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RESEARCH ARTICLE

Vitamin A and Obesity Associated Inflammation in Egyptian Obese Patients

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Abstract

Obesity is a multisystem condition associated with an elevated risk of type II diabetes, coronary heart disease, and cancer**.** Obesity is also associated with a state of chronic low grade inflammation as well as micronutrient deficiencies, as vitamin A deficiency. We thus aimed to investigate the correlation between the concentration of vitamin A, INF-γ, as a marker of obesity associated inflammation, and the markers of high risk obesity in obese Egyptian patients. Serum vitamin A and serum IFN- γ were assessed in 32 obese individuals, as well as in 32 age and sex matched apparently healthy non obese individuals. We subdivided the obese patients into two groups: Group I: included 17 obese patients, with their BMI ranging from 39 to 60.8 kg/m2, and group II: which included 15 patients, of high risk obesity. Serum vitamin A was significantly decreased in cases in comparison to control group (P= 0.004), with the highest mean in the control group and the lowest mean in group II of cases, while serum IFN-γ was significantly increased in obese cases in comparison to controls (P<0.001), with the lowest mean in the control group and the highest mean in group II of cases. There was also a high statistically significant inverse correlation (p=0.001) between vitamin A, IFN-γ, BMI and WT. ***Conclusion:*** This study showed significant inverse correlation between the serum concentration of vitamin A and both BMI and IFN-γ levels suggesting that vitamin A deficiency increases the risk of chronic inflammation associated with obesity and fat deposition .

Introduction

Obesity is the most prevalent global nutritional disorder, with alarming levels in Middle East and North Africa [1]. Obesity is a multisystem condition associated with chronic low grade inflammation and increased circulating levels of several inflammatory markers as C-reactive protein (CRP), serum amyloid A, leptin, tumor necrosis factor α (TNF-α), and interleukin-6 (IL-6). The state of low-grade inflammation in obesity suggests a dominant effect of the pro-inflammatory cytokines on whole body metabolism.

Obesity is also known to be associated with increased risks of many systemic diseases as type II diabetes mellitus, hypertension, asthma, coronary heart diseases, and non-alcoholic steatohepatitis (NASH) together with decrease in overall life expectancy [2],[3]**.** On average, it was assumed that obesity reduces life expectancy by about six to seven years [4]**.** The association between increased circulating levels of inflammatory mediators and the prevalence of metabolic complications in obese individuals, suggests that adipose tissue-derived cytokines may have a potential role in the pathogenesis of these metabolic disorders [5]. Several studies reported that IFN-γ play a key role in obesity associated inflammation, probably through the up-regulation of inflammatory genes expression in adipocytes [6].

Recent studies reported that obesity is also associated with micronutrient deficiencies as vitamin A deficiency. Vitamin A was reported to promote an anti-inflammatory environment and adequate Th2:Th1 ratios [7].

The framework about the concentration of vitamin A and its correlation to inflammatory cytokines and high risk markers of obesity now developed from studies in mice and rat models and data from human studies are scarce [8]. Thus, we aim to investigate the correlation between the concentration of vitamin A and INF-γ, on one side and the markers of high risk obesity on the other side in these patients.

Materials and Methods:

This study was conducted on 32 Egyptian obese individuals attending Ain Shams university hospital. The groups included 5 males and 27 females. Their ages ranged from 19 to 65 years and their BMI > 30 kg/m2. The patients were subdivided into two groups: **Group I:** which included 17 obese patients (3 males, 14 females). Their ages ranged from 19 to 65 years. Their BMI ranged from 39 to 60.8 kg/m2, and **Group II:** which included 15 patients (2 males, 13 females) of high risk obesity, in whom the metabolic syndrome was defined in accordance with the American Heart Association/National Heart, Lung and Blood Institute criteria, including a modification in the waist circumference (WC) value according to the World Health Organization– Asian Pacific region criteria for abdominal obesity. This entity was defined if three or more of the criteria were present, as follows: (1) WC ≥ 90 cm for men and ≥ 80 cm for women, (2) Fasting TG ≥ 1.69 mmol/l (150 mg/dl) or those using antihyperlipidemic medication, (3) high-density lipoprotein-cholesterol < 1.03 mmol/l (40 mg/dl) for men and < 1.29 mmol/l (50mg/dl) for women or those using antihyperlipidemic medication, (4) BP ≥ 130/85 mm Hg or those on antihypertensive medication, and (5) fasting plasma glucose ≥ 5.6 mmol l/1(101mg/dl). The ages of patients in this group ranged from 35 to 58 years. BMI ranged from 41.6 to 67.5 kg/m^2. Patients were compared to a control group (designed as **group III**) comprising 32 non-obese apparently healthy individuals of matched age and sex chosen from our friends and neighbors. The group included (4 males and 28 females). Their ages ranged from 20 to 57 years and their BMI ranged from 21.3 to 27 kg/m^2.

All individuals in the study were subjected to the following:

1) Full history taking laying stress on: diet habits, drug intake and family history of obesity.
2) Anthropometric measurement which included: weight in kilograms, height in centimeters, and body mass index (kg/m2), calculated by the formula: BMI= weight (in kg) / height (in $meter^2$).
3) Clinical examination including blood pressure monitoring.
4) Laboratory investigations which included:
   a. Fasting blood glucose level (FBS) and lipid profile (Cholesterol, HDL, LDL & TG).
   b. Quantitative assay of serum levels of IFN-γ and vitamin A using commercially available ELISA kits, Assaypro Human IFN-γ, USA and Gscience Human Vitamin A (VA), Glory Science, USA respectively, according to the manufacturers' instructions.

Informed consents were obtained from all individuals participating in this study. The study was conducted in accordance with the stipulations of the local ethical and scientific committees of Ain Shams University and the procedures respected the ethical standards in Helsinki declaration of 1964.

Statistical Analysis

Data were analysed using SPSS (version 20) statistical software package under Windows 7 operating system for IBM compatible PC. Student's t-test and Chi-Square test (X^2) were used for comparison of quantitative and qualitative data respectively, while ANOVA test and Mann–Whitney U test were used for comparing groups. A probability < 0.05 was statistically significant, while p< 0.001 was statistically highly significant. Receiver operating characteristic (ROC) curves were constructed and the areas under the ROC curves (AUC) were determined.

Results

Comparitive statistics between cases (Group I & II) and controls (Group III) as regards anthropometric measures showed a highly significant statistical difference (table 1). Moreover, comparison between group I, II and III as regards anthropometric measures individually showed high significant statistical difference between the 3 groups with the highest means in group II Table(2). Serum cholesterol, LDL and FBS showed significant statistical difference between the three groups with the highest means in group II table, while SerumTG and Serum HDL showed no significant difference between the 3 groups (3).

Serum vitamin A showed significant statistical difference between controls and cases (P= 0.004) with higher mean in controls, while serum IFN-γ showed highly significant statistical difference between cases and controls (P <

0.001) with higher mean in cases (table 1). Further statistical analysis for serum vitamin A and IFN-γ among 3 groups showed significant statistical difference between the three groups (with the lowest mean of vitamin A in group II of the cases and the highest mean in group III (controls), and with the lowest mean of IFN-γ in group III (controls) and the highest mean in group II of the cases (table 3). Vitamin A shows no significant statistical difference between group I and group II of cases, while IFN-γ shows a significant statistical difference between group I and group II of cases.

Using correlation studies among the 3 groups, vitamin A showed no statistical significant correlation with TG (r= -0.193, p=0.126), HDL (r= -0.043, p=0.734), LDL (r= -0.189, p=0.134), cholesterol (r= -0.233, p=0.064), or FBS (r= -0.156, p=0.218), while IFN-γ was correlated significantly and directly to FBS (r= 0.574, p< 0.001), cholesterol (r= 0.493, p< 0.001), LDL (r= 0.446, p< 0.001), TG (r= 0.331, p= 0.008), weight (r= 0.735, p=<0.001), BMI (r= 0.743, p< 0.001), WC (r= 0.707, p <0.001), and WT/HIP ratio (r= 0.749, p <0.001). On the other hand , vit A showed significant inverse correlation with weight (r= -0.387, p=0.002), BMI (r= -0.425, p =<0.001), WC (r= -0.347, p=0.005) and WT/HIP ratio (r= -0.317, p=0.011). Correlation of vitamin A to IFN-γ showed a high statistically significant inverse correlation (p= 0.001) (figure 1).

Using Receiver operating characteristic (ROC) curve analysis for controls and cases, it was found that, when the cut-off value for vitamin A was set at 155nmol/L, clinical sensitivity was 81.3% and specificity was 64.7% (AUC was 0.688, 95% CI 0.522-0.855, p=0.031) (figure 2), while when the cut-off value for IFN-γ was set at 1.8 ng/dl, clinical sensitivity was 94.1% and specificity was 90.6%, (AUC was 0.91, 95% CI 0.79-1.00, p< 0.001) (figure 3).

Discussion:

Obesity, with increased BMI above 30, is reported to be associated with increased risks of coronary heart diseases, type II diabetes mellitus, osteoarthritis, as well as certain types of cancers [9]. However, these risks vary markedly among different individuals. Obesity is indeed considered one of the most progressive worldwide economic and social burdens, as the earlier acquisition of obesity and its co-associated morbid conditions results in a prolonged and enhanced threat to the economic development particularly that of developing countries, as Egypt, which are yet not prepared to manage such chronic medical conditions [10].

Obesity is reported to be associated with low-grade systemic inflammation and with micronutrient deficiencies. Many of the deleterious consequences of obesity are attributed to the ability of obesity to induce a state of a low-grade chronic inflammation. Obese individuals, compared to normal individuals, were found to have lower vitamin A levels, which in turn has great impacts on the immune response [7]. Moreover, previous studies have shown that a number of minerals and vitamins including vitamin A, can improve mitochondrial function, promote lipolysis, and increase energy consumption [11]. Thus, understanding the impact of vitamin A deficiency on the immune system in obese populations will indeed provide new insights into the treatment of the obesity associated chronic inflammation processes and thus the control of obesity.

In accordance with other previous studies [12],[13], vitamin A serum levels in this study showed significant statistical difference between the controls & both patients groups (group I & group II), meanwhile, no significant statistical difference between the 2 groups of obese patients as regards vitamin A levels could be found. In addition, vitamin A levels in the current study showed a significant inverse correlation with WT and BMI. This enforces the results of several animal models that point to the relationship between vitamin A metabolism and adiposity and reported that vitamin A supplementation led to a significant weight loss in obese compared with non-obese mice [14]. Likewise, Jeyakumar and Vajreswari [15], observed that vit A enriched diet significantly improved lipids metabolism and development of obesity in both young and adults obese rats [15].

It is evident now that adipose tissue has a key role in immune modulation through the secretion of several adipokines and cytokines that act as mediators of inflammation and are involved in the development of many obesity associated complications [16]. IFN-γ appears to be a key regulator of the adipose tissue macrophages (ATM). By polarizing and maintaining a M1-phenotype in ATMs, IFN-γ can participates in an obesity-associated inflammatory loop [16]. In this study, IFN-γ levels were found to be significantly higher in the two obese patients groups compared to the control group, and these IFN-γ levels were correlated significantly and directly to the patients' weight and BMI. This comes in accordance with other studies [17], who showed that elevated levels of IFN-γ in obese individuals decrease sharply at month 3 following surgery induced weight reduction, as well as after 1 y, accompanying the reduction in BMI. So it is suggested that weight reduction significantly improves the obesity associated systemic and adipose tissue inflammatory states. Moreover, Lackey et al. [18], observed that IFN-γ

plasma levels are increased in metabolically unhealthy obese subjects. In that context, Pacifico and his co-workers [19], observed significantly higher prevalence of IFN-γ secreting T-cells in obese children than in healthy controls. On the contrary, other studies did not found a significant difference in IFN-γ levels between lean and obese patients [20], [21]**.** Similarly, Fabbrini et al. [22], did not identify a correlation between obesity and adipose tissue Th1 derived IFN-γ.and attributed these findings to the presence of anti-inflammatory T cell subsets, Tregs, that could counteract the effect of IFN-γ [23].

Vitamin A promotes differentiation towards Th2 cells and increases the ratio of Th2 cytokines relative to Th1 cytokines [24]**.** In obesity, vitamin A deficiency, even subclinical one, seems to increase the Th1 response, and thus participates in the obesity associated chronic inflammatory process and fat deposition [7]. Likewise, the current study found that there is a statistically significant inverse correlation between vitamin A and IFN-γ serum levels in obese patients. This comes in agreement with the study done by Dawson and his colleagues [25], who found that vitamin A decreased levels of IFN-γ in human peripheral blood mononuclear cells and purified T-cells, but increased the mRNA and protein levels of IL-4 and IL-13. Moreover, Iwata and his co-workers [26], in a study done on mice to investigate the effect of vitamin A on T cells, found that vitamin A down-regulated IFN-γ production in naive T cells after 2 days of their stimulation with antibodies to CD3 and CD28.

In Conclusion, this study showed a strong direct correlation between serum concentration of IFN-γ, as a marker of obesity associated inflammation, and the markers of high risk obesity, and a significant inverse correlation between the serum concentration of vitamin A and both BMI and IFN-γ levels. So it can be hypothesized that vitamin A deficiency increases the risk of chronic inflammation associated with obesity and fat deposition and that vitamin A supplementation might exhibit a beneficial role in preventing obesity-related immune disturbances.

Tables and Figures:

Table (1): Comparison between cases (Group I & II) and control (Group III) as regards anthropometric measures and Serum vit A and IFN- levels

Parameter	Cases (Group I &II)	Controls (Group III)	t test	
	Mean ± SD	Mean ± SD	p value	significance
Weight (Kg)	126.0 ± 19.0	63.66 ± 7.46	<0.001	S
BMI (kg/m^2)	50.7 ± 7.2	24.09 ± 1.53	<0.001	S
WC (cm)	132.6 ± 10.2	76.6 3 ± 4.47	<0.001	S
WT/HIP	0.94 ± 0.03	0.82 7 ± 0.02	<0.001	S
Serum vitamin A (nmol/L)	160.9 ± 34.6	188.1 ± 37.7	0.004	S
Serum IFN-γ (ng/dl)	24.38 ± 17.83	2.25 ± 2.81	<0.001	S

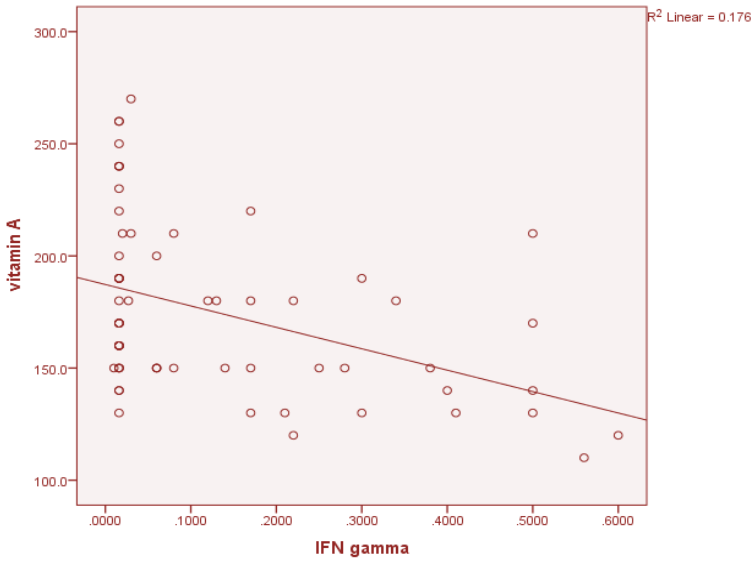
Table (2): Comparison between group I, II and III as regards anthropometric measures

Parameter	Group I	Group II	Group III	ANOVA	
	Mean ± SD	Mean ± SD	Mean ± SD	p value	significance
Weight (Kg)	118.88 ± 14.31	134.00 ± 20.85	63.66 ± 7.46	<0.001	S
BMI (kg/m^2)	48.48 ± 5.23	53.13 ± 8.37	24.09 ± 1.53	<0.001	S
WC (cm)	128.71 ± 6.40	137.00 ± 12.09	76.63 ± 4.47	<0.001	S
WT/HIP	0.92 ± 0.03	0.95 ± 0.02	0.82 ± 0.02	<0.001	S

Table (3): Comparison between group I, II and III as regards laboratory findings

Parameter	Group I	Group II	Group III	ANOVA	
	Mean ± SD	Mean ± SD	Mean ± SD	p value	significance
TG (mgdl)	127.88 ± 66.32	209.13 ± 126.68	126.59 ± 13.29	0.068	NS
Cholesterol (mgdl)	169.71 ± 35.89	229.40 ± 68.21	155.47 ± 15.61	<0.001	S
FBS (mgdl)	88.47 ± 18.80	138.40 ± 42.70	79.59 ±6.94	<0.001	S
HDL (mgdl)	50.29± 15.91	52.47 ± 11.28	50.66 ±9.67	0.856	NS
LDL (mgdl)	94.24 ± 36.64	135.00 ± 53.54	79.47 ±18.99	<0.001	S
Serum vitamin A (nmol/L)	166.47 ± 39.20	154.67 ± 28.50	188.1 ± 37.7	0.010	S
Serum IFN-γ (ng/dl)	14.35 ± 14.72	35.73 ± 14.01	2.25 ± 2.81	<0.001	S

Figure (1): Correlation of vitamin A to IFN-γ (r = -0.391, p= 0.001)



Figure(2): Cut-off value of vitamin A between obese cases and control group by ROC curve

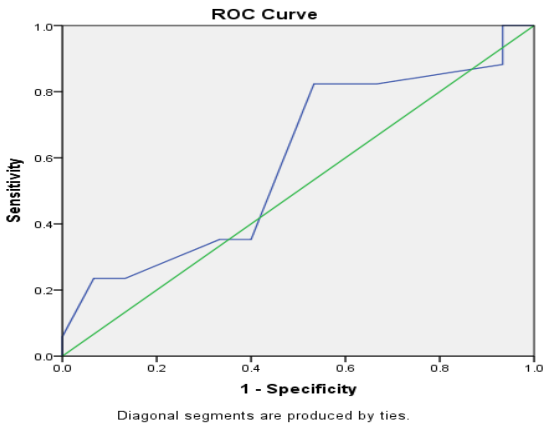
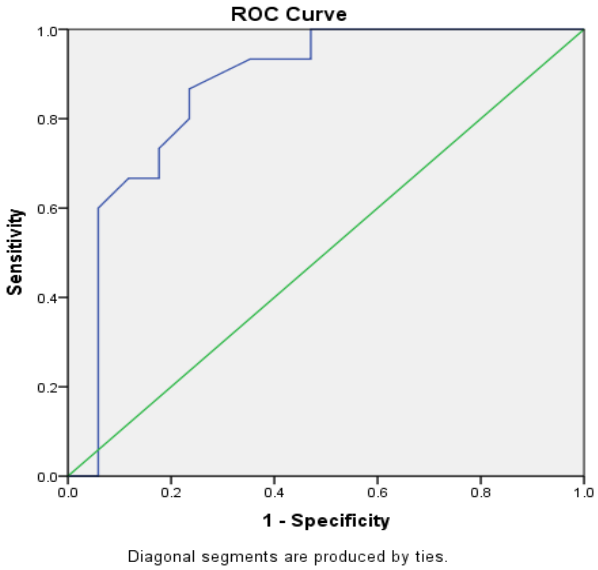


Figure (3): Cut-off value of IFN-γ between obese cases and control group by ROC curve



Conflict of Interest:

The authors declared that there is no conflict of interest regarding the publication of this paper.

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