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Vitamin A, zinc and iron, and their relation to infection in wasted children aged 6 to 24 months from Gaza Strip

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Abstract

Background: Micronutrients paly a pivotal role in nutritional status and health of children. This study assessed vitamin A, zinc and iron, and their relation to infection in wasted children aged 6 to 24 months from Gaza Strip.

Methods: The study is a case-control design and comprised 98 wasted children and 98 controls. The World Health Organization Anthro soft-ware for assessing nutritional status of the world's children was applied. Clinical data of infections were obtained from children records. Blood samples were collected to determine complete blood count (CBC), serum vitamin A, zinc and iron. Statistical analysis was performed using the IBM SPSS software version 22.

Results: Serum vitamin A, zinc and iron were significantly lower in wasted children than controls (546.8±384.0, 68.5±19.6 and 88.3±34.5 *versus* 702.5±487.9 nmol/l, 74.2±7.8 µg/l and 106.3±11.2 µg/dl; P=0.014, 0.008 and <0.001, respectively). White blood cell (WBC) count was significantly increased in wasted children than controls (11.0±3.3 *versus* 9.7±3.4 x 10^3/µl, P=0.003), whereas red blood cel (RBC) count was significantly decreased (4.4±0.4 *versus* 4.6±0.4 x 10^6/µl, P=0.009). In parallel, hemoglobin (Hb) and hematoctit (Hct) were significantly decreased (9.8±0.9 and 30.4±2.5 *versus* 10.9±0.7 g/dl and 32.0±2.7%, P<0.001 and P=0.001, respectively). Similarly, mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) were significantly decreased in wasted children (22.3±2.1 and 32.1±1.2 *versus* 23.9±1.9 pg and 34.3±2.0 g/dl, respectively, P<0.001). Wasting was significantly higher in respiratory and gastrointestinal tract infected children [OR=2.9, 95% CI (1.57-5.17), P<0.001] and [OR=3.1, 95% CI (1.64-5.92), P<0.001], respectively. Serum vitamin A and zinc were significantly lower in wasted children having respiratory tract infection compared to non-infected (385.5±286.3 versus 674.3±468.7 nmol/l, P < 0.001 for vitamin A and 64.0±19.8 versus 72.8±18.6, P=0.038 µg/l for zinc). Gastrointestinal tract infected children showed also significant decreases in serum vitamin A and iron (430.9±352.0 versus 601.2±439.2, P=0.042 nmol/l for vitamin A and 79.8±28.4, 93.9±37.1, P=0.041 µg/dl for iron).

Conclusion: Low levels of vitamin A, zinc and iron, hematological alterations, and frequent respiratory and gastrointestinal infections are the biochemical and clinical features of childhood wasting.

Background

Childhood wasting is the life-threatening result of poor nutrient intake and/or disease. A wasted child is a child who has a weight-for-height Z-score less than -2.0 standard deviations [1]. Millions of young lives are in jeopardy around the globe due to wasting. The global prevalence of wasting among children under 5 years was estimated at 7.3%. Over 49 million children were wasted of which nearly 17 million were severely wasted with high risk of death. More than half of all wasted children in the world (25.3 million) live in Southern Asia [2]. In the Palestinian territories, the prevalence of wasting among children was highest at 6 months (10.0%) but decreased to 3.0% at 24 months [3].

In general, failure to fulfill micronutrient requirements, a challenging environment and the insufficient provision of care, are all factors liable for childhood wasting, particularly among children who are under 5 years of age [4]. Micronutrients (vitamins and minerals) are essential elements required by human or other organisms in varying quantities (for human nutrition, usually below 100 mg/day) throughout life to coordinate a range of physiological functions for health maintenance [5]. Vitamin A, zinc and iron are microelements with specific biochemical functions in human body and their deficiency represents a major threat to the health and development of populations worldwide, particularly children and pregnant women in low-income countries [6]. Multiple micronutrient powder of at least vitamin A, iron and zinc was added to the WHO's list of essential medicines in 2019 [7].

Vitamin A is a fat-soluble vitamin which is important in normal functioning of the visual system, maintaining cell function to promote growth, producing red blood cells, developing immunity, and reproduction [8,9]. Vitamin A deficiency generally results in night blindness, severe anaemia, wasting, reproductive and infectious morbidity, and increased risk of mortality [10,11]. Zinc is essential for cellular differentiation and maturation and zinc deficient young children are prone to infections and growth retardation [12]. The main function of iron is in hemoglobin formation which carries oxygen from lungs to other tissues in the body. Iron deficiency anemia is mostly common during childhood, and iron deficiency can affect the behavior and learning abilities as well as development and growth [13].

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The association of vitamin A, zinc and iron with pediatric wasting was globally assessed, particularly in developing countries [4,14,15]. In Gaza Strip, just recently, few published studies determined vitamin A, zinc and iron deficiency in children under 5 years old [16-18]. However and to the best of our knowledge, no previous research linked directly wasting with these micronutrients deficiency and infection. Therefore, this study is the first to assess vitamin A, zinc and iron, and their relation to infection in wasted children aged 6 to 24 months old in Gaza Strip. Assessment of such micronutrients is the basic step to set a sustainable and effective nutritional intervention strategy that may prevent subsequent health complications of wasting among the Palestinian children.

Methods

Study design and target population

This investigation is a case-control study. The target population was the wasted children attending Ard El Insan Benevolent Association; a Palestinian non-governmental organization in Gaza Strip. It provides nutritional and health services to the needy and marginalized children under five years old, their mothers and families.

Sampling and sample size

Children aged 6-24 months old who were referred to Ard El Insan Benevolent Association in Gaza City, and whom diagnosis were confirmed by their nutritional status indicators and physical examination as wasted children were selected. Children with psychomotor disabilities, thalassemia, endocrine disorders and surgical operation were excluded. Control children were selected from wasted children' neighbours and from wasted children' siblings of different mothers lived in separate houses. Their medical history, nutritional status indicators and physical examination confirmed that they did not have wasting. The sample size calculations were based on the formula for case-control studies [19]. EPI-INFO statistical package version 3.5.1 was used with 95% CI, 80% power, 50% proportion as conservative and OR=2. The sample size in case of 1:1 ratio of case to control was found to be 89:89. Based on our response expectation of 95%, we multiply 89 by 1.05 (100/95). Therefore, the required sample size was found to be 93. For a no-response expectation, the sample size was increased to 98 children. The controls were also 98 children. Wasted and control children were matched for age and gender.

Children records

Clinical data including urinary, respiratory and gastrointestinal tracts infections were obtained from the children records.

Anthropometric measurements

Weight was measured in kg (to the nearest 100 g) using an electronic digital scale (Seca model 770, Seca Hamburg, Germany) and its accuracy was periodically verified using reference weights. The child was weighted in light clothing, by determining the mean weights of light clothes dressed, and a correction for the clothing was made during weighing by subtracting 100 g from each child's weight. Length was measured in cm (measured to the nearest mm) using a pediatric measuring board. Children were measured in a recumbent position i.e. lying down [20].

Nutritional status

The software program for assessing growth and development of the world's children was used to make comparisons to the reference standards [21]. The software program combines the raw data on the variables (age, sex, length, weight) to compare a nutritional status indicators such as weight-for-height, weight-for-age and height-for-age. The indicators were calculated by standard deviation (SD) or Z-score for all children. In the present study, a wasted child is a child who has a weight-for-height Z-score less than -2.0 standard deviations.

Blood sampling and processing

Venous blood samples (about 5.0 ml) were collected from each child and divided into EDTA tubes (about 1.0 ml) for CBC determination and vacutainer plain tubes (about 4.0 ml). Vacutainer plain tubes were left for a while to allow blood to clot. Serum samples were obtained by centrifugation at room temperature by Rotina 46 Hettich centrifuge, Japan at 4000 rpm/10 minutes. Then, serum samples were used for biochemical analysis of vitamin A, zinc and iron.

Complete blood count analysis

Blood samples were processed by an automatic counter for hemoglobin concentration and other whole blood components concentrations (ABX Micros ES60, HORIBA ABX Diagnostics, Japan).

Determination of vitamin A, zinc and iron

Serum vitamin A was determined by enzyme-linked immunosorbent assay (ELISA) using human vitamin A, vitamin A ELISA kit. Microplate reader was used to perform qualitative or quantitative determination of samples in accordance with Lamber-Beer law (MR-96A, Shenzhen Mindray Bio-Medical Electronics Co., Ltd., China). Serum zinc and iron were determined by spectrophotometric methods, using a colorimetric biochemistry auto analyzer system (ChemWell Awareness Technology Inc., USA).

Statistical analysis

Data were computer analyzed using the IBM SPSS statistics version 22. Simple distribution of the study variables and the cross tabulation were applied. Chi-square (χ^2) was used to identify the significance of the relations, associations, and interactions among various variables. Yates's continuity correction test, χ^2 (corrected), was used when not more than 20% of the cells had an expected frequency of less than five and when the expected numbers were small. The independent sample t-test procedure was used to compare means of quantitative variables by the separated cases into two qualitative groups such as the relationship between cases and controls micronutrients. The results were accepted as statistical significant when the P value was less than 5% ($P < 0.05$). Ranges as minimum and maximum values were used. The percentage difference was calculated according to the formula: Percentage difference equals the absolute value of the change in value, divided by the average of the 2 numbers, all multiplied by 100. Percent difference=($|$ (V1 - V2) $|$ / ((V1 + V2)/2)) * 100.

Results

Vitamin A, zinc and iron levels of control and wasted children

Table 1 shows significant decreases in the mean levels of serum vitamin A, zinc and iron in wasted children compared to controls (546.8±384.0, 68.5±19.6 and 88.3±34.5 *versus* 702.5±487.9 nmol/l, 74.2±7.8 μg/l and 106.3±11.2 μg/dl; % difference=24.9, 8.0 and 18.5; P=0.014, 0.008 and <0.001, respectively).

Hematological profile of control and wasted children

As indicated in Table 2, WBC and PLT counts (x 10^3/μl) were increased in wasted children compared to controls (11.0±3.3 and 425.0±125.4 *versus* 9.7±3.4 and 414.8±103.9, % difference=12.6 and

2.4, respectively). However, the difference was statistically significant only for WBC (P=0.003). Conversely, RBC count (x 10^6/µl) was significantly decreased in wasted children (4.4±0.4 *versus* 4.6±0.4, % difference=4.4 and P=0.009). In parallel, Hb and Hct were significantly decreased (9.8±0.9 and 30.4±2.5 *versus* 10.9±0.7 g/dl and 32.0±2.7%, % difference=10.6 and 5.1, P<0.001 and P=0.001, respectively). Similarly, MCV, MCH, MCHC were also decreased in wasted children compared to controls (69.2±4.8, 22.3±2.1 and 32.1±1.2 *versus* 69.7±4.2 µm^3, 23.9±1.9 pg and 34.3±2.0 g/dl, % difference=0.7, 6.9, and 6.6, respectively). However, the differences were found to be significant for MCH and MCHC (P<0.001).

Distribution of urinary, respiratory and gastrointestinal tracts infection among control and wasted children

Table 3 reveals that respiratory and gastrointestinal tract infections were significantly higher among wasted children 51 (52.0%) and 42 (42.9%) than controls 27 (27.6%) and 19 (19.4%), with χ^2=12.266, P<0.001 and χ^2=12.591, P<0.001, respectively. Wasting was 2.9 times higher in respiratory tract infected children [OR=2.9, 95% CI (1.57-5.17)] and 3.1 times higher in gastrointestinal tract infected children [OR=3.1, 95% CI (1.64-5.92)] than non-infected children. Although no statistically significant difference was observed between controls and wasted children in terms of urinary tract infection, yet the distribution of wasting was 2.4 times higher in infected children.

Vitamin A, zinc and iron in relation to urinary, respiratory and gastrointestinal infection in wasted children

As illustrated in Table 4, the mean levels of vitamin A and zinc were significantly decreased in wasted children having respiratory tract infection compared to those who have not (385.5±286.3 versus 674.3±468.7 nmol/l, P<0.001 for vitamin A and 64.0±19.8 versus 72.8±18.6, P=0.038 µg/l for zinc). Gastrointestinal tract infected children showed also significant decreases in the mean levels of vitamin A and iron in comparison to non-infected children (430.9±352.0 versus 601.2±439.2, P=0.042 nmol/l for vitamin A and 79.8±28.4, 93.9±37.1, P=0.041 µg/dl for iron). Urinary tract infection registered no significant differences in the mean levels of vitamin A, zinc and iron between infected and non-infected wasted children.

Table 1. Vitamin A, zinc and iron levels of control and wasted children

Parameter	Control children (n=98)	Wasted children (n=98)	% Difference	t	p-value
Vitamin A (nmol/l) *(min-max)*	702.5±487.9 *(294-1949)*	546.8±384.0 *(152-1386)*	24.9	-2.467	0.014
Zinc (µg/l) *(min-max)*	74.2±7.8 *(55-97)*	68.5±19.6 *(21-104)*	8.0	-2.669	0.008
Iron (µg/dl) *(min-max)*	106.3±11.2 *(83-125)*	88.3±34.5 *(31-173)*	18.5	-4.981	<0.001

All values are expressed as means±SD. P<0.05: Significant.

Table 2. Hematological profile of control and wasted children

Parameter	Control children (n=98)	Wasted children (n=98)	% Difference	t	p-value
WBC×10^3/µl	9.7±3.4	11.0±3.3	12.6	3.055	0.003
RBC×10^6/µl	4.6±0.4	4.4±0.4	4.4	-2.644	0.009
Hb (g/dl)	10.9±0.7	9.8±0.9	10.6	-8.598	<0.001
Hct (%)	32.0±2.7	30.4±2.5	5.1	-3.481	0.001
MCV (µm^3)	69.7±4.2	69.2±4.8	0.7	-0.742	0.459
MCH (pg)	23.9±1.9	22.3±2.1	6.9	-4.673	<0.001
MCHC (g/dl)	34.3±2.0	32.1±1.2	6.6	-7.668	<0.001
Platelet×10^3/µl	414.8±103.9	425.0±125.4	2.4	0.661	0.542

WBC: White blood cell, RBC: Red blood cell, Hb: Hemoglobin, Htc: Hematocrit, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration. All values are expressed as means±SD. P<0.05: Significant, P > 0.05: Not significant.

Table 3. Distribution of urinary, respiratory and gastrointestinal tracts infection among control and wasted children

Infection	Control children (n=98)		Wasted children (n=98)		χ^2	p-value	OR (95% CI)≠
	No.	%	No.	%			
Urinary tract infection					1.318	0.251*	2.4 (0.71-7.99)
Yes	4	4.1	9	9.2			
No	94	95.9	89	90.8			
Respiratory tract infection					12.266	<0.001	2.9 (1.57-5.17)
Yes	27	27.6	51	52.0			
No	71	72.4	47	48.0			
Gastrointestinal tract infection					12.591	<0.001	3.1 (1.64-5.92)
Yes	19	19.4	42	42.9			
No	79	80.6	56	57.1			

*P-value of $\chi^2_{(corrected)}$ test. P<0.05: Significant, P > 0.05: Not significant. ≠: Odds ratio at 95% confidence interval.

Table 4. Vitamin A, zinc and iron in relation to urinary, respiratory and gastrointestinal infection in wasted children

Infection	Wasted Children (n=98)		
	Vitamin A (nmol/l)	**Zinc (µg/l)**	**Iron (µg/dl)**
Urinary tract infection			
Yes *(n=9)*	374.0±375.9	62.6±16.3	70.9±32.3
No. *(n=89)*	541.7±410.3	69.2±16.9	90.6±34.3
t-test	-1.286	-0.967	-1.877
P-value	0.202	0.336	0.063
Respiratory tract infection			
Yes *(n=51)*	385.5±286.3	64.0±19.8	89.9±35.1
No. *(n=47)*	674.3±468.7	72.8±18.6	86.5±34.1
t-test	-3.664	-2.110	0.507
P-value	< 0.001	0.038	0.614
Gastrointestinal tract infection			
Yes *(n=42)*	430.9±352.0	67.3±19.8	79.8±28.4
No. *(n=56)*	601.2±439.2	69.7±19.6	93.9±37.1
t-test	-2.063	-0.565	-2.069
P-value	0.042	0.573	0.041

All values are expressed as means±SD.
P<0.05: Significant, P>0.05: Not significant.

Discussion

Wasting can be used to monitor the evolution of the nutritional status of the population, especially in children less than 2 years old. This age group is particularly susceptible for malnutrition due to their rapid growth, lack of dietary diversity and a high burden of infectious disease [22,23]. The first two years of life are crucial for children present and future health and nutritional status and, more specifically, for their mental, physical, and emotional development [24]. Although wasting is prevalent among children from birth to 24 months (3-10%) in the Gaza Strip [3], the few undertaken studies focused on the risk factors associated with wasting [25], without evaluating the role of micronutrients such as vitamin A, zink and iron in this malnutrition disorder. Determination of micronutrients in wasted children could help nutritionists and other health professionals to improve the quality of diet and establishing new style of micronutrients supplementation or food fortification programs. Therefore, this research is the first to assess vitamin A, zinc and iron in wasted children aged 6-24 months in Gaza Strip.

Although wasting is among the leading nutritional problems causing morbidity and mortality in children, assessment of micronutrients status in wasted children less than 2 years of age is limited in the literature. This may be due to both technical difficulties and failure to identify wasting as an active condition of poor health. In the present study, vitamin A, zinc and iron were significantly lower in wasted children than controls. Several authors reported such micronutrients deficiency in wasted children [26,27]. Inadequate vitamin A status would lead to increased susceptibility to infections, poor zinc status would compromise immunity and neurological function and iron deficiency would produce anemia and affect the development of cognitive function i.e. wasting manifestations [4].

Hematological profile showed significant increase in WBC of wasted children than controls. Leukocytosis was documented in malnourished children under 5 years of age [28]. Elevation of WBC found in wasted children may be related to infectious diseases in which the immune system is stimulated as a defense mechanism against infection [29]. This view is supported by our finding that respiratory and gastrointestinal infections are more prevalent in wasted children. On the other hand, RBC, Hb, Hct, MCH and MCHC were significantly decreased in wasted children compared to controls. The decrease in Hb content may be associated with the observed decrease in iron levels in wasted children. In parallel the RBC count is expected to be decreased. It is known that low RBC and Hb resulting in anemia which is a clinical feature of wasting as an indicator of malnutrition [30]. Other factors contributing to anemia of malnutrition include vitamin A and zinc defieciency as well as infections which were observed in wasted children. The lower value of Hct in wasted children is convenient as it is defined as the percentage of volume occupied by red blood cells compared to the total blood volume [31]. The values of MCH and MCH were also decreased in wasted children. Therefore, the present results do confirm that anemia is a constant feature of wasting. The previous alterations in hematological profile are in agreement with that obtained in malnourished children elsewhere in the leterature [30,32].

Respiratory and gastrointestinal tracts infection was significantly more frequent in wasted children than controls. A consistent association has been demonstrated in the literature between wasting and respiratory and gastrointestinal tracts infection among children [33,34]. This coincides with the fact that children with malnutrition tend to have low immunity and are vulnerable to a number of infections. In particular diarrheal and respiratory infections, occur most frequently during the first 2-3 years of life when immunocompetence is impaired and when, at the same time, children are first being exposed to disease pathogens [35]. A study found that children who are wasted, compared with the well-nourished are almost twice as likely to develop the bacteria*Shigella*whose main symptom is diarrhea [36]. In addition, infection can suppress appetite and directly affect nutrient metabolism, leading to poor nutrient utilization and more likely to wasting [4,37].

When related to infection in wasted children, vitamin A and zinc levels were significantly lower in children having respiratory tract infection compared to non-infected children. Gastrointestinal tract infected children showed also significant decreases in the levels of vitamin A and iron. Pediatric studies showed that deficiency of these micronutrients contributes to an increased incidence and severity of respiratory and gastrointestinal infections such as pneumonia and diahrrea [38-40]. This implies the importance of vitamin A, zinc and iron as anti-infection agents. Recently, it has been established that the complex, integrated immune system needs multiple specific micronutrients, including vitamin A, zinc and iron, which play vital, often synergistic roles at every stage of the immune response to reduce the risk of infection [41]. In this context, vitamin A, zinc and iron collectively function to support all aspects of innate and adaptive immunity [42]. Therefore, the ability of wasted children having vitamin A, zinc and/or iron deficiency to resist diseases such as respiratory and gastrointestinal infections is hampered. On the light of the present findings, one can suggest a bidirectional interaction of malnutrition and infection. With micronutrient feeding strategy of the immune system such a bidirectional cycle could be broken.

Conclusions

Serum vitamin A, zinc and iron were significantly lower in wasted children than controls. The WBC count was significantly increased in wasted children than controls whereas RBC, Hb, Htc, MCH, MCHC were significantly decreased in wasted children. Wasting was 2.9 and 3.1 times higher in respiratory and gastrointestinal tracts infected children, respectively than non-infected. Serum vitamin A and zinc were significantly decreased in wasted children having respiratory tract infection compared to non-infected. Gastrointestinal tract infected children showed also significant decreases in serum vitamin A and iron.

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Authors' contributions

This work was carried out in collaboration between the authors. Maged M. Yassin designed the study, wrote the protocol, helped in the statistical analysis and wrote the first draft of the manuscript. Said S. Alghora performed the experimental work, managed the analyses of the study and revised the final draft of the manuscript. The authors read and approved the final manuscript, and they have taken due care to ensure the integrity of the work.

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Availability of data and materials

All data and materials are fully available and are shown within the manuscript.

Ethical consideration

The necessary approval to conduct this study was obtained from Helsinki Committee. Informed consent was obtained from children mothers of all participants. A full explanation about the purpose of the study, assurance about confidentiality of information and the right to refuse or to participate in the study were given.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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