

Possible risk factors that may play a role in augmenting the liability and intensity of coronavirus disease 2019 infection in obese and nonobese Egyptian children

Nayera E. Hassan^a, Sahar Abd El-Raufe El-Masry^a,
Mohamed S. El Hussieny^a, Samer H. ElKhayat^b, Nihad H. Ahmed^c,
Heba T. Aboud^a, Mohammed I. Mostafa^d, Ayat N. Kamal^a

Departments of ^aBiological Anthropology,
^aClinical Pathology, Medical Research Division,
^cDepartment of Nutrition and Food Science,
National Research Centre, Giza, ^bDepartment
of Pediatrics, Faculty of Post Graduate
Childhood Studies, Ain-Shams University,
Cairo, Egypt

Correspondence to Sahar Abd El-Raufe El-
Masry, PhD, Department of Biological
Anthropology, National Research Centre, 33 El-
Bohooth Street, Dokki, Giza, Cairo 12622,
Egypt. Mob: 00201006606640;
e-mail: masrysa@yahoo.com

Received: 4 May 2021

Revised: 12 July 2021

Accepted: 27 July 2021

Published: 31 December 2021

**Journal of The Arab Society for Medical
Research** 2021, 16:91–99

Background/aim

Obesity, insulin resistance (IR), dyslipidemia, and decreased consumption of essential micronutrients are factors that can compromise the immune response to coronavirus disease 2019 (COVID-19) infection, leading to increased morbidity and mortality among children. The aim of this study was a detection of possible risk factors that may play a role in augmenting the liability and intensity of COVID-19 infection in Egyptian obese and normal-weight children.

Patients and methods

This study was a retrospective observational cross-sectional review including 120 obese children (group 1), in addition to 61 age-matched and sex-matched controls (group 2) from children attending 'the Management of Visceral Obesity and Growth Disturbances Unit' at the Medical Research Excellence Center (MERC), National Research Centre, Egypt. All children were exposed to medical assessment, anthropometric evaluation, and a three 24-h dietary recall for assessment of micronutrient intake. Laboratory assessment of fasting serum blood glucose, insulin, triglycerides, total cholesterol, high-density lipoprotein, and low-density lipoprotein was done and IR was calculated.

Results

Obese children showed higher significant values than the control group regarding all anthropometric measurements with increased blood pressure, waist circumference, and waist-to-hip ratio. Laboratory assessment revealed elevated fasting levels of glucose and Homeostatic Model Assessment for Insulin Resistance denoting IR together with the presence of triglycerides and high-density lipoprotein levels within the high-risk range showing tendency toward dyslipidemia. The intake of vitamins A, D, folic acid, and calcium was lower than the recommended dietary allowances in both groups.

Conclusion

Obesity and its consequent complications, including dyslipidemia and IR together with decreased consumption of vitamins A, D, folic acid, and calcium, were the most prominent risk factors found among the studied sample of Egyptian children that can affect their immune response and predispose to increased severity of COVID-19 infection.

Keywords:

children, coronavirus disease 2019, obesity, risk factors

J Arab Soc Med Res 16:91–99

© 2021 Journal of The Arab Society for Medical Research
1687-4293

Introduction

Since December 2019, the world has been suffering from a severe pandemic generated by a sentimental type of coronavirus infection. It was transmitted expeditiously throughout countries causing severe pneumonia. The disease was termed coronavirus disease 2019 (COVID-19) [1]. It was found to affect almost all age groups but less frequently the pediatric group with less severity and mortality when compared with adults [2].

Obesity was found to be a crucial risk factor determining the necessity of respiratory support

among children infected with COVID-19 [3]. The World Obesity Federation predicted obesity to reach 158 million all over the world in the age group from 5- to 19-year olds [4]. In Egypt, a cross-sectional study, including 1000 primary school students (6–12 years) in 2019, found that the overall prevalence of obesity and overweight was 13.9 and 16.2%, respectively [5].

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

In a study done by Hassan *et al.* [6] among obese Egyptian school children aged 7–11 years found several cardiometabolic risk factors indicated by elevated total cholesterol and low-density lipoprotein (LDL) together with increased fasting glucose level and waist circumferences among obese children in comparison with the control group.

In childhood and adolescence, the relatively high pancreatic reserve of insulin allows hyperinsulinism to occur as a result of obesity-associated hyperglycemia [7]. Although hyperinsulinism keeps blood glucose within normal levels, it can also cause several health consequences, such as dyslipidemia, nonalcoholic fatty hepatitis, arterial hypertension, micronutrient shortage, enhanced oxidative stress, and increased uric acid level [8].

In circumstances of extreme metabolic activity, such as during immune reaction to coronavirus infection, beta cells secrete increased amount of insulin, which may not be accomplished when they are already working at their ceiling as in obesity. SARS-CoV-2 can also cause beta cells to rupture by the interaction with angiotensin-converting enzyme-2 (ACE2), which further aggravates this process [8]. Insulin resistance (IR) can also cause impairment of the vasoprotective and anti-inflammatory effects of nitric oxide as a result of reduction in phosphoinositide 3-kinase [9].

Dyslipidemias are highly prevalent among obese children and adolescents. Decreased level of high-density lipoprotein (HDL) cholesterol and increased LDL cholesterol are certified risk factors for advancement of endothelial dysfunction and atherosclerosis that may provoke COVID-19 vascular complications [7].

A sufficient intake of iron, zinc, and vitamins A, D, C, B6, and B12 is essential for maintaining the immune function. The presence of nutritional deficiencies of these micronutrients among obese children would lead to depressed immune function and increased susceptibility to COVID-19 infection [10].

The present study aims to detect the possible risk factors that may play a role in augmenting the liability and intensity of COVID-19 infection in obese and nonobese Egyptian children.

Patients and methods

Patients and study design

This study is a retrospective observational cross-sectional study that comprised 120 prepubertal obese

(exogenous obesity) children aged 6–less than 12 years old of both sexes (54 males and 66 females) with BMI more than or equal to 95th percentile (Egyptian growth curves 2002) (group 1), in addition to 61 age-matched and sex-matched controls (31 males and 30 females) with BMI=15–less than 85 percentile (group 2). Children with other causes of obesity, congenital anomalies, chronic diseases, or taking medications that can affect their normal growth were excluded. The study was carried out in the Management of Visceral Obesity and Growth Disturbances Unit at 'Medical Excellence Research Center,' which is a part of the 'National Research Centre' during the period from January to November 2019.

Ethical approval

All experiments were approved by the Ethical Committee of the National Research Centre with approval number 16/448, in accordance with the Declaration of Helsinki. A written informed consent was taken from one of the parents of the participated children.

Methods

Anthropometric measurements

All children were subjected to clinical examination and anthropometric assessment, including body weight, height, and waist and hip circumferences following the recommendation of International Biological Program [11]. Then, BMI [(weight (kg)/height² (m))], waist-to-hip ratio and waist-to-height ratio were calculated. Dietary history was taken, including 24 h of average food recall of the last 3 days. Portions consumed were estimated according to Ferguson *et al.* [12]. The total dietary intake was analyzed using the Nutrisurvey computer program to convert the food taken into micronutrients [13], and compared with the recommended dietary intake of micronutrients in children of same age [14].

Nutritional characteristic methods

Children were asked to recall their dietary intakes of the previous 24 h for 3 days and average intake was recorded, any snacks taken between meals were also recorded, and portion sizes consumed were estimated according to Ferguson *et al.* [12].

The total dietary intake was analyzed using the Nutrisurvey for Windows computer program to convert the food taken into micronutrients [13]. The average daily intake was then compared with the recommended dietary allowances (RDA) of micronutrients in children of same age [14].

Sampling and biochemical analysis

A 5-ml sample of venous blood was obtained from each child after 12 h of fasting for laboratory assessment. The blood samples were centrifuged and the serum was separated and kept at -8°C for batch assessment.

Fasting blood glucose was assessed immediately after taking blood samples by enzymatic colorimetric method, using kits of Chemelex S.A. (Barcelona, Spain) according to the method of Tietz [15]. Values less than 100 mg/dl were categorized as normal fasting glucose; values between 100 and 125 mg/dl are categorized as impaired fasting glucose. Values above 126 mg/dl are categorized as prediabetes or provisional diabetes if persistent on repeated testing, according to ISPAD Clinical Practice Consensus Guidelines 2018 [16]. Serum insulin was assessed using enzyme immunoassay test of Immunospec Corporation (9428 Eton Ave, Unit O, Chatsworth, California, USA) according to the method of Burtis *et al.* [17]. Fasting insulin values less than 25 mIU/l are classified as desirable and values equal to or more than 25 mIU/l are classified as high risk [18].

IR was calculated according to Matthews *et al.* [19], using the following equation:

$$\text{IR} = \frac{\text{fasting glucose (mg/dl)} \times \text{fasting insulin } (\mu\text{IU/ml})}{405}$$
The cut-off point in children was defined as more than or equal to 3.16. Results up to 15 were considered as moderate IR. Results higher than 5 were considered as severe IR [20].

In addition, lipid profile (total cholesterol, triglycerides, HDL cholesterol, and LDL cholesterol) was assayed by standard enzymatic procedures according to Tietz [15]. However, serum triglycerides were assessed using the kit of Chemelex S. A.. Serum triglyceride values less than 75 mg/dl are classified as desirable, values between 75 and 99 mg/dl as borderline risk, and values equal to or more than 100 mg/dl as high risk for 6–9-year-old children. Values less than 90 mg/dl are classified as desirable, values between 90 and 129 mg/dl as borderline risk, and values equal to or more than 130 mg/dl as high risk for 10–less than 12-year-old children [21].

Serum total cholesterol was assessed using the kit of Chrono Lab Systems (Barcelona, Spain). Total cholesterol values less than 170 mg/dl are classified as desirable, values between 170 and 199 mg/dl as borderline risk, and values starting from 200 mg/dl as high risk [21].

HDL was assessed using the kit of Chemelex S.A.. HDL values less than 40 mg/dl are classified as major heart-disease risk factor, values between 40 and 45 mg/dl as borderline risk, while values more than 45 mg/dl were considered as low risk against heart disease [21]. LDL was assessed using the kit of Quimica Clinica Aplicada S.A. (Spain). According to polvinylsulfate method of Demacker *et al.* [22], LDL values less than 110 mg/dl are classified as desirable, values between 110 and 129 mg/dl are classified as borderline risk, and values from 130 mg/dl and above as high risk [21].

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS/Windows, Version 18; SPSS Inc., Chicago, Illinois, USA). The total dietary intake was analyzed using the Nutrisurvey computer program to convert the food taken into micronutrients. Normality of data was tested using the Kolmogorov–Smirnov test. The data were normally distributed. The parametric data were expressed as mean $\pm$ SD, where the qualitative ones were expressed as number and percentage. Student's *t* test was used to compare between two parametric groups, and χ^2 test was used to compare between groups with qualitative data. Standards of probability were set to *P* value less than 0.01, which was considered highly significant and *P* value less than 0.05 was considered statistically significant.

Results

Comparisons between obese and controls regarding blood pressure and the studied anthropometric parameters are shown in Table 1. The mean systolic and diastolic blood pressure were higher in the obese children than in children of the control group with a highly significant difference ($P=0.000$). All anthropometric parameters showed a highly significant difference, being higher in obese children than control ones.

Laboratory comparison between obese and control is presented in Table 2. The mean fasting insulin levels showed a highly significant difference between the two groups being higher in obese children ($P=0.000$). The mean fasting insulin levels of both groups were within the desirable range. The mean fasting blood glucose of the obese group was 152.16 ± 20.31 mg/dl, which was above the desirable range carrying the risk of diabetes (if persistent on two separate occasions). The mean fasting blood glucose of the control group was 85.24 ± 7.61 mg/dl, which was within the desirable range with

Table 1 Clinical and anthropometric characteristics of the obese and control (nonobese) groups

	Group 1: obese (N=120)	Group 2: control (N=61)	t	P value
Age (years)	9.28±1.65	8.82±1.73	1.723	0.087
Blood pressure				
Systolic blood pressure (mmHg)	108.17±11.34	95.74±9.17	7.943	0.000*
Diastolic blood pressure (mmHg)	65.33±8.09	59.18±6.34	5.609	0.000**
Anthropometry:				
Weight (kg)	52.69±11.41	26.42±5.32	21.104	0.000**
Weight (Z score)	2.67±1.32	-0.58±0.60	22.725	0.000**
Height (cm)	138.75±10.04	128.66±8.34	6.755	0.000**
Height (Z score)	0.81±1.07	-0.35±0.77	8.372	0.000**
BMI (kg/m ²)	27.11±3.28	15.71±2.21	27.714	0.000**
BMI (Z score)	2.95±1.49	-0.61±0.70	21.890	0.000**
Waist circumference (cm)	85.43±9.81	57.95±6.80	22.010	0.000**
Hip circumference (cm)	95.47±15.32	68.44±6.08	16.880	0.000**
Waist/hip ratio (cm/cm)	0.90±0.07	0.85±0.06	5.196	0.000**
Waist/height ratio (cm/cm)	0.62±0.06	0.45±0.05	20.221	0.000**

All data are expressed as mean±SD. **Highly significant differences at P value less than 0.01.

Table 2 Laboratory characteristics of the obese and control (nonobese) groups

Laboratory results	Group 1: obese (N=120)	Group 2: control (N=61)	t	P value
Insulin (μU/ml)	11.97±1.13	8.00±0.75	28.204	0.000**
Glucose (mg/dl)	152.16±20.31	85.24±7.61	31.950	0.000**
Insulin resistance (HOMA)	4.50±0.79	1.68±0.22	36.427	0.000**
Cholesterol (mg/dl)	168.53±18.17	116.54±13.95	21.332	0.000**
Triglycerides (mg/dl)	137.48±15.53	87.92±20.55	18.138	0.000**
HDL (mg/dl)	28.57±5.66	50.49±8.87	-17.560	0.000**
LDL (mg/dl)	100.51±7.39	74.08±8.44	21.664	0.000**

All data are expressed as mean±SD. HDL, high-density lipoprotein; HOMA, Homeostatic Model Assessment; LDL, low-density lipoprotein.

**Highly significant differences at P value less than 0.01

a highly significant difference ($P=0.000$) in comparison with obese group. Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) was higher in obese children than in controls with a highly significant difference ($P=0.000$). The mean value of HOMA-IR in the obese group was 4.50 ± 0.79 , which was above the cut-off value for IR, while the mean value of HOMA-IR in the control group was 1.68 ± 0.22 , which was within the normal range.

Regarding the lipid profile of our obese and control children, the mean values of cholesterol, triglycerides, and LDL showed statistically significant higher levels in obese children compared with their controls. The mean values of cholesterol and LDL were within the desirable low-risk range in both groups. The mean values of HDL and triglycerides in obese children lied within the high-risk range.

Table 3 shows comparison between obese and controls regarding daily micronutrient intake and it's percent to RDA. The intake of vitamin B1, niacin, vitamin B6, B12, folic acid, vitamin C, vitamin D, sodium, magnesium, phosphorus, iron, and zinc is significantly higher in the obese children than

control ones. Vitamin B1, B2, niacin, vitamin B6, B12, vitamin C, sodium, magnesium, zinc, and iron intake is higher than the RDA in both groups. Phosphorus intake is higher than the RDA in obese children and lower than the RDA in control ones. The intake of vitamin A, vitamin D, folic acid, and calcium is lower than the RDA in the two groups.

Regarding the frequency distribution of risk factors for COVID-19 infection among our studied groups in Table 4, 100% of obese-group hyperglycemia in the prediabetic or diabetic risk range, while only 6.7% of female controls showed the same risk factor. All members of our obese group showed IR and none of our studied groups, either obese or control, showed hyperinsulinemia. Obese males (81.5%) showed elevated serum levels of triglycerides in the high-risk range for age and 90.9% of obese females showed the same risk. Only 6.5% of control males and 20% of control females showed the risk of hypertriglyceridemia. HDL levels were in the high-risk range in 100% of male and female obese children, while 12.9% of male controls and 6.7% of female controls showed the same risk factor. LDL was not elevated to the high-risk range in either of the two groups.

Table 3 Comparison between the obese and control (nonobese) groups regarding their nutritional characteristics

Variables	Obese (N=60)	Control (N=31)	RDA	<i>t</i>	<i>P</i> value
Vitamin A (µg)	522.59±143.75 87%	508.60±146.27 84.7%	600	0.615	0.539
Vitamin D (µg)	1.98±1.87 13.2%	0.92±1.39 6.13%	15	4.270	0.000**
Vitamin B1 (mg)	1.35±0.53 150%	0.96±0.37 106.6%	0.9	5.650	0.000**
Vitamin B2 (mg)	1.42±1.10 157.7%	1.01±1.25 112.2%	0.9	2.244	0.026*
Niacin (mg)	22.35±12.22 186.2%	15.68±8.62 130.6%	12	4.248	0.000**
Vitamin B6 (mg)	2.13±0.81 213%	1.44±0.61 144%	1	6.425	0.000**
Folic acid (mg)	241.34±124.13 80.4%	160.83±85.11 53.6%	300	5.121	0.000**
Vitamin B12 (µg)	4.21±4.15 233.8%	2.35±3.01 130.5%	1.8	3.448	0.001**
Vitamin C (mg)	69.76±38.84 155%	51.55±41.86 114.5%	45	2.904	0.004**
Sodium (mg)	3438.86±1498.68 286.5%	2168.40±865.46 180.7%	1200	7.216	0.000**
Calcium (mg)	484.08±223.59 37.2%	451.21±201.52 34.7%	1300	0.966	0.335
Magnesium (mg)	367.10±123.34 152.9%	272.12±98.90 113.3%	240	5.606	0.000**
Phosphorus (mg)	1420.59±503.31 113.6%	1032.63±383.50 82.6%	1250	5.769	0.000**
Iron (mg)	16.81±6.26 210.1%	11.05±4.02 138.1%	8	7.488	0.000**
Zinc (mg)	13.70±6.82 171.2%	9.45±4.13 118.1%	8	5.202	0.000**

All data are expressed as mean±SD. RDA, recommended daily allowance. *Significant differences at *P* value less than 0.05. **Highly significant differences at *P* value less than 0.01.

Table 4 Frequency distribution (%) of the high risk among obese and control (nonobese) children by sex

Laboratory results	Obese (N=120)		Control (N=61)		χ^2 <i>P</i> value
	Males (N=54)	Females (N=66)	Males (N=31)	Females (N=30)	
Insulin (µIU/ml)					
High risk (fasting ≥25 mIU/l)	0	0	0	0	
Glucose (mg/dl)					
Impaired fasting glucose (100–125 mg/dl)	0	0	0	6.7	
Prediabetic or diabetic (≥126 mg/dl)*	100	100	0	0	0.000**
Insulin resistance (HOMA)					
Cutoff ≥3.16	100	100	0	0	0.000**
Cholesterol (mg/dl)					
High risk (≥200 mg/dl)	0	0	0	0	
Triglycerides (mg/dl)					
0–9 years					
High risk (≥100 mg/dl)	81.5	90.9	6.5	20	0.000**
10–12 years					
High risk (≥130 mg/dl)					
HDL (mg/dl)					
High risk (<40 mg/dl)	100	100	12.9	6.7	0.000**
LDL (mg/dl)					
High risk (≥130 mg/dl)	0	0	0	0	

HDL, high-density lipoprotein; HOMA, Homeostatic Model Assessment; LDL, low-density lipoprotein. **Highly significant differences at *P* value less than 0.01

Table 5 Frequency distribution (%) of the low intake of recommended dietary allowances (high risk) among obese and control (nonobese) children by sex

	Obese (N=120)		Control (N=61)		RDA	χ^2 P value
	Males (N=54)	Females (N=66)	Males (N=31)	Females (N=30)		
Vitamin A (μ g)	81.5	54.5	74.2	33.3	600	0.602
Vitamin D (μ g)	92.6	97	100	100	15	0.076
Vitamin B1 (mg)	14.8	24.2	45.2	60	0.9	0.000**
Vitamin B2 (mg)	25.9	21.2	58.1	46.7	0.9	0.000**
Niacin (mg)	14.8	24.2	38.7	40	12	0.005**
Vitamin B6 (mg)	3.7	3	25.8	20	1	0.000**
Folic acid (mg)	63	90	93.5	100	300	0.001**
Vitamin B12 (μ g)	37	39.4	67.7	53.3	1.8	0.004**
Vitamin C (mg)	18.5	33.3	48.4	60	45	0.000**
Sodium (mg)	7.4	9.1	12.9	6.7	1200	0.736
Calcium (mg)	100	100	100	100	1300	
Magnesium (mg)	11.1	18.2	45.2	46.7	240	0.000**
Phosphorus (mg)	29.6	45.5	64.5	80	1250	0.000**
Iron (mg)	3.7	0	32.3	20	8	0.000**
Zinc (mg)	7.4	21.2	51.6	40	8	0.000**

RDA, recommended dietary allowances. **Highly significant differences at P value less than 0.01.

According to the frequency distribution of decreased intake of vitamins and minerals, vitamin D and calcium intake was deficient among most children of both groups. The deficiency of vitamins B1, B2, B16, B12, folic acid, vitamin C, and minerals, including magnesium, phosphorus, iron, and zinc, was of greater incidence among members of the control group. Vitamin-A intake was lower than the RDA in both groups with no significant difference in deficiency between them (Table 5).

Discussion

The identification of biomarkers for early detection of COVID-19 severity and progression has still been a global concern. Early classification and treatment of COVID-19 patients who may advance into the severe crucial stage can result in better prognosis [23].

The WHO described both the COVID-19 outburst and obesity 'epidemic' as global public health emergencies. Although less frequently, COVID-19 affects the pediatric age group, but recent clinical studies observed that COVID-19 can cause more severe symptoms and complications in obese adults [24] and obese children [3] and that obese patients are at higher risk of hospital admittance, irrespective of their viral status [25].

A direct metabolic link was found between the state of inflammation associated with metabolic syndrome and the cytokine storm that causes decline of the respiratory functions in COVID-19 patients. This metabolic disorder is intensified by preexisting diabetes or

hypertension that is usually accompanied by obesity [26]. Obese children tend to have higher blood pressure than normal-weight children of the same age, which increases the potentials for endothelial damage, one of the bases of COVID-19 pathogenesis [27].

Our study involved 120 obese children in addition to 61 age-matched and sex-matched controls aiming for detection of risk factors that can increase liability and severity of COVID-19 infection in obese and normal-weight Egyptian children. Children of the obese group showed increased IR and increased fasting blood glucose in all patients of this group. IR arises from a defect in insulin action on its target tissues, either due to a defect in insulin receptor or more commonly due to disorders in the postreceptor insulin-signaling cascade [28]. This impaired insulin action is associated with increased circulating insulin concentrations [29].

ACE2, which serves as the ligand through which coronaviruses bind to their target cells [30], is an important link between COVID-19 severity and IR. A recent study has confirmed that several diabetes-related traits are associated with increased lung ACE2 expression [31]; another study found that IR and elevated insulin levels result in increased ACE2 expression in lung tissues, leading to aggravating the intensity of the disease [32].

Also, serum levels of cholesterol, triglycerides, and LDL were significantly higher in the obese children than the control ones; however, the means for

cholesterol and LDL were in the desirable low-risk range. Serum levels of HDL and triglycerides were in the high-risk range in obese children and were prevalent among most members of the group. Dyslipidemia has a high prevalence among obese children [7] and low levels of HDL cholesterol and increased LDL cholesterol are confirmed risk factors for development of endothelial malfunction and atherosclerosis [33].

In viral infections, high levels of LDL cholesterol interoperate with macrophages in atherosclerotic plaques and increase the secretion of pro-inflammatory cytokines [34]. Additionally, low HDL cholesterol causes disturbance in the intrinsic immune response, which is the first line of defense against COVID-19 infection [35]. Finally, elevated LDL cholesterol or triglycerides can cause endothelial dysfunction, which in turn predisposes to cardiovascular complications with more severe outcomes [36]. A recent review was conducted based on meta-analysis of the relationship between dyslipidemia and COVID-19 infection severity, where patients with dyslipidemia were found to be at risk for severe COVID-19 infections [37].

A suitable nutritional status has been considered as an essential component for immune response against coronavirus infection. A study conducted by Zhang and Lui [38] showed that some nutrients are cardinal for better response to coronavirus, such as vitamins A, C, D, and E, omega-3 fatty acids, and the minerals zinc and iron. In obesity, despite eating above energy needs, the quality of dietary intake may not be adequate, so vitamin or mineral deficiencies may be present in those with excess weight 'hidden hunger' [39].

In the current study, vitamin-D intake was lower than the recommended RDA among most children of both obese and control groups. Vitamin D has immunomodulatory effects and also enhances the expression of antimicrobial peptides in neutrophils and monocytes [40]. Furthermore, hypovitaminosis D is found to be interrelated with disorders that have possible influence on COVID-19, such as arterial hypertension, fatty liver, and increased uric acid level [41].

Another finding in our study was the decreased intake of calcium below the RDA in both obese and normal-weight children. SARS-CoV-2 E gene encodes a small transmembrane protein with ion-channel activity that is highly synthesized during infection. These channels are penetrable to Ca^{2+} , so the disturbance of calcium

homeostasis may stimulate the activation of inflammatory pathways, leading to edema and damage of the lung cell [42]. In contrast to moderately infected cases, severe COVID-19 patients were found to be more likely to have hypocalcemia even after adjustment by age and comorbidities [43]. An Italian study of 531 patients establishes that hypocalcemia could anticipate the severity and need for hospitalization of COVID-19 patients [44]. Vitamin-A intake was deficient in both our obese and control children with no significant difference in prevalence between the two groups. Vitamin A helps the renewal of the mucosal barriers damaged by infection and helps the protective role of macrophages, neutrophils, and natural killer cells. Vitamin-A deficiency reduces T-helper 2 response, which culminates in a lack of interleukin-4 and fails to induce immunoglobulin A, hindering the response to influenza virus infection [45].

Zinc deficiency was proved to be present among obese children. Zinc takes part in insulin and leptin metabolism, leading to metabolic deregulation in obese children, causing inadequate inflammatory response [46]. However, the mean intake of zinc was above the RDA in both of the current groups, but the prevalence of its deficiency occurred more among the control group. Zinc deficiency has been also related to decreased production of cytokines and interferon, atrophy of the thymus gland and other lymphoid organs, and changes in the ratio of lymphocytes [47].

Folic acid intake was below the RDA in both groups of the current study, but the prevalence of its deficiency was more among controls than the obese children. Studies have shown that folic acid can reduce the replication of COVID-19 virus either by inactivation of furin endoprotease that is essential for the SARS-CoV-2 virus entry to the host cell [48], or by inactivation of protease 3CL^{pro}, which is vital in the replication of all coronaviruses [49]. Clinical evidence suggests that folic acid supplementation can protect against SARS-CoV-2 infection and pregnant women receiving folic acid supplementation seem to have a lower probability forgetting this infection and even those who are infected have a higher chance of being asymptomatic [50].

Finally, the presence of metabolic comorbidities and dyslipidemia among our obese children, together with the presence of nutrient deficiencies among obese and normal-weight children, represents serious risk factors contributing to the severity of COVID-19 infection.

Conclusion

Current piece of research among this sample of Egyptian children gave an idea about 'What Do We Need to Know about the Risk Factors for COVID-19 Infection among children.' It was observable that obesity and its metabolic consequences, such as dyslipidemia and IR, accompanied with decreased consumption of vitamins A, D, folic acid, and calcium, were the most noticeable risk factors found among the Egyptian children that can impair their immune response and accelerate serious consequences of COVID-19 infection.

Acknowledgements

The authors acknowledge the institute 'National Research Centre; Egypt'; without its fund, this study could not be done. The authors are also grateful to everybody who participated in this study: the children who were the participants of this study, the technicians who helped in the laboratory analysis, and the doctors who participated in collection of the data. Without their help, this study could not have been completed.

Author contribution: Nayera E. Hassan designed the study as well as revised every step and gave conceptual advice; Sahar Abd El-Raufe El-Masry performed the statistical analysis shared in tabulation of the data and publication process; Nihad H. Ahmed was responsible about analysis of the nutritional data; Mohammed I. Mostafa did laboratory analysis; Mohamed S. El Hussieny, Samer H. ElKhayat, Heba Tala, and Ayat N. Kamal collected the nutritional data from participants and took anthropology measurements; Ayat N. Kamal wrote the draft of the paper. All authors read and approved the final paper.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

- González JJE. SARS-CoV-2 and COVID-19. A pandemic review. *Med Crit* 2020; 33:53–67.
- Lee B, Raszka WV. COVID-19 in children: looking forward, not back. *Pediatrics* 2021; 147:e2020029736.
- Zachariah P, Johnson CL, Halabi KC, Ahn D, Sen AI, Fischer A. Epidemiology, clinical features, and disease severity in patients with coronavirus disease 2019 (COVID-19) in a children's hospital in New York City, New York. *JAMA Pediatr* 2020; 174:e202430.
- Lobstein T, Brinsden H. Atlas of childhood obesity. World Obesity Federation; 2019.
- Hamed A, Hassan A, Younis M, Kamal A. Prevalence of obesity and overweight among primary schools children in Qena, Egypt. *Egypt J Hosp Med* 2019; 77:4899–4905.
- Hassan NE, El-Masry SA, Mohsen MA, Zaki ST, Elashmawy E, Al-Tohamy Soliman M, Abd El-Moniem MM. Obesity degree and cardiometabolic risk among school students. *Life Sci J* 2012; 9:293–301.
- Nogueira-de-Almeida CA, de Mello ED. Different criteria for the definition of insulin resistance and its relation with dyslipidemia in overweight and obese children and adolescents. *Pediatr Gastroenterol Hepatol Nutr* 2018; 21:59–67.
- Sattar N, McInnes IB, McMurray JJ. Obesity is a risk factor for severe COVID-19 infection: multiple potential mechanisms. *Circulation* 2020; 142:4–6.
- Korakas E, Ikonomidis I, Kousathana F, Balampanis K, Koun-touri A, Raptis A. Obesity and COVID-19: immune and metabolic derangement as a possible link to adverse clinical outcomes. *Am J Physiol Endocrinol Metab* 2020; 319:105–109.
- Naja F, Hamadeh R. Nutrition amid the COVID-19 pandemic: a multi-level framework for action. *Eur J Clin Nutr* 2020; 74:1117–1121.
- Hiernaux J, Tanner J. Growth and physical studies. In: Weiner JS, Lourie SA, (eds). *Human biology: a guide to field methods*. Oxford, Edinburgh: Blackwell Scientific Publications; 1969. 2–42.
- Ferguson EL, Gadowsky SL, Huddle JM, Cullinan TR, Lehrfeld J, Gibson RS. An interactive 24-h recall technique for assessing the adequacy of trace mineral intakes of rural Malawian women; its advantages and limitations. *Eur J Clin Nutr* 1995; 49:565–578.
- Erhardt J. Nutri-survey for Windows – copyright. Dr. Juergen Erhardt, Seameo-Tropmed. 2007 RCCN. University of Indonesia, Indonesia.
- Dietary Reference Intakes. Summary Tables: Institute of Medicine. Dietary reference intakes. Washington, DC: The National Academies Press 2011.
- Tietz NW. Clinical guide to laboratory tests. Philadelphia: WB Saunders Co. 1995.
- Mayer-Davis EJ, Kahkoska AR, Jefferies C, Dabelea D, Balde N, Gong CX, et al. ISPAD Clinical Practice Consensus Guidelines 2018: definition, epidemiology, and classification of diabetes in children and adolescents. *Pediatr Diabetes* 2018; 19:7–19.
- Burtis CA, Ashwood ER, Brun DE. (eds). *Tietz Textbook of Clinical Chemistry and Molecular Diagnosis* (5th edition). St. Louis, USA: Elsevier; 2012. 2238 pp. 909 illustrations. ISBN: 978-1-4160-6164-9. Cited in: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3547451/> Indian J Clin Biochem 2013; 28(1):104–105.
- Miniello VL, Faienza MF, Scicchitano P. Insulin resistance and endothelial function in children and adolescents. *Int J Cardiol* 2014; 174:343–347.
- Matthews DR, Hosker JP, Rudenski AS. Homeostasis model assessment: insulin resistance and β -cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; 28:412–419.
- Keskin M, Kurtoglu S, Kendirci M, Atabek ME, Yazici C. Homeostasis model assessment is more reliable than the fasting glucose/insulin ratio and quantitative insulin sensitivity check index for assessing insulin resistance among obese children and adolescents. *Pediatrics* 2005; 115:500–503.
- National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents. *Pediatrics* 2011; 128:213–256.
- Demacker PN, Hijmans AG, Breninkmeijer BJ, Jansen AP, van 't Laar A. Five methods for determining low-density lipoprotein cholesterol compared. *Clin Chem* 1984; 30:1797–1800.
- Stefan N, Birkenfeld AL, Schulze MB. Global pandemics interconnected — obesity, impaired metabolic health and COVID-19. *Nat Rev Endocrinol* 2021; 17:135–149.
- Simonnet A, Chetboun M, Poissy J, Raverdy V, Noulette J, Duhamel A. High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. *Obesity (Silver Spring)* 2020; 28:1195–1199.
- Yuen KS, Ye ZW, Fung SY, Chan CP, Jin DY. SARS-CoV-2 and COVID-19: the most important research questions. *Cell Biosci* 2020; 10:40.
- Bornstein SR, Dalan R, Hopkins D, Mingrone G, Boehm BO. Endocrine and metabolic link to coronavirus infection. *Nat Rev Endocrinol* 2020; 16:297–298.
- Mauad Filho F, Caixe SH, Benedetia AC, Garcia J, de Paula Martins W, Del Ciampo LA. Evaluation of echocardiography as a marker of cardiovascular risk in obese children and adolescents. *Int J Clin Pediatr* 2014; 3:72–78.
- Petersen MC, Shulman GI. Mechanisms of insulin action and insulin resistance. *Physiol Rev* 2018; 98:2133–2223.
- Kahn SE. The relative contributions of insulin resistance and β -cell dysfunction to the pathophysiology of type 2 diabetes. *Diabetologia* 2003; 46:3–19.

- 30 Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, *et al.* A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med* 2005; 11:875–879.
- 31 Rao S, Lau A, So CH. Exploring diseases/traits and blood proteins causally related to expression of ACE2. The putative receptor of 2019-nCoV: A mendelian randomization analysis. *Diabetes Care* 2020; 43:1416–1426.
- 32 Finucane FM, Davenport C. Coronavirus and obesity: could insulin resistance mediate the severity of Covid-19 infection?. *Front Public Health* 2020; 8:184.
- 33 Bendor CD, Bardugo A, Pinhas-Hamiel O, Afek A, Twig G. Cardiovascular morbidity, diabetes and cancer risk among children and adolescents with severe obesity. *Cardiovasc Diabetol* 2020; 19:79.
- 34 Soy M, Keser G, Atagündüz P, Tabak F, Atagündüz I, Kayhan S. Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. *Clin Rheumatol* 2020; 39:2085–2094.
- 35 McKechnie JL, Blish CA. The innate immune system: fighting on the front lines or fanning the flames of COVID-19? *Cell Host Microbe* 2020; 27:863–869.
- 36 Kim JA, Montagnani M, Chandrasekran S, Quon MJ. Role of lipotoxicity in endothelial dysfunction. *Heart Fail Clin* 2012; 8:589–607.
- 37 Choi GJ, Kim HM, Kang H. The potential role of dyslipidemia in COVID-19 severity: an umbrella review of systematic reviews. *J Lipid Atheroscler* 2020; 9:435–448.
- 38 Zhang L, Liu Y. Potential interventions for novel coronavirus in China: a systematic review. *J Med Virol* 2020; 92:479–490.
- 39 Cigerli O, Parildar H, DogrukUnal A, Tarcin O, Kut A, Eroglu H, Guvener N. Vitamin deficiency and insulin resistance in nondiabetic obese patients. *Acta Endocrinol (Buchar)* 2016; 12:319–327.
- 40 Sadeghi K, Wessner B, Laggner U, Ploder M, Tamandl D, Friedl J, *et al.* Vitamin D3 down-regulates monocyte TLR expression and triggers hypo-responsiveness to pathogen-associated molecular patterns. *Eur J Immunol* 2006; 36:361–370.
- 41 Wojcik M, Janus D, KalickaKasperczyk A, Sztéfko K, Starzyk JB. The potential impact of the hypo-vitaminosis D on metabolic complications in obese adolescents – preliminary results. *Ann Agric Environ Med* 2017; 24:636–639.
- 42 Nieto-Torres JL, VerdiáBáguena C, Jimenez-Guardeño JM. Severe acute respiratory syndrome coronavirus E protein transports calcium ions and activates the NLRP3 inflammasome. *Virology* 2015; 485:330–339.
- 43 Yang C, Ma X, Wu J, Han J, Zheng Z, Duan H, *et al.* Low serum calcium and phosphorus and their clinical performance in detecting COVID-19 patients. *J Med Virol* 2020; 1–13.
- 44 Luigi DF, Maria FA, Patrizia RQ. Hypocalcemia is highly prevalent and predicts hospitalization in patients with COVID-19. *Endocrine* 2020; 68:475–478.
- 45 Huang Z, Liu Y, Qi G, Brand D, Zheng SG. Role of vitamin A in the immune system. *J Clin Med* 2018; 7:258.
- 46 Marreiro DN, Fisberg M, Cozzolino SM. Zinc nutritional status and its relationships with hyperinsulinemia in obese children and adolescents. *Biol Trace Elem Res* 2004; 100:137–149.
- 47 Nogueira-de-Almeida CA, Del Ciampo LA, Ferraz IS, Del Ciampo IRL, Contini AA, Ued FDV. COVID-19 and obesity in childhood and adolescence: a clinical review. *J Pediatr* 2020; 96:546–558.
- 48 Coutard B, Valle C, de Lamballerie X, Canard B, Seidah NG, Decroly E. The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade. *Antiviral Res* 2020; 176:104742.
- 49 Serseg T, Benarous K, Yousfi M. Hispidin, Lepidine E. Two natural compounds and folic acid as potential inhibitors of 2019-novel coronavirus main protease (2019-nCoV^{Mpro}), molecular docking and SAR study. *Curr Comput Aided Drug Des* 2020; 17:469–479.
- 50 Acosta-Elias J, Espinosa-Tanguma R. The folate concentration and/or folic acid metabolites in plasma as factor for COVID-19 infection. *Front Pharmacol* 2020; 11:1062.