Available online at www.scholarsresearchlibrary.com

Scholars Research Library

Der Pharmacia Lettre, 2016, 8 (9):151-160
(http://scholarsresearchlibrary.com/archive.html)

ISSN 0975-5071
USA CODEN: DPLEB4

Vitamin D status and insulin resistance in obese Egyptian children

Wafaa A. Kandeel[1], Nermin Salah[2], Moushira Zaki[1], Maha Amin[2], Hanaa H. Ahmed[3*], Ahmed S. Ismail[1], Ola Abdel Samie[4] and Hebha Elmalt[5]

[1]Biological Anthropology Department National Research Centre, Dokki, Giza, Egypt
[2]Pediatrics Department Cairo University, Cairo, Egypt
[3]Hormones Department National Research Centre, Dokki, Giza, Egypt
[4]Child Health Department National Research Centre, Dokki, Giza, Egypt
[5]Medical Biochemistry Department National Research Centre, Dokki, Giza, Egypt

---

ABSTRACT

This study aimed to assess vitamin D status in obese Egyptian children and its implication in the metabolic problems that are linked with obesity. Our results indicated that obese children had significantly lower serum levels of 25-hydroxyvitamin D than healthy subjects with 6% and 94% being vitamin D deficient and insufficient, respectively. There were significant negative correlations between vitamin D concentrations and waist circumference, hip circumference, fat % and fat mass. In the current study, hypovitaminosis D appeared to be common feature among obese children and vitamin D level was negatively correlated with obesity parameters. These data provided a clear evidence for the implication of obesity in the development of vitamin D downregulation in children. Interestingly, vitamin D status had no correlation with the metabolic risk factors in obese children.

Key words: Vitamin D, obesity, insulin resistance, metabolic risk factors, children

---

INTRODUCTION

Vitamin D is a fat soluble vitamin essential for calcium homeostasis enabling normal mineralization of bone [1]. During the last decade, it has been shown that vitamin D exhibits other biological actions including regulation of neuromuscular functions and glucose metabolism, immunomodulatory potential as well as endothelial and cardiovascular protective properties [2].Vitamin D deficiency and insufficiency dilemma concerns as much as 30-50% of the common population [3]. Many factors have been found to be included in the development of vitamin D deficiency. These factors include reduced skin synthesis, malabsorption, obesity, acquired and heritable disorders of vitamin D metabolism and responsiveness [4].

The sedentary life style usually exhibited by obese children, limited exposure to sunlight [5] and highly caloric food that might be low in mineral and vitamins[6,7] are considered as powerful risk factors for vitamin D downregulation. Moreover, bioavailability of vitamin D in obese children might be low as a result of its deposition in the fat tissue [8,9].

Several studies reported an association between low 25(OH) vitamin D concentrations and insulin resistance [10,11] and it was found an improvement in Beta-cell function after the management of vitamin D in animals [12] and humans [13]. In adults, low-serum 25(OH) D levels were correlated with glucose tolerance impairment, metabolic syndrome, and diabetes, regardless obesity [14].However, few studies are available in pediatric cases.

In addition, several studies reported that cardiovascular disease subjects had a higher tendency to vitamin D deficiency [defined as 25-hydroxyvitamin D (25(OH) D) levels <20 ng/mL] than those without [15,16].

Accordingly, this research study was planned to investigate the prevalence of vitamin D deficiency among Egyptian obese children and adolescents and to assess vitamin D status in relation to cardio-metabolic risk factors that may be present in this population.

MATERIALS AND METHODS

Study population

This study is a cross sectional case-control study undertaken at Diabetic Endocrine Metabolic Unit, Cairo University Hospital, between August 2010and April 2011consisted of 50 obese children and adolescents (cases) aged between 8 - 15 years(29males and 21 females) who were compared with 50 age and sex matching healthy non obese (control) children and adolescent (23 males and 27 females).Subjects with identified causes of obesity or identified factors that may affect vitamin D concentrations or on any medication that may alter vitamin D metabolism or with type 1 diabetes were excluded.

Ethical considerations

The study protocol was approved by the Ethical Committee Board of the National Research Centre, Egypt. An informed written consent was obtained from all participants.

Clinical examination

All patients and controls were subjected to a careful physical examination, blood pressure measurement. The data of the systolic and diastolic blood pressure were assessed according to blood pressure tables for children and adolescents of the fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents [17].

Anthropometric measurements

Anthropometric parameters included: weight (was measured using a calibrated digital scaleto the nearest 0.01 kg), height (was measured to the nearest 0.1 cm using a calibrated stadiometer) and body mass index (BMI) (was calculated as [weight (kg)/height 2(m)]).Obese children were defined as having BMI above the 95th percentile for age and sex based on established percentile curves for Egyptian children and adolescents[18].BMI and blood pressure Z scores were used because these variables are age and gender dependent in children. Waist and hip circumferences were measured and the readings were approximated to the nearest 0.1 cm [19]. Waist to hip ratio (WHR) was calculated by dividing waist circumference by hip circumference. In this study, body composition was measured using body composition analyzer (Computerized Holtain Body Composition Analyzer - Holtain's BCA, Holtain ltd., UK, Wales, Crosswell No.646512) displaying water content, fat-free mass, fat mass, fat % and basal metabolic rate (BMR). Puberty was assessed by rating breast development in girls [20] and genital, pubic and axillary development in boys [21].

Laboratory investigations

Regarding laboratory investigations, morning fasting blood samples were collected and serum 25-(OH)D was measured using enzyme-linked immunosorbent assay(serum 25 (OH)D concentration < 20 ng /ml was considered vitamin D deficiency and 21-29ng/ml was considered vitamin D insufficiency [22].Lipid profile was also measured including serum triglycerides, cholesterol, high density lipoprotein (HDL) by colorimetric method using Stanbio kit(USA) and low density lipoprotein(LDL) by kinetic method using Quimica Clinica S. A .kit(Spain) and compared with the normal values for age and sex: cholesterol (100-200mg/dl),TG(35-160mg/dl),LDL (≤130mg/dl),HDL(30-70mg/dl) [23].CRP was determined by immunoenzymometric assay. Serum glucose level was quantified using colorimetric method and insulin level was detected using immunoenzymometric assay. From the last two parameters, the following measurements were assessed:

- Insulin resistance by Homeostatic Model Assessment-Insulin Resistance (HOMA-IR) = [Fasting Insulin (µ U/ml) x Fasting Glucose (mg/dL)]/405
-ß cell function by Homeostatic Model Assessment- ß cell function (HOMA- ß) = (Fasting Insulin (µ U/ml) x 360) / (Fasting Glucose (mg/dL) - 63)
-Insulin sensitivity by Quantitative Insulin Sensitivity Check Index (QUICKI) =1 / (log (Fasting Insulin) + log (Fasting Glucose)).
Insulin resistance was defined as values of HOMA-IR ≥2.68 and QUICK1 ≤ 0.34.

Statistical analysis

The present data were tabulated and analyzed using the computer program SPSS (Statistical Package for Social Science) version 16.

RESULTS

Fig (1) represents sex distribution in cases and control. The results in Tables (1and 2) show the anthropometric and biochemical parameters of cases and control. Anthropometric measures show higher values in cases than control except for lean % which shows lower value in cases (Table 1). Biochemical items are significantly higher in cases than control except for HDL which shows significant lower value in cases than control. Meanwhile, LDL shows a higher insignificant value in cases than control (Table 2).

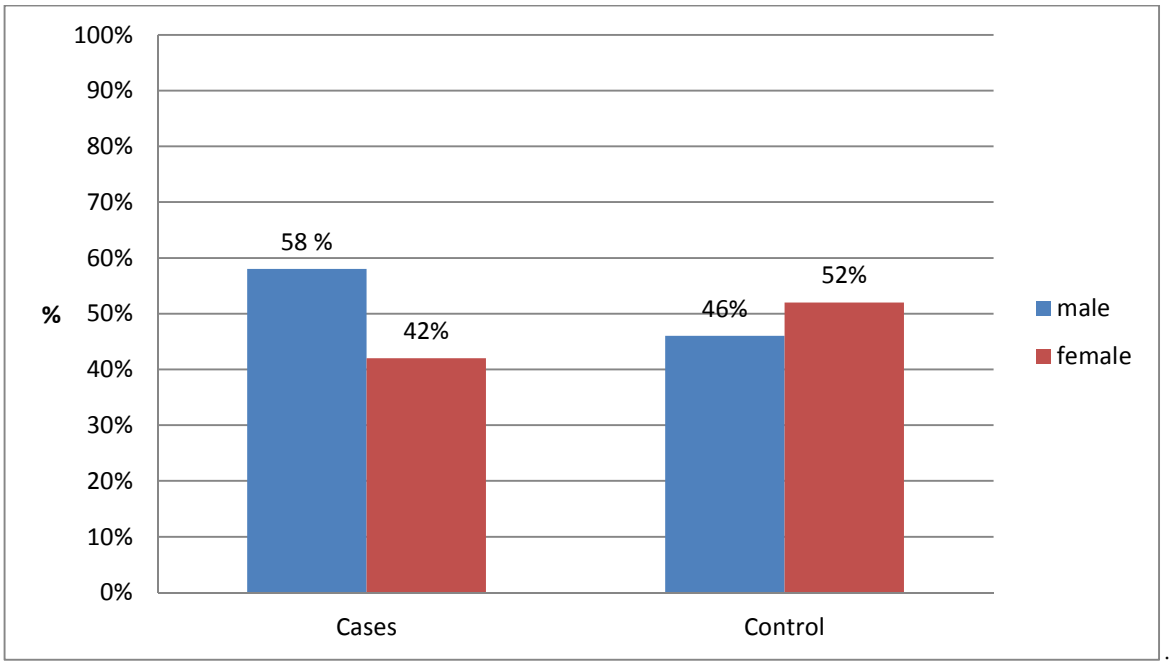

Fig. 1. Sex distribution in cases and control

Table1. Anthropometric and clinical characteristics of cases and control

	Cases	Control
	Mean ± SD	Mean ± SD
Age(Years)	10.71±2.21	10.43±2.5495
Weight(Kg)	59.45±14.58***	33.69±11.88
Height(Cm)	140.92±12.87	135.59±13.64
BMI (Kg/m^2)	29.43±3.45	17.68±2.75
Waist circumference(cm)	87.86±8.704	59.89±7.28
Hip circumference(cm)	101.90±10.256	73.30±9.78
Waist to Hip ratio	0.86±0.05	0.81±0.05
Fat %	40.98±8.13	17.62±5.29
Fat mass	24.49±8.36	6.19±3.57
Lean %	59.01±8.17	82.38±5.29
Lean mass	34.80±9.55	27.578±8.82872
Systolic BP(mmHg)	111.70±13.91	99.40±10.67
Diastolic BP(mmHg)	72.30±12.78	60.40±3.89

****P <0.001*

The findings in Table (3) show correlation between 25(OH) D and clinical, anthropometric and biochemical variables among obese subjects. Results show significant negative correlations between 25 (OH) D and waist circumference, hip circumference, fat % and fat mass, while significant positive correlation has been estimated between 25 (OH) D and lean%. No correlations have been found between 25 (OH) D and BMI z score, systolic BP, diastolic BP, CRP, insulin, glucose, HDL, HOMA-IR, HOMA-B and QUICKI. Figs (3,4,5,6,7) represent the correlations between 25 (OH) D and anthropometric and metabolic parameters.

Table 2. Biochemical characteristics of cases and control

	Cases	Control
	Mean± SD	Mean ±SD
25 (OH) D(ng/ml)	23.35±2.26***	40.81±10.97
CRP(mg/L)	2.63±0.18***	0.74±0.11
Cholesterol(mg/dL)	174.71±9.81***	163.69±9.36
HDL(mg/dL)	48.37±5.56***	53.73±6.42
LDL(mg/dL)	102.30±13.47	97.28±13.36
TG(mg/dL)	98.81±12.22***	84.43±7.54
Fasting Glucose(mg/dL)	95.18±9.82***	88.27±9.63
Fasting Insulin(µIU/mL)	26.32±6.00***	9.89±3.07
HOMA-IR	5.70±1.284***	2.15±0.73
HOMA-β	337.51±176.49***	168.62±101.68
QUICKI	0.29±0.01***	0.34±0.02

*HDL = high density lipoprotein, LDL =low density lipoprotein, TG= triglyceride, CRP = C- reactive protein, BP=blood pressure, HOMA-IR (Homeostasis Model Assessment- Insulin Resistance) = [fasting insulin ((µ U/ml) x fasting glucose (mg/dL)]/405, HOMA-β (Homeostasis Model Assessment-β) = (fasting insulin (µ U/ml) x 360) / (fasting glucose (mg/dL) - 63), QUICKI (Quantitative insulin sensitivity check index) = 1/ [log (fasting insulin (µ U/ml)) + log (fasting glucose (mg/dl)]. ***P <0.001*

Fig (2) illustrates the mean value of 25 (OH) D levels in obese subjects (cases) and control. The data reveal that there is significant reduction in serum 25 (OH) levels in obese subjects versus the control ones

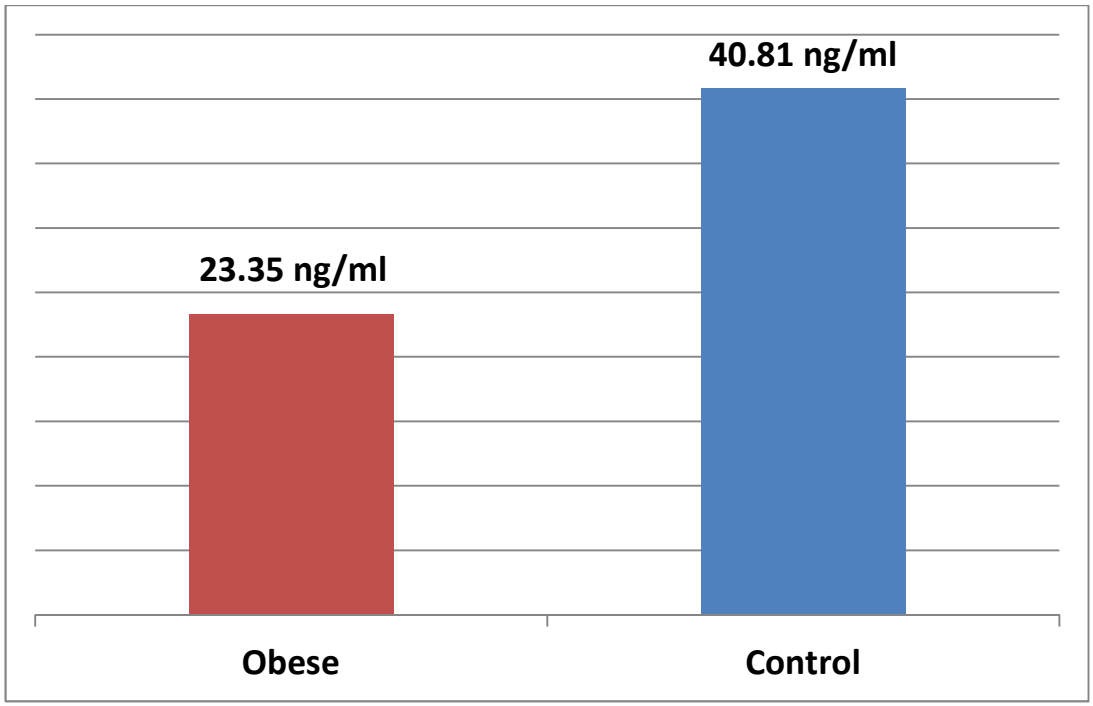

Fig. 2. Comparison between obese subjects (cases) and control regarding 25 (OH) D levels

Table 3. Correlation between 25(OH) D and the measured variables among obese subjects

	25(OH)D	
	R	p
Age	-0.141	0.330
BMI	-0.246	0.086
BMI z score	-0.070	0.630
Systolic BP	-0.006	0.968
Diastolic BP	-0.061	0.675
Waist Circumference(Cm)	**-0.299**	**0.035**
Hip Circumference (Cm)	**-0.317**	**0.025**
Waist: Hip ratio	0.002	0.992
Fat%	**-0.374**	**0.007**
Lean %	**0.373**	**0.008**
Fat mass	**-0.388**	**0.005**
Insulin(μIU/mL)	-0.175	0.225
CRP(mg/L)	0.070	0.627
Cholesterol(mg/dL)	0.180	0.212
Glucose(mg/dL)	-0.068	0.640
TG(mg/dL)	0.281	0.09
HDL(mg/dL)	0.172	0.233
LDL(mg/dL)	0.129	0.372
HOMA-IR	-0.207	0.149
HOMA-β	0.079	0.585
QUICKI	0.179	0.214

*HDL = highdensity lipoprotein, LDL =low density lipoprotein, TG= triglyceride, CRP = C- reactive protein, BP=blood pressure, HOMA-IR (Homeostasis Model Assessment- Insulin Resistance) = [fasting insulin ((μ U/ml) x fasting glucose (mg/dL)]/405, HOMA-β (Homeostasis Model Assessment-β) = (fasting insulin (μ U/ml) x 360) / (fasting glucose(mg/dL) - 63), QUICKI (Quantitative insulin sensitivity check index) = 1/ [log (fasting insulin (μ U/ml)) + log (fasting glucose (mg/dL)]. ***P <0.001*

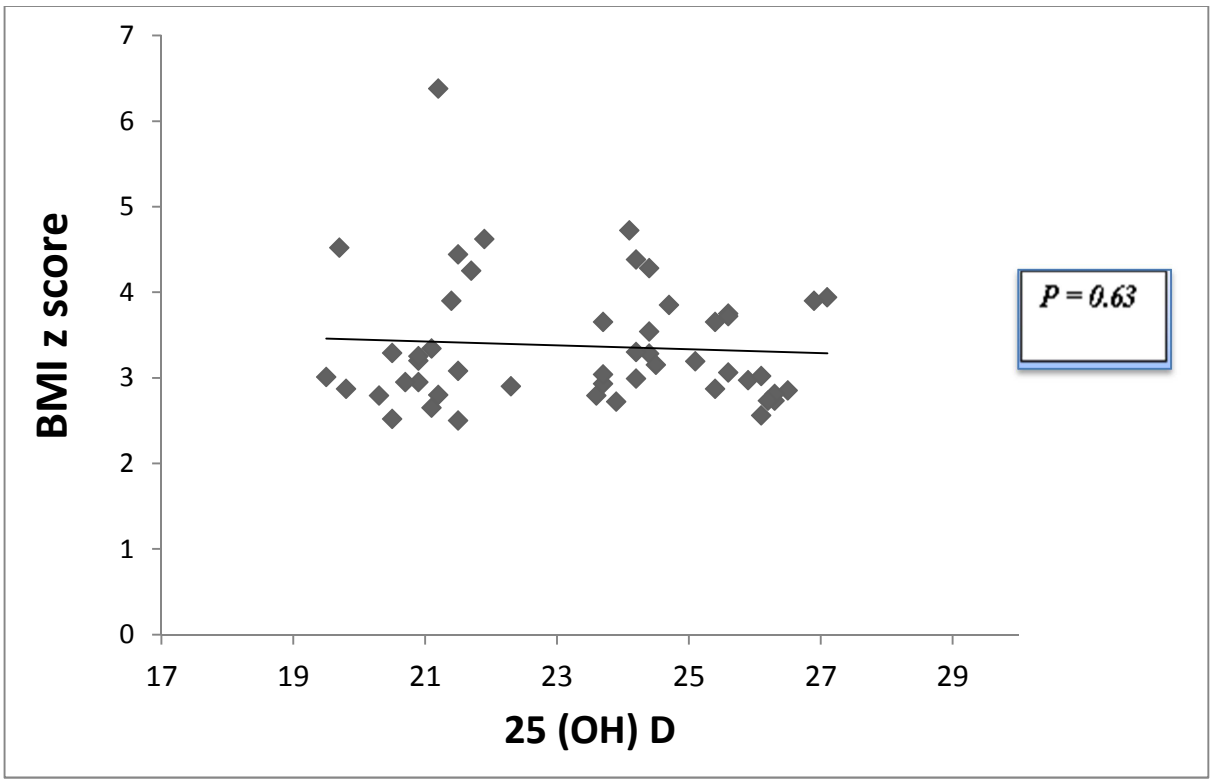

Fig. 3. Correlation between BMI z score and 25 (OH) D

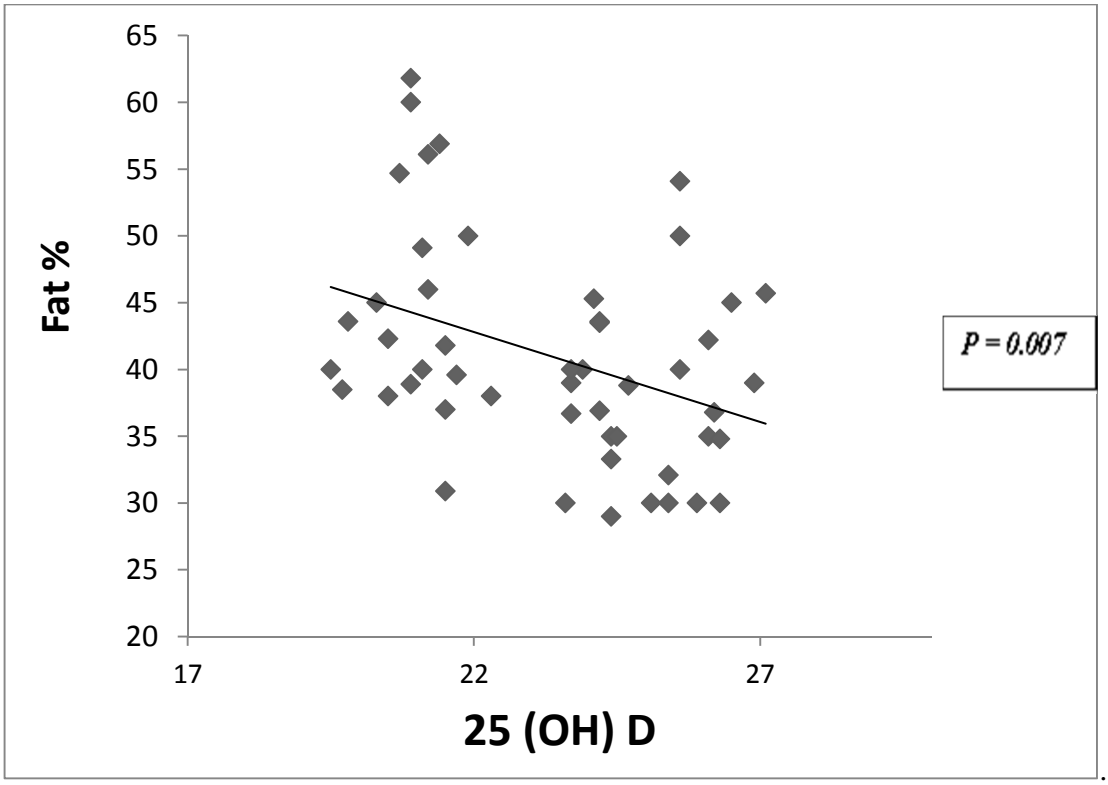

Fig. 4. Correlation between Fat % and 25 (OH) D

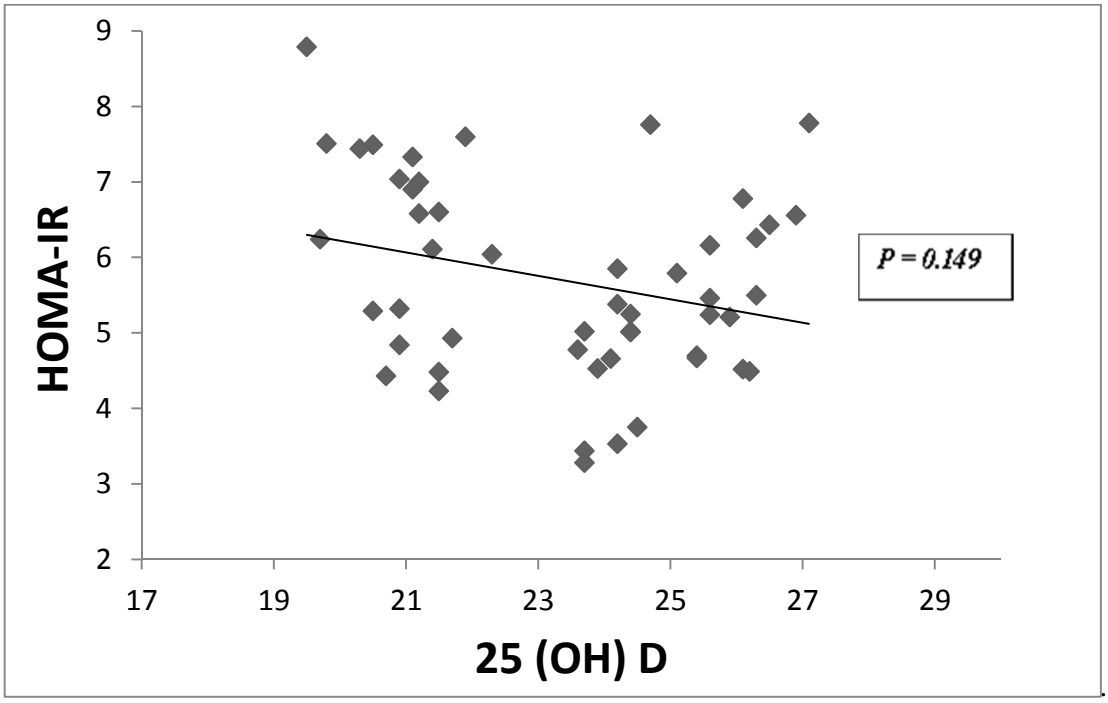

Fig. 5. Correlation between HOMA- IR and 25 (OH) D

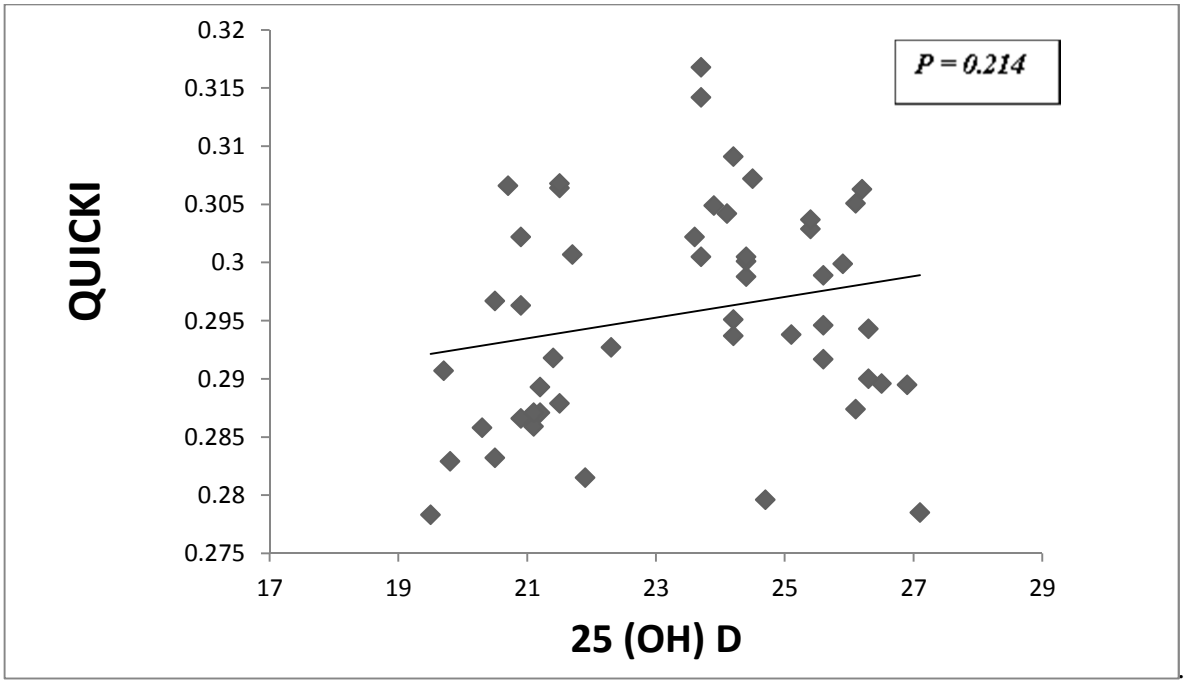

Fig. 6. Correlation between QUICKI and 25 (OH) D

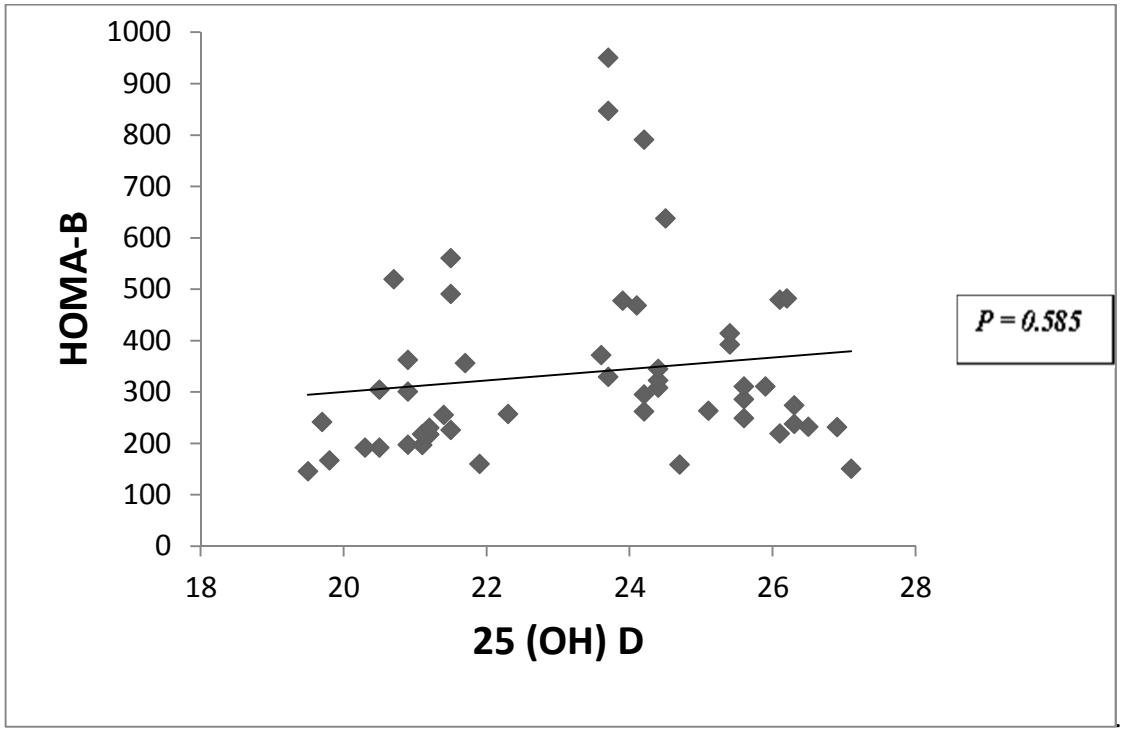

Fig. 7. Correlation between HOMA- β and 25 (OH) D

DISCUSSION

A growing body of evidence suggested an association between obesity and hypovitaminosis D in children and adolescents [5] . In the current study, hypovitaminosis D was recorded in 100% of obese subjects; 94% had vitamin D insufficiency and 6% had vitamin D deficiency, while in control subjects, only 10% had vitamin D insufficiency. The insufficiency level of vitamin D (10%) in the control group is in agreement with the emerging studies showing that there was a state of hypovitaminosis D among healthy adolescents [24].This means that even among apparently healthy children, vitamin D deficiency may be present regardless of the latitude, sunny area and other causes other than obesity to blame [4].

The 100% hypovitaminosis D among obese subjects in the present work is accordant with other studies conducted in different countries[25],where among a group of 217 obese children (7-18 years) in New York-USA, 55.2% had vitamin D insufficiency while severely low vitamin D levels were reported in 21.6%. Furthermore, another study conducted in Netherlands by Reyman et al.[26] revealed that 25 (OH) D level, was significantly lower in a group of 64 obese children compared to 32 healthy ones. This makes obesity a risk factor in term of hypovitaminosis D in children and adolescent.

Insignificant difference existed in our study between both genders which is consistent with studies in Western countries while those conducted in Middle East demonstrated a significant deficiency in the girls due to veiling [27,28]. Our finding might be attributed to that a large number of the females under study were below the age of veiling.

The current work recorded a significant inverse correlation between 25(OH) D and fat % and fat mass within the obese group. This is similar to the results of Alemzadeh et al.[29] who found that 25(OH) D was inversely correlated with weight, BMI, fat % and fat mass in children with obesity. A study conducted by Garanty-Bogacka et al.[30]cited the same observation in a group consisted of 64 obese adolescents.

Central obesity has been identified to be associated with the cardiometabolic risks[31].In the current study, a significant inverse correlation between 25(OH) D and waist circumference (surrogate of central adiposity) was observed which is in conformity with the results of other studies on adult [32] and children[30].This result is consistent with the hypothesis that increased adipose tissue decreases vitamin D bioavailability by sequestration in body fat [33]. When serum concentration of 25(OH)D was further categorized into quartiles, there was an association of vitamin D with fat % and fat mass indicating the more the link between vitamin D insufficiency and adiposity.

Our current study also investigated the correlation between 25 (OH) D with both age and puberty in the whole recruited subjects. MacLaughlin and Holick[34] stated that there was an inverse correlation between the concentrations of provitamin D3 in the epidermis and age. This was attributed to the reduced capacity of human skin to produce vitamin D by aging. Also, during puberty the conversion of 25(OH) D to 1, 25 dihydroxyvitamin D increases to meet the demands of growth with a concomitant decrease in 25(OH) D stores. This explanation is documented by some other studies [30, 35]which demonstrated a significant inverse correlation between 25(OH) D and puberty. In the present work no correlation was detected between 25 (OH) D and either age or puberty and this may be due to the limited number of subjects in our study group and the refusal of some subjects to be submitted for pubertal assessment.

Considering the influence of vitamin D on glucose homeostasis, many mechanisms have been suggested.Vitamin D stimulates insulin receptor expression and promotes insulin responsiveness for glucose transport. Also, it regulates extracellular and intracellular calcium which is insulin-mediated intracellular processes [36]. Moreover, it modulates the immune system [37] which is associated with insulin resistance [38].

In the present work there was no correlation between 25 (OH) D and insulin resistance, insulin sensitivity and β cell function. These results are in disagreement with previous studies conducted by Roth et al[39] on a sample of German children and by Olson et al[40]on a sample of American children. These studies demonstrated that hypovitaminosis D is a risk factor for type 2 diabetes and metabolic syndrome. Meanwhile, our findings are accordant with the studies conducted by Ashraf et al.[41]Al-Sultan et al.[42] and Creo et al.[43]. These results could be explained by the fact that in the present study a single blood sample was used to estimate fasting blood sugar and fasting insulin and to calculate insulin resistance instead of the gold standard for the estimation of insulin sensitivity which is the use of the euglycemic clamp. Moreover, indices of insulin sensitivity/resistance derived from fasting values of insulin and glucose accurately reflect insulin sensitivity of the liver as opposed to whole-body insulin sensitivity [44].

Regarding the correlation of 25(OH) D with the blood pressure, Zittermann et al[45] reported that vitamin D may regulate BP through different mechanisms such as suppression of vascular proliferation, inhibition of vascular calcification and regulation of pro-inflammatory cytokines. The current results showed no correlation between 25(OH) D and both systolic and diastolic blood pressure. The lack of such association between vitamin D status and blood pressure in our study agrees with the results of the study conducted on adult by Snijder et al[46]. The explanation of this finding has been set as 25(OH) D deficiency only affects blood pressure at lower levels, where only 10% of patients were vitamin D deficient, the same situation as in the present study where only 6% were vitamin D deficient. The same results were also reported in the study conducted by Olson et al[40].

Vitamin D insufficiency has been associated with elevated inflammation markers [47].The location of vitamin D receptors on inflammatory cells is reason to believe that vitamin D also mediates the immune system response and inflammatory process[37]. C-reactive protein (CRP) is considered as a good marker of inflammation [48]. In contrast to Timms et al. [49],who found an inverse correlation between vitamin D and CRP, our study didn't find such association. Meanwhile,our results come in line with those of Michos et al[50] and Ganji et al [51].This might be attributed to small sample size and limited proportion of vitamin D deficient subjects.

Although the biological mechanism linking vitamin D deficiency to the risk of dyslipidemia is not fully understood [52], some proposed possible mechanisms have been hypothesized. One mechanism involves the activation of circulating vitamin D precursor (25(OH) D) into active vitamin D metabolite by 1-α hydroxylase enzyme present in cardiac myocytes, endothelial, and smooth vascular muscle cells which acts on vitamin D receptors present on these cells leading to increasing lipoprotein lipase enzyme levels and subsequently decreasing triglycerides level[53].Another mechanism is through the influence of vitamin D on peripheral insulin resistance [54].

Kumar et al[55] found an inverse correlation between 25(OH) D and LDL and total cholesterol, however the present study didn't find any association between markers of lipid profile and 25(OH) D which agrees with the results of Ashraf et al[41]. This might be attributed to limited number of cases and limited proportion vitamin D deficient subjects within the study sample.

In conclusion, obese children showed hypovitaminosis D and no associations were observed between 25 (OH) D concentrations and abnormal metabolic variables in obese Egyptian children.

REFERENCES

[1] A Cranney; T Horsley; S O'Donnell ; H Weiler; L Puil; D Ooi; S Atkinson; L Ward; D Moher; D Hanley; M Fang; F Yazdi; C Garritty; M Sampson; N Barrowman; A Tsertsvadze; V Mamaladze. *Evid Rep Technol Assess*, **2007**,158,1-235.
[2] J Rojas-Rivera; C De La Piedra; A Ramos; A Ortiz ; J Egido . *Nephrol Dial Transplant*, **2010**, 25, 2850-65.
[3] MF Holick; TC Chen. *Am J Clin Nutr*, **2008**, 87,10805-65.
[4] MF Holick . *N Engl J Med*, **2007**,357, 266–81.
[5] K Rajakumar; JD Fernstrom; MF Holick; JE Janosky; SLGreenspan. *Obesity*, **2008**, 16, 90-5.
[6] ML Bradlee; MR Singer; MM Qureshi; LL Moore. *Public Health Nutr*, **2010**, 13,797-805.
[7] G Muscogiuri ; GP Sorice; A Prioletta; C Policola ; S Della Casa ; A Pontecorvi ; A Giaccari . *Obesity*, **2010**,18,1906-10.
[8] G Targher; L Bertolini ; L Scala ; M Cigolini; L Zenari ; G Falezza; G Arcaro. *Nutr Metab Cardiovasc Dis*, **2007**, 17,517-24.
[9] CM Lenders ; HA Feldman; E Von Scheven; A Merewood ;C Sweeney; DM Wilson; PD Lee; SH Abrams ; SE Gitelman; MS Wertz; WJ Klish; GA Taylor; TC Chen; MF Holick; Elizabeth Glaser Pediatric Research Network Obesity Study Group. *Am J Clin Nutr*, **2009**,90,459-67.
[10] Z Maghbooli ; A Hossein-Nezhad ; F Karimi ;AR Shafaei ; B Larijani. *Diabetes Metab Res Rev*, **2008**, 24, 27-32.
[11] G Zhao ; ES Ford; C Li. *Diabetes Care*, **2010**, 33,344-7.
[12] S Kadowaki; AW Norman. *J Clin Invest*, **1984**, 73,759-66.
[13] JA Alvarez; A Ashraf . *Int J Endocrinol* , **2010**, 2010, 351385.
[14] E Hyppönen; BJ Boucher; DJ Berry; C Power. *Diabetes*, **2008**, 57, 298-305.
[15] JP Reis; D von Muhlen; ER Miller; M Appel ; MJ Appel. *Pediatrics*, **2009**, 124, e371–e9.
[16] J Kendrick; G Targher ; G Smits; M Chonchol. *Atherosclerosis*, **2009**, 205,255-60.
[17] National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. *Pediatrics*, **2004**, 114, 555–76.
[18] I. Ghalli, N. Salah, F. Hussien et al., "Egyptian growth curves for infants, children and adolescents," In Crecere nel Mondo, A. Satorio, J. M. H. Buckler, and N. Marazzi, Eds., **2008**, Ferring Publisher, Milan, Italy.
[19] JS Weiner; JA Lourie. Comp. Human Biology: A Guide to Field Methods. 9th ed., Blackwell Scientific Publ, Oxford, England,**1969**; pp. 1-71.
[20] WA Marshall; JM Tanner. *Arch Dis Child*, **1969**, 44,291-303.
[21] WA Marshall ; JM Tanner. *Arch Dis Child*, **1970**, 45,13-23.
[22] MF Holick; NC Binkley; HA Bischoff-Ferrari; CM Gordon; DA Hanley; RP Heaney; MH Murad; CM Weaver; Endocrine Society. *Clin Endocrinol Metab*, **2011**, 96, 1911-30.
[23] The Lipid Research Clinics Program Prevalence Study.*Circulation*, **1980**, 62,IV1-136.
[24] FM Çizmecioğlu; N Etiler; U Görmüş ; O Hamzaoğlu; S Hatun. *J Clin Res Ped Endo*, **2008**, 1, 89-96.

[25] M Smotkin–Tangorra; R Purushothaman; A Gupta; G Nejati ; H Anhalt; S Ten. *Pediatr Endocrinol Metab*, **2007**,20, 817-23.
[26] M Reyman; AA Verrijn Stuart; M vanSummeren; M Rakhshandehroo; R Nuboer; FK de Boer ; HJ van den Ham; E Kalkhoven; B Prakken; HS Schipper . *Int J Obes*, **2014**, 38, 46-52.
[27] CM Gordon; KC DePeter ; HA Feldman ; E Grace ; SJ Emans. *Arch Pediatr Adolesc Med*, **2004**, 158, 531-7.
[28] S Hatun; O Islam; F Cizmecioglu ; B Kara; K Babaoglu ; F Berk ; AS Gökalp. *J Nutr*, **2005**, 135, 218-22.
[29] R Alemzadeh ; J Kichler ; G Babar ; M Calhoun. *Metabolism*, **2008**, 57, 183–91.
[30] B Garanty-Bogacka ; M Syrenicz ; J Goral ; B Krupa ; J Syrenicz ; M Walczak; A Syrenicz . *Endokrynol Pol*, **2011**, 62, 506-11.
[31] MA Abolfotouh; LA Soliman ; E Mansour; M Farghaly ; AA El-Dawaiaty. *East Mediterr Health J*, **2008**, 14,57-68.
[32] MH Gannagé-Yared ; R Chedid; S Khalife; E Azzi; F Zoghbi ; G Halaby . *Eur J Endocrinol*, **2009**, 160, 965-71.
[33] J Wortsman ; LY Matsuoka ; TC Chen ; Z Lu ; MF Holick . *Am J Clin Nutr*, **2000**, 72, 690-3.
[34] J MacLaughlin ; MF Holick. *J Clin Invest*, **1985**, 76, 1536-8.
[35] M Buyukinan ; S Ozen; S Kokkun ; EU Saz. *J Pediatr Endocrinol Metab* , **2012**, 25,83-7.
[36] AG Pittas ; J Lau ; FB Hu ; B Dawson-Hughes. *J Clin Endocrinol Metab*, **2007**, 92, 2017-29.
[37] DD Bikle. *J Clin Endocrinol Metab*, **2009**, 94, 26-34.
[38] SE Shoelson ; L Herrero ; A Naaz. *Gastroenterology*, **2007**, 132, 2169-80.
[39] CL Roth ; C Elfers ; M Kratz ; AN Hoofnagle. *J Obes*, **2011**, 2011, 495101.
[40] ML Olson ; NM Maalouf ; JD Oden ; PC White ; MR Hutchison. *J Clin Endocrinol Metab*, **2012**, 97, 279-85.
[41] A Ashraf ; J Alvarez ; K Saenz ; B Gower ; K McCormick; F Franklin. *J Clin Endocrinol Metab*, **2009**, 94, 3200–06.
[42] AI Al-Sultan ; TT Amin ; MA Abou-Seif ; MR Al Naboli. *Eur Rev Med Pharmacol Sci*, **2011**, 15, 135-47.
[43] AL Creo; JS Rosen; AJ Ariza; KM Hidaka; HJ Binns. *J Pediatr Endocrinol Metab*, **2013**, 26, 97-104.
[44] RP Hoffma. *Pediatr Diabetes*, **2008**, 9, 57-61.
[45] A Zittermann ; SS Schleithoff ; R Koerfer. *Br J Nutr*, **2005**, 94, 483-92.
[46] MB Snijder , P Lips ; JC Seidell ; M Visser ; DJ Deeg ; JM Dekker ; RM van Dam. *J Intern Med*, **2007**, 261, 558-65.
[47] KL Jablonski ; M Chonchol ; GL Pierce ; AE Walker ; DR Seals. *Hypertension*, **2011**, 57, 63-9.
[48] AC Oliveira ; AM Oliveira; LF Adan ; NF Oliveira ; AM Silva; AM Ladeia. *Obesity*, **2008**, 16, 1094-8.
[49] PM Timms; N Mannan ; GA Hitman ; K Noonan ; PG Mills; D Syndercombe-Court ; . E Aganna; CP Price ; BJ Boucher . *QJM*, **2002**, 95, 787-96.
[50] ED Michos ; EA Streeten ; KA Ryan ; E Rampersaud ; PA Peyser ; LF Bielak ; AR Shuldiner; BD Mitchell; W Post . *Calcif Tissue Int*, **2009**, 84, 195-202.
[51] V Ganji ; X Zhang ; N Shaikh ; V Tangpricha. *Am J Clin Nutr* , **2011**, 94, 225-33.
[52] T Johnson ; G Avery ; L Byham-Gray. *Topics in Clinical Nutrition*, **2009**, 24, 47-54.
[53] L Rejnmark ; P Vestergaard; L Heickendorff ; L Mosekilde. *Int J Endocrinol*, **2010**, 2010, 957174.
[54] S Reddy Vanga; M Good ; PA Howard ; JL Vacek . *Am J Cardiol*, **2010**, 106, 798-805.
[55] J Kumar; P Muntner; FJ Kaskel ; SM Hailpern ; ML Melamed. *Pediatrics* , **2009**, 124, e362-e70.