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between each serum and its QMRA counterpart in the whole study population demonstrated high significance when measuring Zn levels by both methods (ρ= 0.43; p= 0.00) but not when measuring Cu (ρ= 0.04; p= 0.75).

The linear regression predictions of the relationship between serum Zn and Cu levels observed readings against QMRA coefficients revealed that Zn regression was significant by the ANOVA (F= 13.011; p= 0.001) and coefficient (t= 3.607; p= 0.001). The regression curve for Zn showed converging of values by both methods towards the trendline with the linear equation (Zn Serum=13.924* ZnQMRA+ 46.478 µg/ dl; R2= 0.1832). On the other hand, unlike the expected results manifested by the laboratory method, QMRA expressed heterogeneous Cu levels in the two groups. The linear regression prediction of the relationship between serum and QMRA Cu levels showed no significance with ANOVA (F= 0.102; p= 0.751) and coefficient (t= 0.32; p= 0.751). This unstable relationship resulted in a curve with wide- spaced scattering of values away from the trendline, which was almost isometric with the linear equation (Cu Serum=4.6743* CuQMRA + 121.49 µg/ dl; R2= 0.0017).

Evaluation of QMRA method sensitivity was 84% when measuring Zn levels but only 60% when measuring Cu levels while specificity was 87% for Zn but only 60% for Cu. Moreover, the ability of QMRA to detect patients having abnormal Zn values when test is positive or Positive Predictive Value (PPV) is (91%) and its ability to detect not having abnormal Zn values when test is negative or Negative Predictive Value (NPV) is (77%). On the other hand, for Cu, PPV is 43% and NPV is 75%.

In short, QMRA is still a disputed scientific invention.[35] Even though it is touted by the manufacturers as being developed by a team of medical and computer experts based on the study of 100.000.000 clinical cases over a period of many years with alleged accuracy rate falling between 85-95%,[36] only a few studies are published using QMRA scientifically. Castañeda Antonio et.al. (2018) in Mexico and Muflih et.al. (2019) in Indonesia were the only researchers that questioned the use of QMRA comparing it to reference measurement methods and demonstrated no correlation between QMRA and these reference methods.[21][22] Our results for measuring Cu agree to some extent with these opponents of QMRA. However, measuring trace elements is only one function that QMRA does among more than 40 other functions as reported by QMRA proponents and manufacturers.

On the other hand, our results for measuring Zn by QMRA were satisfactory to a great extent and substantiating its use as an adjunctive diagnostic tool as was reported by other scientists in their studies in patients with disabilities and similar conditions as in our study.[37][38][7][17][16][8][15][19][11][9][10][20]

Conclusion:

The (QMRA) as a possible diagnostic non- invasive tool, among whose functions is to measure body trace elements (such as Zn and Cu) accurately to 85- 95% precision, does not provide an accurate picture of the Zn and Cu levels of the study participants compared with the traditional laboratory (Direct Colorimetric) method. In particular, the change in the participants' serum Cu value did not follow the same change in the QMRA coefficient value. However, it was successful in measuring the zinc levels compared to the reference laboratory method. Sensitivity and specificity tests were high in measuring Zn but not Cu levels.

Among the results, the significantly low plasma Zn, high Cu and low Zn/Cu ratio in children with ASD compared to the control group of children stood out. However, it is noted that both groups had a low Zn level that may have resulted from poor diet quality.

Recommendations:

1. QMRA can be used as a screening or adjunct tool for measuring Zn levels in humans but not for measuring Cu levels until further more controlled studies are performed.
2. Addition of Zn to food in the case of its insufficiency, especially in cases of neurodevelopmental diseases such as ASD.

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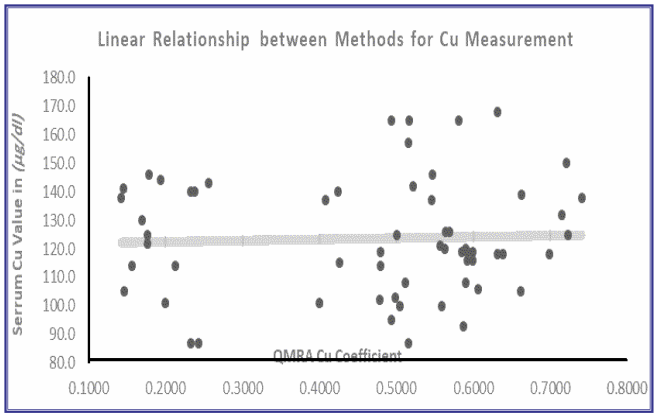

Figure (2) Linear Regression Analysis for both Methods in measuring Cu.

The linear relationship between the two methods when measuring Cu levels shows a wide- spaced scattering of values away from the trendline, which is almost isometric with the linear equation (Cu Serum= 4.6743* Cu QMRA+ 121.49 (µg/dl); R2=0.0017).

- QMRA Specificity And Sensitivity: Cross- tabulation (two- by- two) of the measurements of serum vs. QMRA Zn levels and Cu levels to find out the true and false positive and negative readings.

Table (9) Sensitivity, Specificity PPN and NPV Values for QMRA in Reference to Direct Colorimetric Method

Qmra Zn Sensitivity& Specificity			QMRA Zn			
			Positive	Negative	PPV	NPV
Serum Zn	Positive	Count	31 (Tp)	3 (Fp)	91%	77%
		%	83.80%	13.00%		
	Negative	Count	6 (Fn)	20 (Tn)		
		%	16.20%	87.00%		
QMRA Cu Sensitivity& Specificity			QMRA Cu			
			Positive	Negative	PPV	NPV
Serum Cu	Positive	Count	12 (Tp)	16 (Fp)	43%	75%
		%	60.00%	40.00%		
	Negative	Count	8 (Fn)	24 (Tn)		
		%	40.00%	60.00%		

Elements	Sensitivity	Specificity
Zinc	84%	87.00%
Copper	60.00%	60.00%

TP= true positive, FP= false positive, FN= false negative, TN= true negative, Sensitivity= (true positive)/ (true positive + false negative)= Probability of being test positive when disease present. Specificity= (true negative)/ (true negative+ false positive)= Probability of being test negative when disease absent. Positive Predictive Value (PPV)= (true positive)/ (true positive + false positive)= Probability (patient having disease when test is positive) and Negative Predictive Value (NPV)= (true negative)/ (false negative + true negative)= Probability (patient not having disease when test is negative).

Discussion:

ASD is a group of a long- term disabilities and a neurodevelopmental disorder as defined by APA in the DSM-V.[1] Many studies suggested an association between serum levels of Zn and Cu and ASD, and that Zinc to copper (Zn/Cu) ratio, being low, can be a biomarker of ASD.[2][3] Thus, it is indispensable to find simple, accurate, selective and reliable alternative analytical methods that conveniently and promptly assess these elements levels.[4] The aim of the present study was to determine the levels of Zn and Cu in ASD children's blood. The assay was done using a new technology (QMRA) method and its results compared with a reference laboratory method (direct colorimetry) to determine the sensitivity and specificity of the new measurement method.

The study was performed in a group of children (M= 19; F= 11; age range= 3- 15) with ASD (n= 30) and a control group of typically developing children (n= 30) matched in terms of sex and age. The value of Zn and Cu measurement was performed with a QMRA- 998 8th Generation device and in patients' sera by the reference direct colorimetric method.

As for anthropometric measurements, results showed significant differences in head circumferences (ASD= 54.27± 4.54; Controls= 51.90± 2.35 cm; ANOVA: F= 6.42; p= 0.01) and, generally, body composition and anthropometric measures of both groups revealed the ASD group has taller, heavier with higher BMIs subjects than the control group subjects. The study agrees with those of other authors who found a higher prevalence of bigger head circumferences,[27] taller[28] and heavier with greater BMIs[29] in ASD than in TD children. The head circumference significantly increased in females or older children, suggesting the relative overgrowth of the brain in this sample of Egyptian children with autism. Zn levels correlated inversely with age, height, weight, head circumference and body mass index (BMI) in both groups.

Concerning medical history and clinical findings, the ASD group expressed higher frequencies of clinical findings with significant differences than the control group with GIT symptoms, e.g. diarrhea, and pica (χ^2= 13.58; p- value= 0.00) and respiratory system, e.g. upper and lower recurrent chest infections (χ^2= 15.36; p- value= 0.00) in agreement with other researchers.[30] Also, in ASD, the range of co- morbid disorders, particularly gastrointestinal greatly exceeded that compared to the general population.[31] Zn levels correlated significantly with gastrointestinal system and respiratory system findings coinciding with the same differences between the two study groups in agreement with literature who report correlation of chronic diarrhea with zinc deficiency[32] and that pica interferes with the absorption of zinc leading to Zn deficiency.[33] In addition, the recurrent chest infections exhibited in the ASD group may be related to low immunity in which case, by correlation, low Zn maybe responsible serving as a biomedical marker relating to inflammation, immune dysfunctions, intestinal dysfunctions and infections.[34][30]

As regards the measurement of the two trace elements by the two methods, both methods showed lower means for Zn levels in the ASD group than the control group and the QMRA method was even more sensitive to detection of the difference between groups when measuring Zn (ANOVA F= 39.57; p= 0.00). In addition, the serum method showed higher values of Cu in the ASD group. This was in agreement with other authors where the results of our study revealed lower serum Zn level and higher serum Cu level in the ASD group than normal reference values and when compared to another group of normal children[5][4][2] However, they differed in their measurements for Cu levels as the QMRA method showed the opposite of the expected results. Results also demonstrated lower Zn/Cu ratio in ASD group agreeing with other sources in the literature.[5][4]

Correlation of both measurement methods as regards Zn and Cu levels

Shams University) and/ or national research committee. The Scientific Ethics Committee of the faculty approved the study protocol. This research does not contain any studies involving animals performed by any of the authors.

Results:

- Anthropometry:

Table (2) Head Circumference Descriptive Statistics and Differences between Groups

Descriptive Statistics	ASD		Controls		ANOVA	
	Mean	Std. Dev.	Mean	Std. Dev.	F	Sig.
Head Circumference	54.27	4.54	51.9	2.35	6.42	0.01

There were no significant differences between groups anthropometric means except with head circumferences (F= 6.42; p= 0.01). However, generally, the ASD group demonstrated taller, heavier and higher BMIs subjects than the control group subjects.

Table (3) Head Circumference Significant Correlations with Anthropometrics and Zn Levels

Variables	Correlation	Age	Height	Weight	BMI	Qmra Zn
Head Circumference	Pearson	0.67	0.72	0.74	0.47	- 0.21
	Sig.	0	0	0	0	0.05

By way of correlation, the head circumference tended to increase in the ASD group and, generally, with age (ρ= 0.67, p= 0.00), height (ρ= 0.72, p= 0.00), weight (ρ= 0.74, p= 0.00) and BMI (ρ= 0.47, p= 0.00). When measured by QMRA, it also correlated inversely with Zn levels.

- Clinical Findings:

Table (4) Significant Clinical Findings Distribution of Study Groups.

Findings	ASD	Control	χ^2	P- Value
Constipation	2	6	13.58	0.00
Diarrhea	19	6		
Pica	6	0		
Recurrent Infections	17	6	15.36	0.00
Wheezes	5	6		

Through the history, general and systemic clinical examination, the ASD group had significant differences with the control group. They had more GIT and respiratory abnormalities frequencies such as diarrhea, and pica (χ^2=13.58; p- value= 0.00) and higher frequencies of upper and lower recurrent chest infections (χ^2=15.36; p- value= 0.00).

Table (5) Significant Clinical Findings Distribution as regards Zn& Cu Levels by both Methods

Method	Serum Zn		Qmra Zn		Serum Cu	
System	χ^2	P- Value	χ^2	P- Value	χ^2	P- Value
GIT	10.62	0.00	5.66	0.02	16.19	0.00
Respiratory	18.22	0.00	10.09	0.00	0.02	0.55

Significant differences between both methods measuring Zn levels and clinical findings were found in the whole study sample. These were evident with gastrointestinal system (serum χ^2= 10.62, p- value= 0.00; QMRA χ^2= 5.66, p-value= 0.02) and respiratory system (serum χ^2= 18.22, p- value= 0.00; QMRA χ^2= 10.09, p- value= 0.00). These findings coincide with the differences between groups shown in the previous table. Only the gastrointestinal findings demonstrated significant difference with Cu levels when measured by the laboratory method (χ^2= 16.19, p- value= 0.00). It appears that low Zn and/ or high Cu levels in ASD patients may be responsible for these clinical findings.

- Measurement of Zn and Cu by Both Methods: The values of Zn and Cu of both groups of children were measured by both traditional (Direct Colorimetric Method) and QMRA (Validation) methods.

Table (6) Descriptive Statistics and ANOVA of Zn& Cu levels by both Methods

Descriptive Statistics	ASD		Controls		ANOVA	
	Mean	Std. Dev.	Mean	Std. Dev.	F	Sig.
Serum Zn Value (µg/dl)	59.51	11.17	63.77	10.92	2.23	0.14
Qmra Zn Coefficient	0.87	0.18	1.31	0.33	39.57	0
Serum Cu Value (µg/dl)	125.33	23.56	122	16.63	0.4	0.53
Qmra Cu Coefficient	0.45	0.2	0.48	0.17	0.69	0.41

Table (7) Correlation of both Measurement Methods of Zn& Cu levels.

Elements	Pearson Correlation	Sig.
Serum Zn * Qmra Zn	0.43	0.00
Serum Cu * Qmra Cu	0.04	0.75

Table (8) Linear Regression Model and Coefficients for QMRA to Serum Zn& Cu Levels

Model Summary		R	R Square	Adjusted R Square	Std. Error of the Estimate
Serum Zn*QMRA Zn levels		0.428	0.183	0.169	10.175
Serum Cu*QMRA Cu levels		0.042	0.002	- 0.015	20.441
ANOVA	Sum Of Squares	df	Mean Square	F	Sig.
Zn Regression	1347.03	1	1347.03	13.011	0.001
Cu Regression	42.43	1	42.43	0.102	0.751
Coefficients For QMRA Levels	Unstandardized Coefficients	Std. Error	Standardized Coefficients	(t)	Sig.
Qmra Zn Coefficient	13.924	3.86	0.428	3.607	0.001
Zn (Constant)	46.478	4.404		10.555	0
Qmra Cu Coefficient	4.67	14.67	0.042	0.32	0.751
Cu (Constant)	121.49	7.32		16.6	0

- The independent variables are QMRA Coefficients:

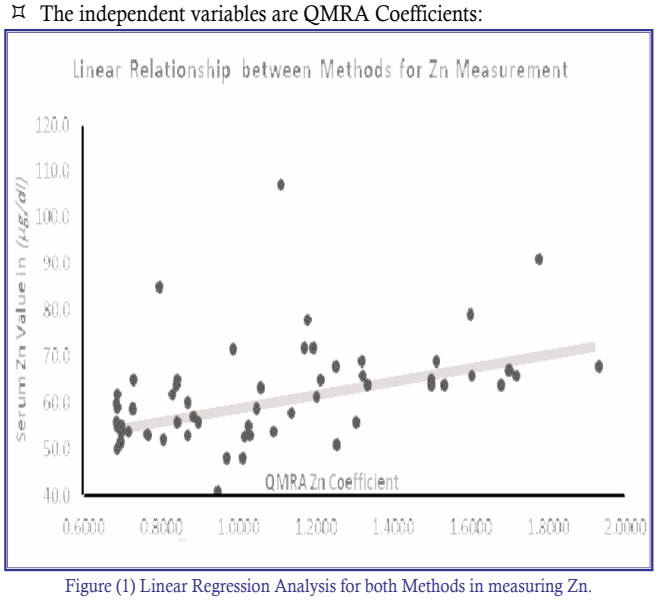

Figure (1) Linear Regression Analysis for both Methods in measuring Zn.

The linear regression analysis demonstrated the curve above when measuring Zn levels showing converging of values by both methods towards the trendline and expressing the linear equation (Zn Serum=1 3.924* ZnQMRA + 46.478 (µg/ dl); R2=0.1832).

Introduction:

Autism is a long- term disability and a developmental disorder defined by the American Psychiatric Association in the Diagnostic and Statistical Manual of Mental Disorders (DSM-V).[1] Serum levels of Zn and Cu have been associated with ASD, and that (Zn/ Cu) ratio can be a biomarker of ASD[2] being abnormally low in ASD individuals.[3] Thus, it is indispensable to avail simple, accurate and reliable alternative analytical methods that conveniently and promptly assess these elements levels.[4] The normal range of serum Zn is 60- 90 µg/ dl between the ages of (1- 12) months, (80- 110) µg/ dl between the ages of 1- 10 years and 90- 120 µg/dl between the ages of (10- 15) years. The normal range of serum Cu is (70- 150) µg/dl or (10.7- 22) µmol/L.[4] The normal Zn/Cu ratio is approximately 1: 1 and its lower limit is 1.4.[5]

One of the non- invasive diagnostic tools available now is Quantum Magnetic Resonance Analyzer (QMRA), which can display the coefficient value of the trace elements in the human body. Up until now, very few scientific studies applied QMRA in research and none has been published stating that this tool is equivalent to the trace elements serum reference method. Accordingly, the sensitivity and specificity of the QMRA tool should be confirmed by comparing it with a reference serum test in measurement of the Zn and Cu levels. The comparison of these measurements is expected to provide scientific evidence related to the accuracy of QMRA.

To date, there is not an FDA approval for the device.[6] In a Google Scholar recent search, the total studies using QMRA in scientific research that showed up were few and published only in Indonesia and Nigeria. Fist, in Indonesia, five of them used it as an adjunctive diagnostic tool in the medical field and relied completely on its results as a proven method.[7][8][9][10][11] In Nigeria, there were other studies using it in the same manner.[12][13][14][15][16][17][18][19][20] The only studies that questioned the use of QMRA by actually comparing it to reference laboratory methods were two studies.[21][22]

Aim of the Study:

The purpose of this study was to compare two methods of measurement of Zn and Cu levels in the body; namely, Quantum Magnetic Resonance Analyzing (QMRA) compared to the reference laboratory direct colorimetry method.

Methodology:

This present study is a comparative cross- sectional study. The study was carried out in The Center for Children with Special Needs of The Faculty of Postgraduate Childhood Studies; Ain Shams University; Cairo and a Private Pediatric Clinic in Giza; Egypt from Jan 2019 to Sep 2021.

Subjects:

The present study enrolled 60 children; a study group of ASD patients (n= 30) diagnosed as per DSM- V criteria[1] and a control group (n= 30) typically developing (TD) children, matched in terms of mixed sex and ages between (3- 15) years. Included groups were of well- hydrated and receiving adequate daily intake of water and not on any supplements in the last two months. Excluded were those with chromosomal or neurological disorders other than autism and those on medications that affect serum Zn or plasma Cu level.

Methods:

- History, clinical and psychometric examination: All children in this study passed history and anthropometric measurements taking and clinical examination. The ASD group had a psychometric assessment including Intelligence quotient (IQ) assessment by Stanford–Binet Intelligence Scale for Children.[23] diagnosis of autism according to DSM-V[1] and assessment of the severity of autistic symptoms using the Childhood Autism Rating Scales (CARS).[24]
- Laboratory Investigation:
  1. The Direct Colorimetric Method with Ready- to use Kit (Reference Method): Serum levels of zinc and copper were measured with Ready- to- use Kits as follows:
     a. Zinc Assessment: Colorimetric Method with 5- Brom- PAPS.[25] The normal range for all children was (64- 110) µg/dl.
     b. Copper Assessment: Colorimetric Test with Dibrom- PAESA.[26] The normal range for all children was (51- 121) µg/dl.
  2. The Proposed Quantum Magnetic Resonance Analyzer (QMRA) (Validation Method): The QMRA tool used in this research was the Korean- design QMRA Model Number: QMR- 998/ 2021.1 manufactured by Guangzhou Zhenyuesheng Electric Co. Ltd; PRC in 2021. In this study, the values used were the electromagnetic coefficients of Zn and Cu levels. Unfortunately, the coefficient values of the measurement of Zn and Cu levels using electromagnetic waves through the QMRA tool have not been explained in the manual. The normal value ranges for both metals are shown in the table below.

Table (1) QMRA Reference Standards for Zn& Cu Levels.

Reference Standard	Normal (-)	Mildly Abnormal (+)	Moderately Abnormal (++)	Severely Abnormal (+++)
Zinc	1.143- 1.989	0.945- 1.143	0.532- 0.945	<0.532
Copper	0.474- 0.749	0.241- 0.474	0.082- 0.241	<0.082

Statistical Analysis:

For statistical assessment of the differences between the groups according to levels of Zn and Cu in the serum and by QMRA device, analyses of variance (ANOVA), Chi- square, linear regression and Pearson's correlation coefficients were performed. Sensitivity and specificity of QMRA were calculated by cross- tabulation 2x 2.

Consent& Ethical Aspects:

Researchers declare that an informed written consent from parents of and/ or verbal assent from all individual participants involved in the study. Confidentiality was maintained. The authors declare that they have no conflicts of interest. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional (Faculty of Postgraduate Childhood Studies and the Ain

Quantum Magnetic Resonance Analyzer (QMRA)

As A Method For Assessment of Copper and Zinc Serum Levels in Autistic Children

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Summary

Introduction: Autism is a long- term developmental disorder demonstrating an association with low serum levels of zinc and high copper.

Aim: To determine Zn and Cu levels in ASD children using a new technology Quantum Magnetic Resonance Analysis (QMRA) method compared to a reference method to determine the sensitivity and specificity of the new method.

Method: This study is a comparative cross- sectional study. It was carried out in The Children with Special Needs Center, Faculty of Postgraduate Childhood Studies; ASU and a Private Clinic from Jan 2019 to Sep 2021. The study groups included children with ASD (n= 30; M= 19; F= 11; age range= 3- 15) and an equal control group of typically developing children matched in sex and age. Zn and Cu were measured by a QMRA- 998 8th Generation device and the reference direct colorimetric method.

Statistical Analysis: Results were analyzed using descriptive statistics, Pearson's correlation, Chi- square, analysis of variance (ANOVA) and linear regression and a sensitivity and specificity cross- tabulation test to evaluate the QMRA in measuring Zn and Cu levels.

Results: Both methods showed lower means for Zn levels in the ASD group than in the control group with a significant correlation on measuring Zn but not Cu. By reference method, but not with QMRA, serum Cu was higher in ASD than in control group. Sensitivity of QMRA was 84% when measuring Zn levels but only 60% for Cu and specificity was 87% for Zn but only 60% for Cu.

Conclusion: Non- invasive measurement devices such as QMRA can be used as a screening or adjunct tool for measurement of Zn levels but not Cu. It is recommended to test blood levels of Zn and Cu in all autistic children and give them a Zn supplement if needed.

Key Words: ASD, Autism, Zinc, Copper, Quantum Magnetic Resonance Analyzer, QMRA.

الرنين المغناطيسى الكمى

كطريقة لقياس مستويات النحاس والزنك بالدم فى الأطفال المصابين بالتوحد

مقدمة: التوحد هو إعاقة طويلة الأمد واضطراب فى النمو حيث اقترحت العديد من الدراسات وجود ارتباط مع المستويات المنخفضة من الزنك وارتفاع مستوى النحاس فى الدم.

الهدف: الهدف من هذه الدراسة هو تحديد مستويات معادن الزنك والنحاس فى دم الأطفال المصابين باضطراب طيف التوحد (ASD) باستخدام تقنية جديدة لتحليل الرنين المغناطيسى الكمي (QMRA) ومقارنة نتائجها مع طريقة اختبار معملية مرجعية لتحديد صحة وحساسية وخصوصية طريقة القياس الجديدة.

الطريقة: هذه الدراسة هى دراسة مقطعية مقارنة تم إجراؤها فى مركز الأطفال ذوى الاحتياجات الخاصة بكلية الدراسات العليا للطفولة بجامعة عين شمس وعيادة خاصة من يناير ٢٠١٩ إلى سبتمبر ٢٠٢١. تضمنت مجموعات الدراسة مجموعة من الأطفال المصابين بالتوحد (عدد= ٣٠؛ ذكور= ١٩؛ إناث= ١١؛ الفئة العمرية= ٣- ١٥ سنة) ومجموعة ضابطة متساوية من الأطفال الذين يتطورون بشكل نموذجى والمتطابقين معهم فى الجنس والعمر. وقد تم قياس الزنك والنحاس بواسطة جهاز QMRA- 998 من الجيل الثامن وطريقة القياس المرجعية اللونية المباشرة.

التحليل الإحصائي: تم تحليل النتائج باستخدام الإحصاء الوصفي، ارتباط بيرسون، مربع كاي، تحليل التباين ANOVA والانحدار الخطى واختبار الجدولة المتقاطعة للحساسية والنوعية لتقييم QMRA فى قياس مستويات الزنك والنحاس.

النتائج: أظهرت كلتا الطريقتين متوسطات أقل لمستويات الزنك فى مجموعة ASD مقارنة بالمجموعة الضابطة مع وجود ارتباط معنوى بينهما فى قياس الزنك وليس النحاس. وبالطريقة المرجعية، ولكن ليس مع QMRA، كانت نسبة النحاس فى الدم أعلى فى مجموعة ASDعنها فى مجموعة التحكم وكانت حساسية QMRA ٨٤% عند قياس مستويات الزنك ولكن ٦٠% فقط للنحاس وكانت النوعية ٨٧% للزنك ولكن ٦٠% فقط للنحاس.

الخلاصة: يمكن استخدام أجهزة القياس غير الغازية مثل QMRA كأداة فحص مساعدة لقياس مستويات الزنك ولكن ليس النحاس كما يوصى بفحص مستويات الزنك والنحاس فى الدم لدى جميع الأطفال المصابين بالتوحد وإعطائهم مكملات الزنك إذا لزم الأمر.

الكلمات المفتاحية: التوحد، مرض طيف التوحد، الزنك، النحاس، محلل الرنين المغناطيسى الكمومي.