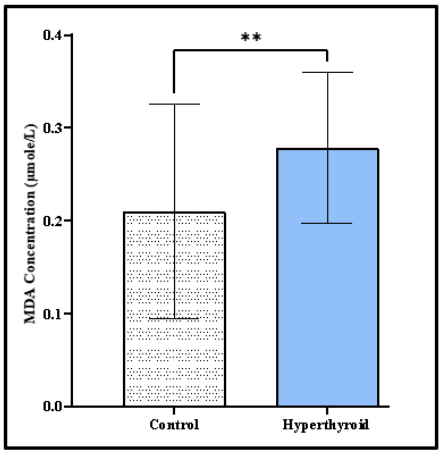

Figure 3: MDA level comparison between the hyperthyroid and control groups during the study (P-value = 0.001). The patient groups' and the control group's differences that are statistically significant are marked by different letters ($P < 0.05$).

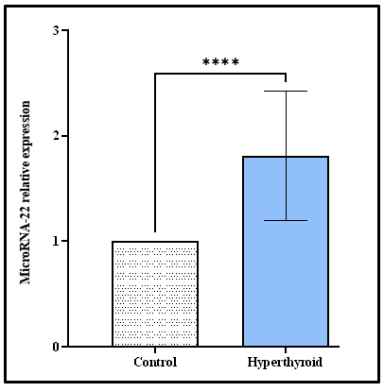

Figure 6: The study groups' levels of microRNA-22 expression were compared, and the hyperthyroid group control (P-value < 0.001). Patient groups' and the control group's differences that are statistically significant are marked by different letters ($P < 0.05$).

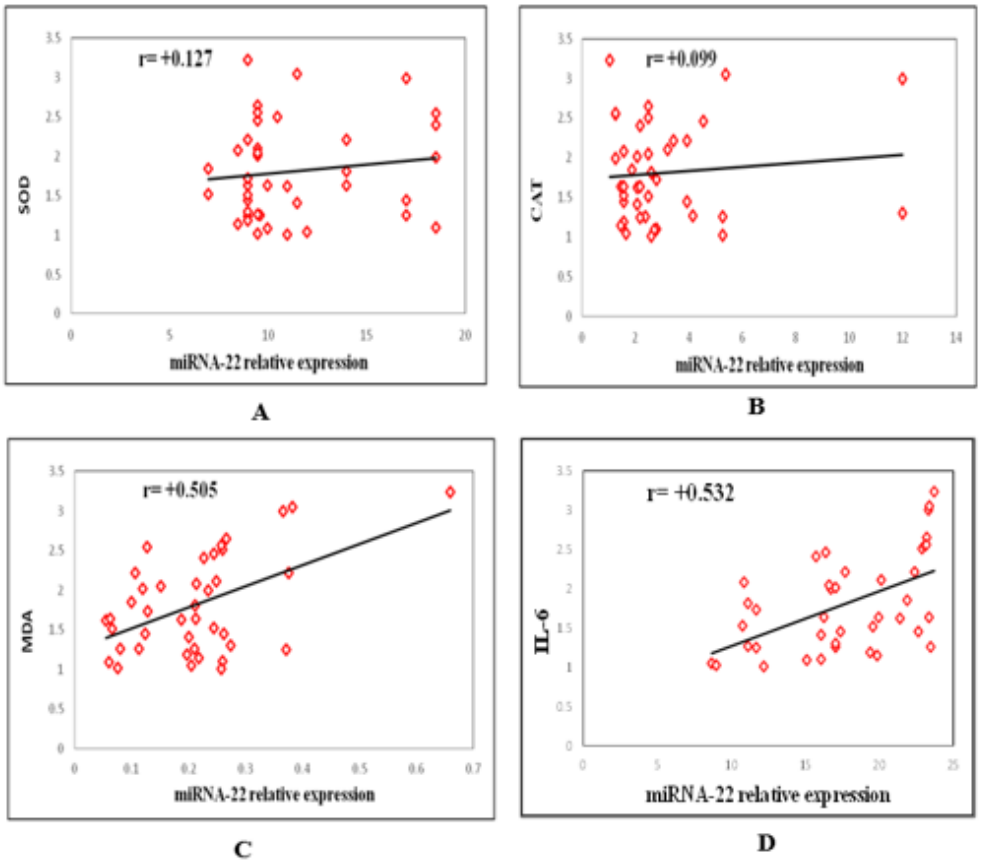

Figure 7: Correlation between microRNA-22 and other biomarkers in the hyperthyroid group (A) with SOD, (B) with CAT, (C) with MDA, and (D) with IL-6. r: means the value of the correlation coefficient.

In the hyperthyroid group, miRNA_22 showed little significant positive relationships with SOD and CAT but significant positive, strong associations with MDA and IL-6 (Figure 7).

6 Discussion

There was a decrease in the patient group's TG, TC, and HDL-C values related to the control groups (Table 2) because of increased excretion of cholesterol and an increase in the turnover of LDL-C, causing a reduction in TC [18]. Thyroxine levels affect LDL oxidation., An increase in thyroid hormone levels can influence HDL-C metabolism by enhancing cholesteryl ester transferase activity, which turns cholesteryl esters and TG in HDL-C into VLDL-C in the opposite direction [19]. This result is consistent with other research conducted by Khinteel Jabbar, N. Al-Abady et al. (2022) [20]. Under normal circumstances, epithelial cells of the thyroid have a moderate production of reactive oxygen species (ROS) that are physiologically required to form thyroid hormones. These are not necessarily toxic because they are continuously detoxicized by the synthesis of the hormone or the endogenous antioxidant system [21]. It is deduced that oxidative stress occurs when reactive free radicals cause oxidative damage to the macromolecular structures of the cell. The thyroid gland contributes significantly to the production of general oxidative stress in disease states [22].

Thyroid hormones help to control the state of oxidative metabolism and basic metabolism. These hormones have the potential to significantly alter the quantity and activity of molecules in the mitochondrial respiratory chain, which could enhance the formation of reactive oxygen species (ROS) [23]. When compared to the control group, the findings indicated that MDA levels were higher in women with hyperthyroidism. The oxidant and antioxidant status of the human body is correlated with thyroid hormones [24]. Oxidative stress is significantly influenced by thyroid hormones, according to results from in vitro and in vivo investigations. Untreated hyperthyroidism is linked to a rise in serum/plasma levels of oxidative stress markers such as lipid peroxides, hydrogen peroxide, and MDA when compared to euthyroid patients [25]. The finding of elevated lipid peroxidation is consistent with Erem, Suleyman et al. (2015) [26].

When compared to the control group, the findings revealed that AOPP was higher in women with hyperthyroidism. Increased ROS production in hyperthyroidism is caused by an enhanced metabolic state and increased oxygen demand [27]. It can oxidize a variety of biological components, including proteins, lipids, and DNA, changing how tissues function. In several tissues with experimental hyperthyroidism, increased protein oxidation has been demonstrated. The plasma of patients with hyperthyroidism showed an increase in the protein oxidation biomarker [28]. The results is consistent with Khinteel Jabbar, Al-Abady et al. (2022) [29].

Two enzymes involved in the production and oxidation of hydrogen peroxide, SOD and CAT, are significantly influenced by the body's thyroid function. In fact, an increase in some antioxidant enzymes' activity, like CAT and SOD, The primary antioxidants in the body, maybe a sign that the produced oxidative stress has not been adequately compensated for. These enzymes may remove excess.O-2, H2O2, and peroxides ROOH generated by free radicals. SOD, for instance, catalyzes the transformation of the superoxide anion radical into H2O2. The enzymes GPx and CAT then break down the hydrogen peroxide that results from this process. Our findings showed an increased activity of CAT and SOD in women with hyperthyroid, which is a reflex mechanism against increased oxidative stress induced by hyperthyroidism; the results agree with Messarah, Boumendjel et al. (2010) [30].

The results showed a statistically significant increase in the concentration of IL-6 in the women with hyperthyroidism compared with the control group. The thyroid gland produces IL-6, which is induced by TSH, IL-1, and maybe TSH receptor antibodies [31]. In cases of hyperthyroidism, IL-6 may come from the thyroid gland, mononuclear cells, and bone tissue, among other potential sources [32]. According to some research, elevated IL-6 levels in people with Graves' disease may indicate how severe the condition is because of the size of the increase [33]. Our increased serum IL-6 levels again suggest that a similar immunological effector mechanism may mediate hyperthyroidism. Thus, one cause of elevated serum IL-6 levels is increased intrathyroid development of IL-6 in hyperthyroid patients. Our finding is consistent with Senturk, Kozaci et al. (2003) and Jha, Kondhalkar et al. (2021) [31, 34].

Research demonstrated a statistically significant increase in miRNA-22 expression in women with hyperthyroidism for the first time. Additionally, Hashimoto's thyroiditis and hyperthyroidism are closely related to the expression of mir-22. In thyroiditis and hyperthyroidism, Mir-22 is inappropriately expressed, which raises the possibility that miRNA-22 is connected to the emergence of thyroid disorders. However, it is unclear if mir-22 influences the aberrant thyroid cell growth brought on by TSH [35].

This could be explained by the relationships that were reached, as a solid rapport existed. Found between miRNA-22 and MDA. It is possible that the reason for the increase in oxidative stress in this group led to an increase in the expression of miRNA-22 or vice versa, and another reason could also be that the rise of IL-6 has a relationship with the rise of miRNA-22, where this relationship was confirmed by correlations that worked between miRNA-22 and IL-6, where a strong positive relationship was observed between them as showed in (Figure 7).

7 Conclusion

Serum-circulating microRNAs play an important role in common pathogenic mechanisms and may be particularly useful markers and targets for treating hyperthyroidism, where the results showed the strongest statistical evidence for the level of microRNA-22 was in the hyperthyroid group. A change in microRNA-22 expression may indicate a possible role for this biomarker in the pathogenesis of hyperthyroid. This research found a strong correlation between miRNA-22's gene expression and its stimulus of oxidative stress.

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Conflict of Interest: No conflicts of interest exist between the authors and the publication of this work.
Ethical consideration: The ethical committee approved the study at College of Science, University of Al-Qadisiyah, Al-Qadisiyah, Iraq.

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