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The correlation between micro-RNA 146a and IL-17 in the serum of Iraqi patients with cystic echinococcosis

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Abstract

Cystic echinococcosis (CE) is an endemic disease that causes serious disease and economic loss in the majority of countries around the world. MiRNAs are an epigenetic factor that is essential to the regulation of the immune response by interfering with cytokine expression; one such miRNA is microRNA-146a. The aim of the present study was to assess if we could use microRNA 146a as a biomarker for the detection of CE and to determine the relationship between microRNA 146a gene expression and IL-17 in patients with CE. The study included 50 CE patients who were admitted to the hospital in Baghdad, Iraq, for CE removal surgery and 50 healthy controls. The serum was collected from September 2022 to June 2023. The sample's age range was 20–55 years. Rural patients were infected at a higher rate than urban patients (74.00% and 42.00%, respectively), The lung was the most affected organ (74%), followed by the liver (18%), then the liver and lung together (8%). CE patients had significantly higher miRNA-146a fold expression than control group members (4.33 ± 1.01 and 1.00 ± 0.23, respectively). The serum level of IL-17 was significantly higher in the control group, at 129.15 ± 4.73ng/L, than in patients, at 105.99 ± 5.81ng/L. According to our findings, miRNA-146a is upregulated in the sera of CE patients, which leads to the development of novel biomarkers for echinococcosis and it is associated negatively with IL-17 levels. This may interfere with their immune system's inflammatory response and contribute to the pathogenesis of CE.

Keywords: Cystic echinococcosis, cytokine, hydatid cyst, IL-17, miRNA-146a, microRNA.

Introduction

Cystic echinococcosis (CE) is a widespread helminthic illness caused by infection with ***Echinococcus granulosus*** tapeworm metacestodes (larval stage) [1]. According to published data from widely dispersed geographic areas, CE is considered to be a considerable public health problem[2-3]. In Iraq, numerous research projects have made the attempt to determine if the parasite can be controlled[4-8], but CE continues to be a serious public health issue in Iraq, with CE still considered one of the most significant diseases that have been neglected by the World Health Organization[9]. CE is typically the result of accidental ingestion of ***E. granulosus*** eggs by humans and intermediate hosts (herbivores like sheep, horses, cattle, pigs, goats, and camels) where, as a result of the immune reaction of the host, ***E. granulosus*** hydatid cysts form as fluid-filled bladders in internal organs. These cysts have two parasite-derived layers: an inner nucleated germinal layer and an outer acellular laminated layer. They are surrounded by a fibrous capsule made by the host[10]. The size and

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location of the cysts within the affected organ, the complications brought on by cyst rupture, and the subsequent immunologic reactions, all play a role in the disease's clinical manifestations, which are highly variable[11]. Intermediate host immunity is crucial in determining the host-parasite relationship. The parasite's excretory compounds have an effect on human immune-competent cells. In order to avoid their hosts' immune responses, parasites have developed a variety of mechanisms which promote their survival and that, ultimately, lead to chronic infection. Chronic persists in CE, with detectable humoral and cellular immune responses against the parasite[12]. To successfully establish infection and survive in the host, E. granulosus releases chemicals that directly influence the host's immune responses, favoring a potent anti-inflammatory response[13]. Unlocking the molecular mechanisms underlying host responses to helminthic infections and comprehending the interplay between a host and a parasite has recently attracted extensive research efforts[14]. The degree to which host immunity interacts with the host-parasite system is poorly understood[15]. One of the primary means of cell-to-cell communication and an essential component in the control of the immune system are cytokines, which are released by diverse cells in response to various stimuli. The primary characteristic of helminth infections is a predominance of type II cytokines (particularly IL-4 and IL-10) and a decrease in type I cytokines (TNF). Understanding the character of the polarization towards type I or type II responses is complicated by the complexity of cytokine function in experimental infections[16].

MiRNA is an important factor that can interfere with the expression of cytokine-encoding genes. MicroRNAs are a family of short, non-coding single-stranded RNAs that are known to negatively regulate gene expression by binding to the 3' untranslated region (UTR) of numerous target mRNAs[17].

MicroRNAs are sometimes referred to by their acronym, miRNA. MiRNAs have been shown to have a role in a variety of pathophysiological processes, including the immunological response, the inflammatory response, and oxidative stress and are used as a biomarker for disease detection [18, 19]. Perry et al.[20] found that this microRNA is essential for the negative regulation of proinflammatory cytokine production, which in turn changes how strong the inflammatory response is. MiRNA-146a is essential for modulating immune cell proliferation and suppressing inflammatory responses[21]. In recent years, miRNAs have become significant regulators of both innate and adaptive immune responses in a range of murine model systems via modulation of cytokine production. The IL17 family of cytokines is characterized by its pro-inflammatory cysteine knot structure[22]. T helper 17 cells, a subset of T helper cells, generate them in response to IL-23 activation. As chemoattractants, these chemokines attract immune cells, such as monocytes and neutrophils, to the site of inflammation. The preceding signaling events typically occur after pathogens have invaded the body. By collaborating with tumor necrosis factor and interleukin-1, IL-17 promotes inflammation[23]. Accordingly, the primary goal of this study is to determine if we could use microRNA 146a as a biomarker for the detection of CE and to determine the relationship between microRNA 146a gene expression and IL-17 levels in the serum of Iraqi patients with hydatid cysts in order to assess the role of miRNA in the immune response.

Materials and Methods

Sample collection

A total of 100 Iraqi subjects were distributed to 50 patients with hydatid cysts and 50 healthy controls (the control group consisted of healthy individuals whose sera had a C-reactive protein (CRP) and an Erythrocyte Sedimentation Rate (ESR) that was within normal limits as an indicator of health conditions). Patients with hydatid cysts were selected for surgical removal after being admitted to a hospital in Baghdad that wasn't treated with any hydatid cysts therapy. The infection was diagnosed using one of various imaging modalities, such as ultrasound (US) or computed tomography (CT), which are the most important methods used in diagnosis. The hospitals that collected the CE patients included Ghazi Hariri Surgical Specialties, Gastroenterology and Hepatology Teaching Hospital, Medical City, and Baghdad Teaching Hospital during the period from September 2022 to June 2023.

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Examination of fertility cyst

There are two distinct approaches to administering the CE examination. The first approach is via the field of radiography, where the identification of calcification on an X-ray or CT scan commonly signifies a condition of inactivity. In the second approach, the surgical treatment involves the excision of cystic echinococcosis (CE) cysts from either liver or lung tissue. Following that, the cysts' surface is cleansed using a 70% ethanol solution. The cyst fluid can then be obtained by means of a single-use syringe and afterward examined at a macroscopic level. The presence of turbidity in the cyst fluid is indicative of the cyst's fecundity. In order to enhance the accuracy of the findings, a microscopic analysis can be conducted on the fluid of cystic echinococcosis (CE) to ascertain the existence of protoscolices.

Serum collection

Five ml of venous blood was collected, dispensed into a plain tube, and left to clot at room temperature for 15 minutes. It was then centrifuged at 1000 rpm for 10 minutes to separate into two eppendorf tubes. In the first part, using a pipette, 250 µl of serum was taken and placed on 500 µl of Trizol in an Eppendorf tube, mixed properly, and kept for half an hour, after which the mix was stored frozen at -20°C until miRNA extraction. The second eppendorf tube was used for the assessment of IL-7 levels and stored at -20°C until the assay was performed.

Evaluation of IL-17 serum level

The levels of IL-17 in the serum of patients with CE and the control group were assessed using a sandwich Enzyme-Linked Immunosorbent Assay (ELISA). Commercially available kits from the Bioassay Technology Laboratory in China were utilized for this purpose.

Total RNA extraction

According to the manufacturer's instructions (TRIzolTM Reagent, 2023), total RNA was extracted using the TRIzolTM Reagent and the TRIzolTM RNA isolation kit (Invitrogen, USA).

Assessment of RNA quantity and purity

Following the manufacturer's instructions, the Qubit TM RNA HS Assay Kit (Q32852) from ThermoFisher® (USA) was used to determine the quantity and purity of the extracted RNA. All samples contain miRNA at concentrations between 10 pg/L and 100 ng/L, indicating that miRNA is highly selective for miRNA over other forms of RNA.

MiRNA-146a specific primer

The primer sequences miRNA-146a used in laboratory work were designed and created by Applied Biological Materials (Macrogen)/South Korea, with melting temperatures ranging from 60 to 95°C. RNA was extracted according to the instructions of the trizol reagent. The primers are listed below. miR-146a forward primer: 5' -CAGTGCGTGTCGTGGAGT-3' , reverse primer: 5' -GGGTGAGAACTGAATTCCA-3'. Product size: 158 bp [24] miR-146a Reverse transcription (RT) (GTCGTATCCAGTGCGTGTCGTGGAGTCG GCAATTGCACTGGATACGAACCCA)[25],While housekeeping U6-F 5'-GAGAAGATTAGCATGGCCCCT-3' and U6-R 5'-ATATGGAACGCTTCACGAATTTGC-3' [26]

Complementary DNA (cDNA) synthesis, with specific primer

The production of cDNA can be used as a direct template in RT-PCR, which can be used to study miRNA expression. The procedure was performed in line with the New England Biolabs (NEB) manufacturer's instructions in a reaction volume of 20 µl. A total volume of 20 µL of RNA was required for reverse transcription. The primary stage of the project has been partitioned into two distinct segments. The initial step entails the generation of complementary DNA (cDNA) from microRNA (miRNA) by the utilization of a primer that specifically targets miRNA. The cDNA synthesis kit from Protoscript® was used in conjunction with miRNA-146a Table 1.

Table 1. lists the components of the reaction mix along with their quantities

Component	Volume
Luna Universal qPCR Master Mix	10 µl
Forward primer (10 µM)	0.5 µl
Reverse primer (10 µM)	0.5 µl
Template DNA	6 µl
Nuclease-free Water	3 µl

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Quantification of microRNAs

According to the manufacturer's protocol, small RNA was quantified using QubitTM microRNA assay kits from ThermoFisher® (USA). This microRNA quantification reagent permits rapid detection of all small RNA types (Table2).

Table 2. List the components of the reaction mix along with their quantification.

Component	Volume
Template RNA	4 µl
MiR-146RT Primer	2 µl
ProtoScript II Reaction Mix (2X)	10 µl
ProtoScript II Enzyme Mix (10X)	2 µl
Nuclease-free Water	2 µl

Statistical analysis

IBM SPSS, version 26 (SPSS Inc., Chicago, Illinois, USA) was used to analyze the data. Skewness, Kurtosis, and Q-Q plots were used to verify data normality. Kolmogorov-Smirnov and Shapiro-Wilk normality tests were variables with non-normal distributions that were log-transformed for analysis and converted to standard units for presentation. Continuous variables have a mean ± SEM. The Chi-squared test was used to compare proportions. The Student's t-test and Levene's test for variance equality were used to compare groups. Pearson correlation analysis was used to assess variable associations. ROC is also used to calculate area under curve (AUC).

Results and Discussion

Presentation of Subjects

From a total of 50 patients with CE, 31 (62%) were females and 19 (38. %) were males. The control group consisted of 10 females (20%) and 40 males (80%). Moreover, 21 patients (42%) lived in urban areas, while 29 (58%) lived in rural areas. The ages of these patients ranged between 20 and 55 (33.85 ± 1.96). According to the fertile cyst examination, there were 42 (84%) active cysts, while 8 (16%) of the patients had non-fertile cysts. Moreover, hydatid cysts were located in the lung tissue in 37 patients (74%), while in nine (18%) of patients, the CE was located in the liver, and four (8%) of patients had CE in both the lung and liver, as reported in Table 3.

Table 3. General characteristics of the studied groups

Parameters	Groups		
	Control (No. = 50	Patients (No. = 50)	P value
Age (year)	33.85 ± 1.96	33.79 ± 2.36	0.98
Gender			
Male	40 (80%)	19 (38%)	0.00*
Female	10 (20%)	31 (62%)	
Residence			
Rural	20 (40%)	29 (58%)	
Urban	30 (60%)	21 (42%)	
Cyst location			
Lung	----------	37 (74%)	
Liver	----------	9 (18%)	
Lung and liver	----------	4 (8%)	

miRNA- 146a expression of samples

The results were evaluated the expression level of miRNA 146a in the sera of the patients with CE before the surgery. As presented in Fig. 1, the folding of miR-146a in the CE patients were significantly different from those of the control (p = 0.002). The means of miRNA-146a folding gene among 50 samples were 4.33 ± 1.01, while in the control, they were 1.00 ± 0.23.

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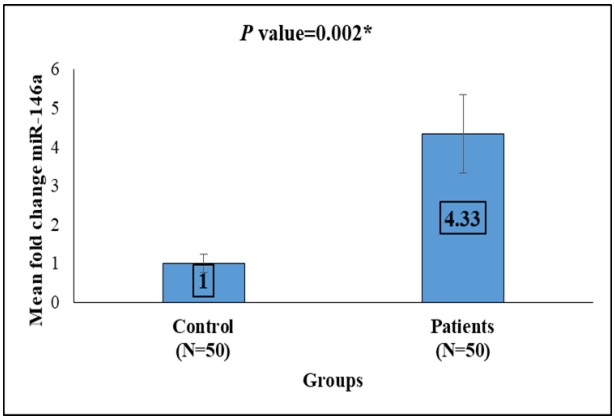

Figure 1: The mean of gene expression of miR-146a levels for both the control and patient groups.

Further, the Receiver operating characteristic (ROC) curves shown in Fig. 2 reveal that miRNA-146a had an area under curve (AUC) of 0.87 at a cutoff value of 2.27, 78.10% sensitivity, and 81.60% specificity.

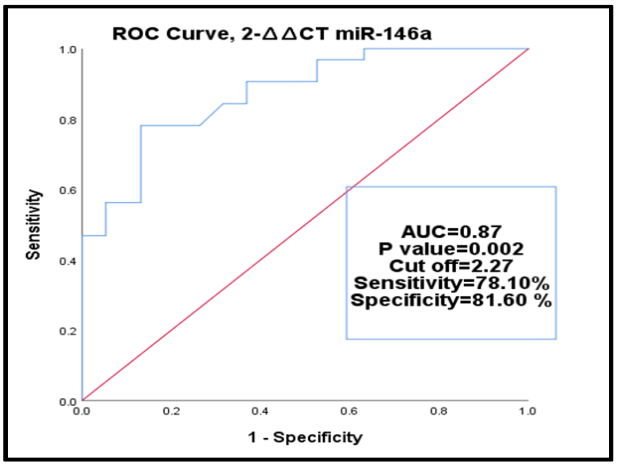

Figure 2. ROC curve for miRNA 146a fold of expression in discriminating between the patient group and control group

In general, it was observed that there was a high expression of miR146a in non-fertile cysts as compared to fertile cysts. The average value of miRNA-146a folding gene was found to be 5.67 ± 1.39 in non-fertile CE cysts and 3.82 ± 1.02 in fertile CE cysts (P = 0.00), as shown in Fig. 3.

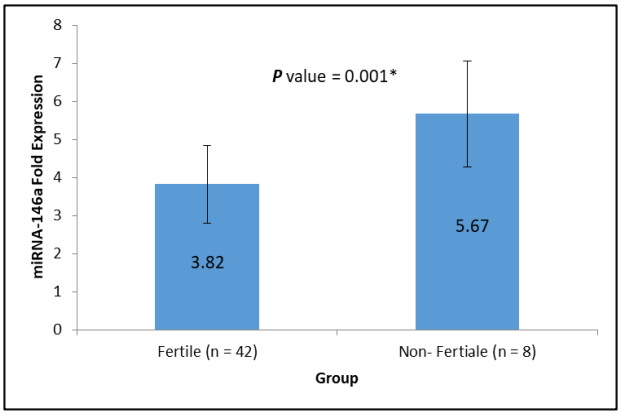

Figure 3. The mean of miRNA -146a gene expression in fertile and non-fertile patient groups

Serum Level of IL-17

The serum concentration of IL-17 in patients with CE was compared with serum of control. The results demonstrated that the concentration of IL-17 in the serum of patients with CE was significant (P < 0.05) compared to that of the healthy controls. As shown in Fig. 4, the mean serum level of IL-17 in patients was 105.99 ± 5.81ng/L, compared to 129.15 ± 4.73 ng/L in the control group.

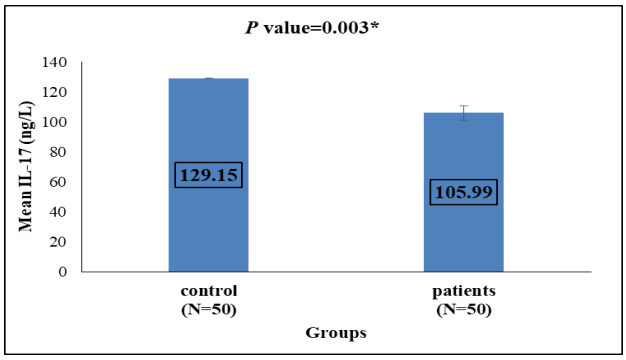

Figure 4. Levels of IL-17 in the control and patient groups

Correlation between Fold miRNA-146a Level and IL-17

The present study utilized Pearson's coefficient of correlation to examine the relationship between the levels of miRNA-146a IL-17 in the patient group. The results indicated that there was no significant association between these variables, as demonstrated in Fig. 5.

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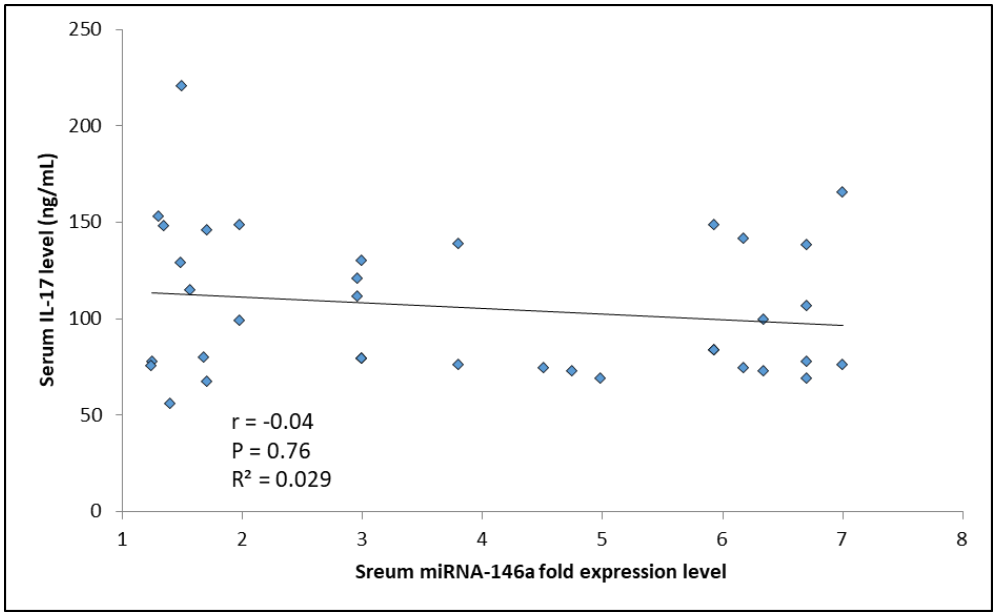

Figure 5. Simple scatter plot of miRNA-146a expression with IL-17 level in CE patients

Cystic echinococcosis is a neglected and chronic parasitic disease caused by the larval stages of Echinococcus granulosus sensu lato (***E. granulosus*** s.l.) [27, 28]. Humans act as accidental intermediate hosts. E. granulosus has a worldwide distribution; at least 50 million people are thought to be infected with CE[29]. The immune response to E. granulosus is unique because it features both Th1 and Th2 responses simultaneously; early Th1 cell activation confers host protective immunity, while Th2 cell activation is connected to the progression of the chronic stage when infected with E. granulosus[29, 30]. Hence, it is generally acknowledged that in most parasite diseases, a Th1- or Th2-type response is able to manage infection[31].

MiRNAs play a crucial function in both the innate and adaptive immune systems, according to numerous studies, via the modulation of cytokine production[32]. MiRNA-mediated posttranscriptional gene regulation is one of the more complex processes that regulate the maturation, proliferation, differentiation, and activation of T and B cells at many levels[33]. This is the first study in Iraq to investigate the role of miRNA-146a and its target IL-17 in the pathogenesis of CE.

This study determines whether miR146a is involved in inflammatory diseases due to its function in regulating inflammation. In chronic CE, miRNA-146a expression correlates with disease severity. The present study revealed a significant variation in microRNA-146a gene expression of chronic serum samples compared to the control group control group, (4.33 ± 1.01) in CE patients, while the expression value was recorded (1.00 ± 0.23) in control. The current outcome is corroborated by another finding indicating that miRNA 146a was up-regulated in CE patients in comparison to healthy controls, according to the findings by Mahami-Oskouei et al when patients with hydatidosis had higher levels of miR-146a than those in the control [34].

In addition, the ROC curve analysis shows that the level of miR-146a has a good diagnostic accuracy AUC of 0.87. This means that this miRNA can be used as a specific biomarker to diagnose CE with a relatively high sensitivity of 78.10% and specificity of 81.60%. These findings are consistent with the study conducted in [35], which found that the overexpression of miR-146a and miR-155 in plasma can serve as potential biomarkers for the diagnosis of echinococcosis. One potential explanation for the elevated presence of miRNAs in hydatidosis could be their involvement in the regulation of the immune system. These microRNAs are likely to be regarded as among the most significant biomarkers in assessing the severity of hydatidosis. The confirmation of this finding is supported by the

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observation that microRNA-146a was detected in both fertile and non-fertile samples.

Also, another study conducted in China examined the presence of circulating miRNAs in the serum of mice infected with E. multilocularis. According to the findings, the levels of miRNA 146a, with other miRNAs, namely miR-21a-3p, miR-103-3p, and miR-107-3p, were significantly elevated in the mouse serum compared to their levels during the initial four weeks of infection. Furthermore, previous research has demonstrated that miR-146a specifically regulates the expression of the TRAF6 and IRAK1 genes, both of which have been implicated in the promotion of inflammatory responses and detrimental immunological reactions within human serum[36].

The present study revealed that the mean serum level of IL-17 was significantly lower in patients with CE compared to healthy controls. Consequently, the current study evaluates a miRNA-146a regulatory role in gene expression by measuring the concentration of its target IL-17. Based on the findings of this investigation, the correlation between IL-17 and miRNA 146a in CE patients revealed a non-significant inverse correlation.

The study concluded that miRNA-146a may interfere with IL17 expression by inhibiting its production. This inverse correlation may be attributable to the high level of miRNA-146a, which resulted in a decrease in IL-17 and may be associated with chronic CE.

Increased levels of miRNA-146a inhibited the release of the proinflammatory chemokine IL-17. These studies indicate that a rapid increase in the expression of miRNA-146a provides a novel mechanism for the regulation of the negative effects of severe inflammation during the innate immune response. Indeed, these results were in agreement with previous studies that have demonstrated that the excretory-secretory products released by *Echinococcus granulosus* protoscolices have the ability to effectively suppress proinflammatory reactions. This suppression is achieved via the direct stimulation of B10 cells and the inhibition of B17 and Th17 cells, resulting in the downregulation of the immune response to the parasite [37]. The result also agreed with ref. [36], who found that the overexpression of miRNA-146a resulted in the downregulation of IL-17 and IL-35 production in the periodontal ligament stem cells (PDLSCs) obtained from teeth affected by periodontitis. Thus, it may be inferred that miRNA-146a has the potential to enhance periodontitis via the suppression of expression of IL-17 and IL-35, as well as reducing the proliferation of PDLSCs.

These results point to the role of miR-146a in innate immunity, which protects against CE. Indeed, any changes in miRNA expression resulted in changes in phenotype, which indicates how important microRNAs actually are in controlling how immune cells work and how they develop. Due to the function of microRNAs in modulating immune responses, dysregulation in their expression may contribute to the pathogenesis of CE

Our results agreed with other studies that found that miRNA-146a plays a crucial role in immunological responses, especially the innate immune response. Hong et al. showed in their study that miR-146a/b, miR-155, and a few other microRNAs (miRNAs) had different roles in controlling the immune responses of mice infected with Schistosoma japonicum[38]. These miRNAs achieved this modulation by maintaining a delicate equilibrium between Th1 and Th2 responses[39]. Van Loon et al., demonstrated that the involvement of miRNA-146a in the innate immune response is facilitated through a negative feedback loop that encompasses two crucial molecules downstream of the Toll-like receptor (TLR) machinery, namely interleukin-1 receptor-associated kinase (IRAK)-1 and TNF receptor-associated factor (TRAF)-6.[40] and further that miR-146a regulates Th1 immune responses and interferes with the production of interferon (IFN) [35].

MicroRNA-146a is linked to a decrease in Th1 levels and a decrease in the function of the cellular immune system, resulting in the persistence of infections. While a clear bias towards Th1/Th17 responses cannot be avoided, miR-146a is necessary. According to some research, miR-155 and miR-146a play a key role in both initiating and controlling Th2 responses in allergy and helminthic diseases[41]. The miRNA -146a knockout mouse

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model has recently demonstrated its significance. Such mice exhibit hyper responsiveness to lipopolysaccharide (LPS) and an increased pro-inflammatory response when exposed to endotoxins, in addition to developing autoimmunity. Aged knockout mice also have myeloproliferation and develop tumours in their secondary lymphoid organs, demonstrating that miRNA-146a controls immune cell proliferation[41, 42]. miRNA -146a-deficient animals develop myeloid malignancies as a result of persistent NF-B signaling dysregulation, which is consistent with the latter observation[41].

Other studies have shown that miR-146a plays a crucial role in controlling inflammation and oxidative stress and is associated with a number of illnesses, including several forms of cancer, arthritis, coronary heart disease, Alzheimer's disease, and ankle fracture[43-47].

Conclusion

Our conclusion, according to our findings, is that miRNA-146a is upregulated in the sera of CE patients, which leads to the development of novel biomarkers for echinococcosis, and is associated negatively with IL-17 levels. This may interfere with their immune system's inflammatory response and contribute to the pathogenesis of CE.

Acknowledgment

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Authors' Declaration

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are ours. Furthermore, any Figures and images, that are not ours, have been included with the necessary permission for re-publication, which is attached to the manuscript.
- Authors sign on ethical consideration's approval.
- No animal studies are present in the manuscript.
- The project was approved by the local ethical committee in University of Baghdad, College of Science for Women (approval number 22/111) in cooperation with the Ministry of Health, (approval number 1618).

Authors' Contribution Statement

NSM; Collected sample, prepared and wrote the manuscript, drew figures, and created tables; EMI. Supervised, planned, oversaw project administration, and reviewed and edited the manuscript. MA contributed through the diagnoses of CE patients, and reviewed and edited the manuscript.

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العلاقة بين الحامض النووي الدقيق146a و البين الابيضاضي-17 في مصل المرضى العراقيين المصابين بداء المشوكات الكيسي.

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الخلاصة

داء المشوكات الكيسي (CE) هو مرض وبائي يسبب مرضًا خطيرًا وخسائر اقتصادية في معظم بلدان العالم. MiRNAs هي عامل جيني ضروري لتنظيم الاستجابة المناعية من خلال قدرته على التدخل في التعبير الخلوي ؛ واحد هذه الحوامض النووية الدقيقة -146 أ. هدفت الدراسة الحالية تقييم إذا كان بإمكاننا استخدام microRNA 146a كمؤشر حيوي للكشف عن CEو تحديد العلاقة بين التعبير الجيني microRNA 146a و IL-17 في مرضى CE.حيث اشتملت الدراسة على 50 مريضًا من CE تم إدخالهم إلى المستشفى في بغداد ، العراق و 50 من الأصحاء. تم جمع المصل للفترة من ايلول 2022 إلى حزيران 2023 . تراوحت أعمار العينات بين 20 - 55 سنة. بلغت اعلى نسبة الاصابة بالمشوكات الكيسية عند الاشخاص الذين يعيشون بالمناطق الريفية مقارنة بالذين يعيشون في المدن الحضرية (74.00٪ و 42.00٪) ، وشكلت الرئة العضو الأكثر إصابة (74٪) ، يليها الكبد (18٪) ، ثم الكبد والرئة معًا (8٪). لوحظ بان التعبير الجيني لل miRNA-146a في مرضى CE أعلى بكثير من أعضاء المجموعة الضابطة (4.33 ± 1.01 و 1.00 ± 0.23 على التوالي). هذا كما اظهرت النتائج بان مستوى IL-17 زاد بشكل ملحوظ في امصال المجموعة الضابطة 129.15 ± 4.73 نانوغرام / لتر مقارنة بالمرضى 105.99 ± 5.81 نانوغرام / لتر. الخلاصة: وفقًا للنتائج التي توصلنا إليها ،ارتفاع التعبير الجيني miRNA-146a في مصل مرضى CE يمكن ان يعد عاملا حيويا في تشخيص المشوكات، وهذا الزيادة تؤثر سلبًا بمستويات IL-17 المنخفضة مما يؤثر ويتداخل مع الاستجابة الالتهابية لجهاز المناعة وبالنتيجة يسهم في التسبب في CE.

الكلمات المفتاحية: المشوكات الكيسي، المحركات الخلوية، الاكياس المائية، البين الابيضاضي-17، الحامض النووي الرايبي الدقيق 146، الحوامض النووية الرايبية الدقيقة.