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ORIGINAL ARTICLE

Up-regulation of MiR-146a-5p and MiR-155-5p are Involved in Inflammatory Immune Dysregulation in Patients with Hashimoto's Thyroiditis and Helicobacter Pylori Infection

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ABSTRACT

Helicobacter pylori (HP) is an infection related to metabolic and autoimmune disease Hashimoto thyroiditis (HT). HP-modified microRNA (miRNA) expression leads to various disorders. We aimed to evaluate circulatory miR-146a-5p and miR-155-5p expression in HT and to investigate their correlations with the clinical profile of HT and HP infection.

Methods: We enrolled 100 subjects; 50 participants as healthy control and 50 patients with HT. The diagnosis of HP- infection by-HP antigen in stool and antibodies against cytotoxic- associated gene A (Cag-A). We tested serum antibodies against thyroid antigens. We used Quantitative real-time RT-PCR for the assessment of serum miR-146a-5p and miR-155-5p.

Results: Among 100 studied participants, patients inf*. Concerning had significantly higher values of miR-146a-5p (3.94±0.8), compared to HT patients without HP infection (1.84±0.3) and control group (0.98±0.1), p value<0.001*. Concerning miR-155-5p, there were statistically significant higher values in HP infection (3.61±2.2) compared to HT patients without HP infection (1.91±1.1) and control group (0.90±0.35), p value<0.001*. There were significantly positive correlations with nausea, vomiting, heartburn, anti-TPO, anti-TG, TSH, HP antigen, and Cag-A. On the opposing, they were negatively correlated with FT3 and FT4. linear regression analyses revealed that the only variables independently associated with miR-146a-5p were anti-TPO and FT4. Whereas the only variables independent associated with miR-155-5p were anti-TPO and FT3, p value<0.001*.

Conclusion: miR-146a-5p and miR-155-5p overexpressed in patients with HT, more specifically in patients infected by HP and they were significantly correlated to gastrointestinal symptoms thyroid dysfunction, and autoimmunity.

Keywords: cytotoxic-associated gene A; Quantitative real-time RT-PCR; microRNAs; anti-thyroid peroxidase antibodies; H. Pylori.

Introduction

Hashimoto thyroiditis (HT) is characterized by thyroid infiltration by lymphocytes that leads to the destruction of thyrocytes. It is well established that there was Striking evidence of crosstalk between environmental and genetic factors in the Patho mechanisms of HT [1].

It is established that Helicobacter pylori (HP) infection contributes to the development of HT [2]. Several researchers have discovered many roles of HP in the pathogenesis of HT. It is noteworthy to mention that one of the most important of HP roles is the cross-reactivity between HP and thyroid follicles, indicating the presence of antigenic similarity

between both of them [3]. There is a wealth of research highlighting the dysregulation of immunity by HP infection as it initiates cellular immunity, which leads to increased production of proinflammatory cytokines [4].

MicroRNAs (miRNAs) are noncoding RNAs that participate in many disorders including autoimmunity [5]. Indeed, it has been reported that H. pylori may deregulate miRNA expression to avoid host defenses and successfully persist in the gastric niche. It must be emphasized that H. pylori regulates the expression of miRNAs that regulate gene expression to control inflammation and prevent autoimmunity [6,7].

It has been demonstrated that MiR-146a is associated with immunological reaction to H. pylori [8]. There is growing evidence emphasizing the signaling pathways of MiR-146a in controlling cytokine production [9].

Several studies detected that infection with HP is very common in our region in particular our country [10-12]. This is not surprising given the well-recognized connection between HP infection and HT. Despite these pieces of evidence, there is a substantial gap in our knowledge about the pathological role of miRNAs in HP infection complications and HT. In this regard, we aimed in this research to evaluate if circulatory miR-146a-5p and miR-155-5p expression in HT, and to investigate the miR-146a-5p and miR-155-5p correlations with the clinical profile of HT and HP infection.

Subjects and methods

This current research conducted 50 patients with HT and 50 apparent health subjects as controls. The diagnosis of HT is established by a combination of clinical signs, thyroid function, serum antibodies against thyroid antigens; anti-TPOAb and TgAb, and thyroid color Doppler [13]. The flowchart of the study is shown in figure1. All subjects underwent comprehensive history, clinical examination, investigations, and examination of stool samples for H. pylori fecal antigen test and anti-cagA antibody, IgG class by anti-cagA antibody kit.

Written informed consent was obtained from all participants and the study was approved by the research ethical committee of the Faculty of Medicine, Zagazig University. (Ethics number. 11101), The work has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for students involving humans.

Micro-RNA	Forward primer	Reverse primer
miRNA-155	CGTGCTCATTTTAATGCTAATC	CCAGTGCAGGGTCCGAGGTA
miR-146a	CTCGCTTCGGCAGCACA	AACGCTTCACGAATTTG
U6	GCTTCGGCAGCACATATACTAAAAT	CGCTTCACGAATTTGCGTGTCAT

Statistical analysis

All statistical analyses were performed using IBM Corp. Released in 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp. Descriptive and analytical statistics were performed for all the studied variables. Several statistical tests were used during the analysis process including ANOVA, and X^2 tests for comparisons of numerical and categorical data, respectively for three or more groups. We used LSD (least significant difference) of Post-Hoc Test for further evaluations . The normality of variables was confirmed with the Kolmogorov-Smirnov test. For the variables that are not normally distributed, the Mann-Whitney U test was used. The relationships of miRNA expression levels with clinical and biochemical characteristics were tested with the Spearman and Pearson correlation, and further evaluation of independent factors correlated with miRNAs in the HT group were investigated with linear regression test .The diagnostic power of miRNA-155 and miR-146a were investigated by ROC test.

Results

We enrolled 100 subjects, including 50 Patients with HT (17 patients without HP infection and 33 patients with HP infection) and 50 healthy controls. Both patients and control were matched regards age and sex. Interestingly, patients with HP infection had more frequent attacks of abdominal pain, nausea and vomiting, bloating, and heartburn in c comparison to

other groups. anti-TPO, anti-TG, and TSH levels were increased in HP infection compared to other studied groups, p value<0.001*. On the contrary, the HP infection group had lower values of FT3 and FT4, compared to other studied groups, p value<0.001*.

We investigated our participants by Quantitative real-time RT-PCR for assessment of circulatory miR expression. Regarding miR-146a-5p, there were statistically significant higher values in HP infection (3.94±0.8) compared to HT patients without HP infection (1.84±0.3) and control group (0.98±0.1), p value<0.001*. Table 1

Concerning miR-155-5p, there were statistically significant higher values in HP infection (3.61±2.2) compared to HT patients without HP infection (1.91±1.1) and control group (0.90±0.35), p value<0.001*. Table 1

In the HT group, (n=50), miR-146a-5p levels were significantly positively correlated with gastrointestinal symptoms including nausea and vomiting as well as heartburn. Furthermore, miR-146a-5p levels s were significantly positively correlated with anti-TPO, anti-TG, and TSH. Even more interestingly, miR-146a-5p levels were significantly positively correlated with HP antigen and Cag-A. On the contrary, miR-146a-5p levels were negatively correlated with FT3 and FT4,p value<0.001* (Table 2).

Regarding miR-155-5p, there was a significantly positive association with gastrointestinal symptoms including nausea and vomiting as well as heartburn. Furthermore, miR-155-5p levels s were notably positively associated with anti-TPO, anti-TG, and TSH. Intriguingly, miR-155-5p levels were significantly positively associated with HP antigen and Cag-A. On the contrary, miR-155-5p levels were negatively associated with FT3 and FT4, p value<0.001* (Table 2).

Stepwise linear regression analyses in HT detected that among the studied significant correlated variables, the only variables independently associated with miR-146a-5p were anti-TPO and FT4. Whereas the only variable independent associated with miR-155-5p were anti-TPO and FT3 p value<0.001* (Table 3).

The strength of miR-146a-5p to detect HT was estimated via ROC analysis. The AUC was 0.978 (95% CI = 0.955–1.000) with sensitivity = 96%, specificity = 96%, and the cutoff values (1.37). When comparing our patients with control, p value<0.001* (Fig. 2 a). Regarding miR-155-5p, the AUC was 0.976 (95% CI = 0.955–1.000) with a sensitivity of 96%, specificity of 88%, and the cutoff values (1.04), p value<0.001* (Fig. 2 a).

If we used both epigenetic markers for the differentiation of HT from control. The AUC was 0.978 (95% CI = 0.954–1.000) with sensitivity = 96%, specificity = 76%, p value<0.001*, (Fig. 2 b).

The diagnostic power of miR-146a-5p had an AUC of 0.939 (95% CI = 0.858–1.000) with sensitivity = 93.3%, specificity = 82.4%, and cutoff values (1.37). When comparing our patients with control, p value<0.001* (Fig. 3 a). Regarding miR-155-5p, the AUC was 0.848 (95% CI = 0.726–0.971) with sensitivity = 92%, specificity = 93%, and the cutoff values (1.04), p value<0.001*, (Fig. 3 a).

If we used both epigenetic markers for the differentiation of HP infection from other studied case groups. The AUC was 0.934 (95% CI = 0.852–1.000) with sensitivity = 93.9%, specificity = 93.9%, p value<0.001*. (Fig. 3 b).

Table 1: - Clinical and laboratory characteristics of participants

Parameter	Control group (*n*=50)	HT group, (*n*=50)		*P* value
		Without HP infection (n=17)	With HP infection (n=33)	
Age (years)	34.1±8.8	34.5±5.2	34.8±7.3	0.990
Sex (male/female)	17/33	7/10	17/16	0.542
Systolic blood pressure	118.4±5.3	117.5±5.1	117.4±4.9	0.617
Diastolic blood pressure	76. 4±3.7	75.1 ±7.1	76.2 ±7.1	0.894
Body mass index	22.4±3.4	23.1±1.8	23.8±1.9	0.989
Abdominal pain	4(8%)	7(41.2%) *	24(72.7%) $, &	<0.001*
Nausea and vomiting	6(12%)	7(41.2%) *	28(84.8%) $, &	<0.001*
Bloating	4(8%)	9(52.9%) *	21(63.6%) $, &	<0.001*

Parameter	Control group (*n*=50)	HT group, (*n*=50)		*P* value
		Without HP infection (n=17)	Without HP infection (n=17)	
Heart burn	12(24%)	5(29.4%) *	20(60.6%) $, &	<0.001*
FT3(pg/ml)	1.71±0.11	0.95±0.12*	0.76±0.23$, &	<0.001*
FT4(ng/dl)	1.45±0.3	0.74±0.11*	0.54±0.12$, &	<0.001*
TSH (µIU/ml)	3.5±1.17	5.1±1.97*	6.5±3.97$, &	<0.001*
Anti TPO(IU/ml)	28.3±8.3	206.5 ±11.4*	365.1 ±18.2$, &	<0.001*
Anti TG(IU/ml)	45.6±22.3	393.4±24.6	398.4±34.5$	<0.001*
miR-146a-5p relative expression levels	0.98±0.1	1.84±0.3*	3.94±0.8$, &	<0.001*
miR-155-5p relative expression levels	0.90±0.35	1.91±1.1*	3.61±2.2$	<0.001*

TSH, thyroid stimulating hormone; FT3 free triidothyronine ,FT4;free thyroxine , Anti TG ;anti thyroglobulin antibodies, anti-TPO; anti-thyroid peroxidase antibodies * *P*< 0.05 when compared with control group.

*Significant P values (P < 0.05) when comparing the control group with patients without HP infection.

$ Significant P values (P < 0.05) when comparing the control group with patients with HP infection.

&Statistically significant P values (P < 0.05) when comparing patients without HP infection with patients with HP infection.

Table 2: Correlation of circulatory levels of miR-146a-5p and miR-155-5p expression levels with clinical and laboratory characteristics in HT groups.

parameters	miR-146a		miR-155	
	r	p		
Abdominal pain	0.228	0.111	0.202	0.160
Nausea and vomiting	0.397	<0.001*	0.314	<0.001*
Bloating	0.215	0.133	0.097	0.501
Heart burn	0.432	<0.001*	0.347	<0.001*
FT3(pg/ml)	-0.575	<0.001*	-0.519	<0.001*
FT4(ng/dl)	-0.482	<0.001*	-0.491	<0.001*
TSH (µIU/ml)(	0.833	<0.001*	0.651	<0.001*
Anti TPO(IU/ml)	0.827	<0.001*	0.645	<0.001*
Anti TG(IU/ml)	0.233	0.104	0.180	0.211
HP	0.453	<0.001*	0.398	<0.001*
Cag-A	0.373	<0.001*	0.343	<0.001*

HP ; helicobacter pylori ,Cag-A ,antibodies against cytotoxic- associated gene A
, * P < 0.05.

Table 3: Stepwise linear regression analyses in HT to test the influence of the main independent variables against miR-146a-5p and miR-155-5p levels (dependent variable) .

Model		Unstandardized Coefficients		Standardized Coefficients	t	P value	95.0% C.I	
		B	Std. Error	Beta			Lower Bound	Upper Bound
	(Constant)	0.645	0.085		7.553	<0.001*	0.476	0.815
miR-146a-5p	**Anti TPO**	0.009	0.000	0.919	23.030	<0.001*	0.008	0.009

	(Constant)	-1.356	0.590		-2.299	<0.05*	-2.527	-0.185
	Anti TPO	0.012	0.001	1.307	10.940	<0.001*	0.010	0.015
	FT4	1.342	0.392	0.409	3.426	<0.001*	0.564	2.119
miR-155-5p	**(Constant)**	0.597	00.121		4.921	<0.001*	0.356	0.838
	Anti TPO	0.008	0.001	0.838	15.214	<0.001*	0.007	0.009
	(Constant)	-1.626	1.096		-1.484	0.141	-3.800	0.549
	Anti TPO	0.012	0.002	1.219	6.276	<0.001*	0.008	0.016
	FT3	1.241	0.608	.396	2.041	<0.05*	0.034	2.447

* Significant P value *(P* < 0.05).

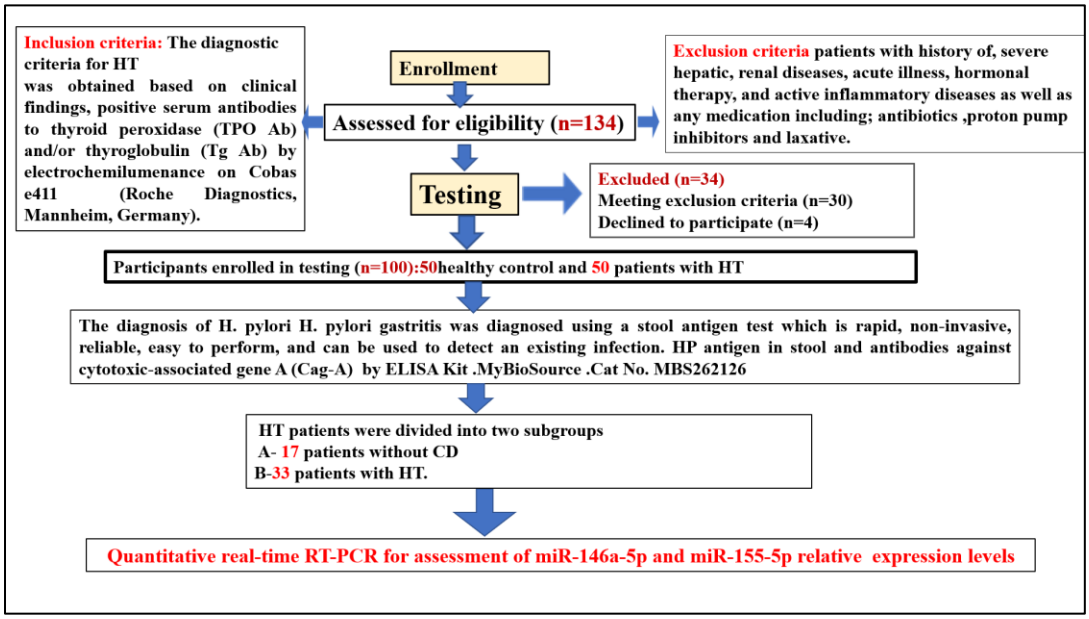

Figure 1: The flowchart of the study

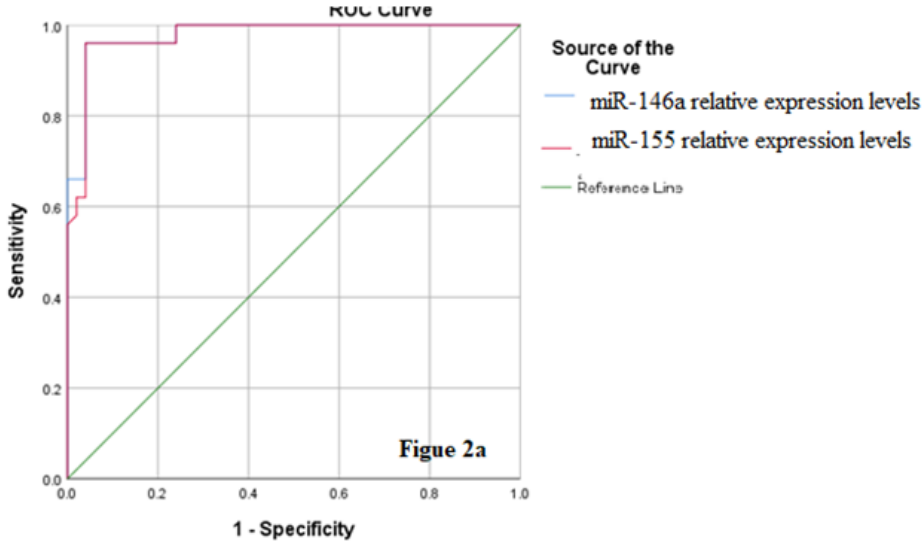

Figure 2a: The accuracy of miR-146a and miR-155 level for distinguishing patients with HT from control group.

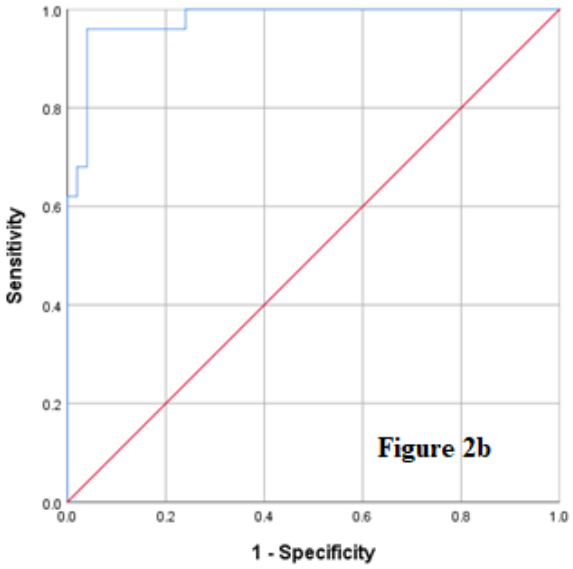

Figure 2b: The accuracy of combined miR-146a and miR-155 level for distinguishing patients with HT from control group.

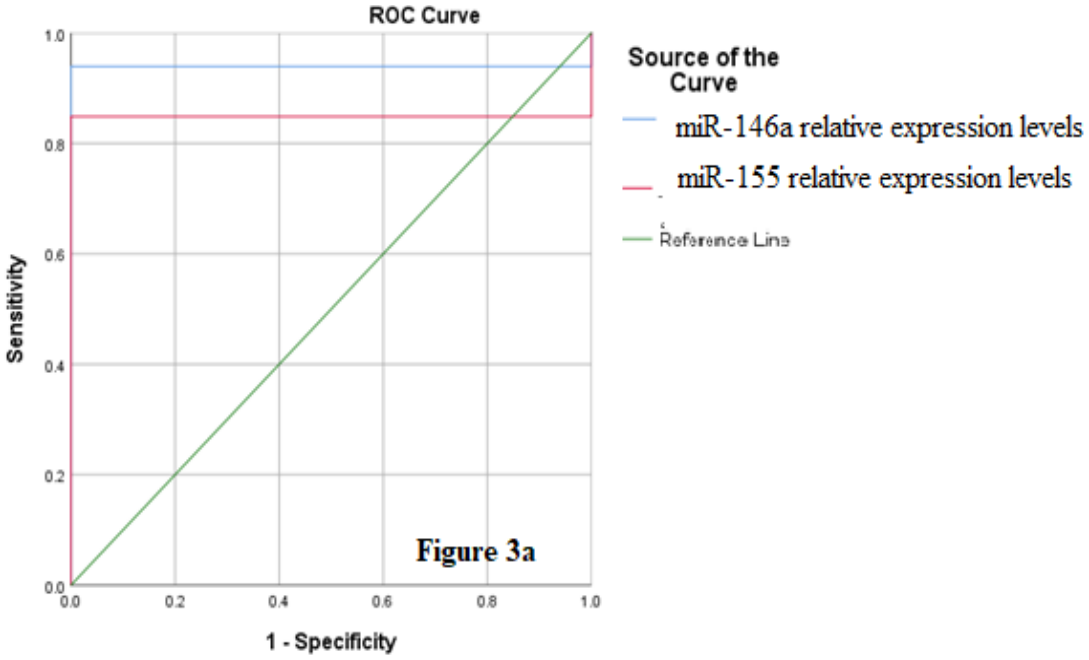

Figure 3a: The accuracy of miR-146a and miR-155 level for distinguishing patients with HP infection from patients without HP among studied case group.

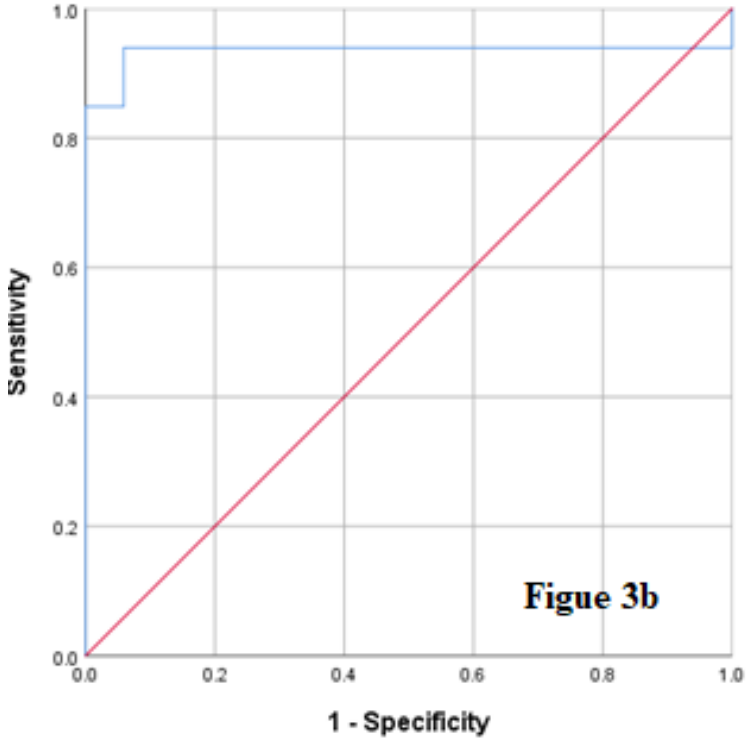

Figure 3b: The accuracy of combined miR-146a and miR-155 level for distinguishing patients with HP infection from patients without HP among studied case group.

Discussion

Many reports have reviewed microorganisms share in the pathogenesis of autoimmune disorders [14], including HT. Noteworthy, H pylori is believed to have important pathogenic role in HT [15]. Thus, our objective was to investigate the relationship between HT and HP infection about the epigenetic connections between both diseases.

Our study results detected that among 50 patients with HT,33 patients had positive HP infection, the diagnosis of HP infection was based on both HP antigen in stool and Cag-A. Interestingly, current results revealed a significantly lower level of FT3 and FT4 in HP infected group compared to other groups. Similar results were observed in our previous study [16].

Cons similarity was shown in other studies, they detected more thyroid autoantibodies among HP cases [17,19]. In agreement with our findings, Luis et al. noticed a greater titer of Cag-A in HT patients in comparison to the general population. They explained their results by the hypothesis of cross-similarity between the thyroid and stomach that initiates autoimmune antibody production [20]. On the opposite, studies by Tomasi et al discovered no correlation between H.P infection and HT [21]. the inconsistent results between Tomasi et al and the current results could be due to different methods of diagnosis of HP infection as we used both HP antigen in stool and Cag-A for diagnosis while they used urea breath test for diagnosis of HP infection.

The most important findings in the current research were the assessment of circulatory miR-146a-5p and miR-155-5p in the studied group to assess their levels in patients with HT in particular patients with HP infection in correlation with clinical and laboratory features of the enrolled patients. Interestingly, we confirmed that there were statistically significant higher values of miR-146a-5p and miR-155-5p in the HP infection group compared to HT patients without HP infection and the control group.

Consistent with these findings, Wang et al as they demonstrated that HP infection leads to overexpression of the Toll-like receptor and so increase both miRNA-146a and miRNA-155 [22]. Similar results were conducted by Lario and his colleagues they detected that miR-146a and miR-155 levels were up-regulated in patients with chronic active gastritis and these markers may be useful as a surrogate marker for determining the presence of H. pylori [23].

Other Egyptian studies investigated miRNA-146a and miRNA-155 polymorphisms in different autoimmune diseases for example Behcet's disease

and they found these polymorphisms are associated with Behcet's disease progression [24]. On the contrary, another Egyptian study on the same disease detected that patient with Behcet's disease had considerably reduced miR-146a levels than other healthy subjects [25].

For further assessment of our current results, we assess the associations between miR-146a-5p and miR-155-5p levels with clinical and laboratory features of HT and we detect that there were significant positive correlations with nausea, vomiting, heartburn, anti-TPO, anti-TG, TSH, HP antigen and Cag-A. On the opposing, they were negatively correlated with FT3 and FT4.Additionally, linear regression analyses revealed that the only variables independently associated with miR-146a-5p were anti-TPO and FT4. Whereas the only variable independent associated with miR-155-5p were anti-TPO and FT3.

Based on our results, we suggest that miR-146a-5p and miR-155-5p could help in the assessment of HT and HP infection progression, so we applied the ROC curve to evaluate their diagnostic power and we found that the power of these miR in the differentiation of HT from control had sensitivity (93.3%%, 92%, respectively) and specificity (96%, 88% respectively). While the power in the differentiation of HP infection from other non-infected had sensitivity (96%, 96%, respectively) and specificity (82.4%, 92% respectively).

Consistent with the findings we used combined epigenetic markers for differentiation of HT from control had a sensitivity of 96% and specificity of 76%. However, the precision of combined miR-146a-5p and miR-155-5p relative expression for differentiation of HP infection from other studied case groups had a sensitivity of 93.9% and specificity of 93.9%. An interesting study conducted by Karimi and his colleagues to evaluate the power of miR-146a and miR-155 in expectation of HP infections and observed that by applying the ROC curve analysis of miR-146a and miR-155 RNA level, the two miRNAs have an applicable sensitivity and specificity for diagnostic goals [26].

Conclusion

miR-146a-5p and miR-155-5p overexpressed in patients with HT more specifically in patients infected by HP. Intriguingly, their levels were significantly correlated to gastrointestinal symptoms thyroid dysfunction, and autoimmunity. Hence, they could be used as epigenetic predictive and prognostic markers of HT and HP infection.

Study Strengths and Limitations

This study has several unique strengths. To date, according to our information, no study has evaluated the role of miR-146a-5p and miR-155-5p in the prediction of HT and HP infection among Egyptian patients. Our study also has a few potential limitations. Small sample size and the study enrolled Egyptians only, therefore, it remains unclear whether our findings apply to other ethnic groups. Thus, we recommend further research on a large sample size of participants from different ethnicities.

Authors contributions

NMR, AME, AHA, AME, RHMS, and ATH collected patients' samples and clinical data. MAA, MHS, and HMA prepared samples for laboratory investigations. NMR and MOW wrote the paper. Statistical analysis, interpretation of data, and preparation of the paper for submission international and critical revision of the manuscript were performed by all of the authors. All authors read and approved the final manuscript.

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