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Research Article

MULTIPLE MARKERS OF DIABETES IN RELATION TO ABDOMINAL OBESITY IN OBESE EGYPTIAN ADOLESCENT GIRLS

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ABSTRACT

Inflammation is believed to be the 'common soil' leading to the development of type 2 diabetes but the trigger of inflammation is unclear. Elevated plasma concentrations of many inflammatory markers are associated with obesity in adult but this association is less clear in children and adolescents. Our objective was to examine the relation between some inflammatory markers and the adolescent's central obesity in a group of obese adolescent girls (n=90). Waist to hip ratio (WHR) was taken as a measure of central obesity and used to divide the participating students into two groups: group I with WHR> 0.8 and group II with WHR< 0.8.The determined markers were C-reactive protein (CRP), ApolipoproteinB (ApoB) and Ferritin. There were a very high significant ($p<0.05$) increase in CRP,ApoB and Ferritin levels in group I when compared to group II with a high positive significant correlation between CRP and both ofApoBand Ferritin at r=0.895 and r=0.618 respectively and positive significant ($p<0.05$) correlation between ApoBand Ferritin at r=0.818 in group I. A very high significant ($p<0.05$) correlation was found between WHR and the measured markers CRP, ApoB and Ferritin at r=0.766, r=0.650 and r=0.442respectively.CRP, ApoB and Ferritin were the corner stone markers of inflammation and can be used as early predictors of diabetes. In conclusion, this study focused on avoiding of being obese with remarked central obesity throughout adolescent period in Egypt by recommending an effective program to follow up the central obesity, to decrease the risks of the initiated inflammatory molecules for the protection from the associated complications in the future.

Keywords: CRP, ApoB, Ferritin, Adolescent girls, Obesity, Central obesity, Diabetes.

INTRODUCTION

The prevalence of obesity and diabetes is increasing rapidly in both industrialized and developed nations.Obesity is also on the rise among children and adolescents with alarming complications for the nation's future cardiovascular health (1).

Obesity, in particular, central or abdominal obesity is a recognized pro-inflammatory state prone for broad alterations of the metabolic milieu, which include insulin resistance, impaired glucose tolerance, dyslipidemia and hypertension. It is unclear whether the pro-inflammatory state determines the insulin resistance condition or insulin resistance causes increased systemic inflammation (2). Central obesity is defined according to International Diabetes Federation (IDF), by the measure of waist circumference. An excessive accumulation of abdominal fats is most tightly associated with type 2 diabetes (3).

A feature of inflammatory activity is the increase in circulating plasma concentration of acute phase proteins produced by the liver. One of the most sensitive acute-phase proteins is C-reactive protein (CRP) which is released in response to acute injury or inflammation which occurs whenthe body is exposed to a major trauma or infection (4).

CRP is a marker of inflammation resulted in many different diseases and conditions such as heart disease, atherosclerosis, strokes, obesity, arthritis, diabetes,cancer and Alzheimer's. Obesity is one of the important causes of inflammation as fat cells secrets proteins which stimulate the production of CRP (5). CRP found to predict increased risk of developing type 2 diabetes. The synthesis of CRP is regulated by adipocyte cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor (TNF)-α (6).

ApolipoproteinB (ApoB) is synthesized by the liver and is responsible for carrying cholesterol to the tissues (7). It is a key structural component of all atherogenic lipoprotein particles. Each of these particles carries only one ApoB molecule, thus, the total ApoB level represents the total number of circulating atherogenic lipoprotein particles (8). There is considerable evidence that levels of ApoB are a better indicator of heart disease and type 2 diabetes risks than total cholesterol or LDL (9). Hyper ApoB was found to increase the risk of developing the incidence of diabetes (10).

Ferritin, one of the key protein regulating iron homeostasis, is a widely available clinical biomarker to evaluate iron status and especially important for detecting iron deficiency. However, growing evidence has shown that event moderately increased iron stores, represented by high-normal Ferritin concentrations are associated with the increased risk of type 2 diabetes by the observed association between elevated body iron and glucose homeostasis indexes (11, 12). More recently,it has been suggested that iron overload could predict the development of abnormal glucose metabolism (13). Metabolic syndrome,in particular, type 2 diabetes is the main contributor to the high Ferritin levels reported in obesity (14).

The aim of this study is to determine CRP, ApoB and Ferritin levels as predictors of the incidence of type 2 diabetes in obese adolescent girls group with marked central obesity compared to obese group.

SUBJECT AND METHODS

The current study was carried out on obese adolescent girls with age range from 13 to 18 years old through a project conducted in the National Research Centre, Egypt, to estimate the prevalence of obesity among school adolescents. It was a cross-sectional survey. Four local public schools in Cairo were enrolled in this study regarding adolescents (two preparatory schools and two secondary schools). Permission to perform the study was granted by the Ministry of Education, and the directors of the school included in the research. The protocol was approved by the "Ethical Committee" of the "National Research Centre", in accordance with the code of ethics of the world medical association (declaration of Helsinki). Of the total sample, ninety adolescents girls with the complaint of obesity were included in the current research after obtaining written informed consent from their parents. Student assent was also obtained. The adolescents were required to meet the following inclusion criteria: age, 13–18 years and BMI> 97 percentile for age and gender based on the Egyptian Growth Reference Charts 2002 (15). The 90th percentile values for waist circumference for gender and age generated in the national health and nutrition examination survey (NHANES III) were used as cut off values to identify children with abdominal obesity. Then, WHR (waist to hip ratio) was calculated by dividing waist (cm) by hip circumference (cm), and abdominal obesity was diagnosed when the WHR was 0.80 in girls (16). Each adolescent underwent a complete physical examination,

including anthropometric measures. The height and the weight were recorded. The height was measured to the nearest 0.5 cm on a Holtain portable anthropometer, and the weight was determined to the nearest 0.1 kg on a Seca scale Balance with the subject dressed minimum clothes and no shoes. Body mass index (BMI) was calculated as Weight (kg)/Height (m^2). Waist circumference was measured to the nearest 0.1cm by using non stretchable stain steel tape, considering the smaller circumference between the iliac crest and first rib as the anatomical point to perform the measurement (17). Hip circumference was measured to the nearest 0.1 cm at the maximal gluteal protrusion or at the most prominent area of buttocks at the level of symphysis pubis in a horizontal plane the tape measure was held snugly against the body but without compression (18).

The participating adolescents were divided into two groups according to central obesity Group I: with WHR > 0.8 and group II with WHR<0.8. Blood samples were drawn from the obese students and the serum was separated and kept frozen until analysis at -70.

Biochemical assays

Serum CRP levels were determined with an enzyme-linked immunosorbant assay (Eliza) method using commercial kits produced by BioCheck (Inc 323 Vintage Park Drive Foster City, CA 94404) and the sensitivity of detection level was 0.1mg/l.Serum ApoB levels were determined with Eliza method using kit produced by assaypro (E.mail:Support@assaypro.com) and minimal detectable dose is 20 ng/ml. Serum Ferritin levels were determined with Eliza method using kit produced by BioCheck (Inc 323 Vintage Park Drive Foster City, CA 94404) and minimal detectable concentration by this kit is estimated to be 5 ng/ml.

Statistical Analysis

The results were expressed as mean ± standard deviation, statistical analysis of difference between means were performed using student "t" test. Spearman correlation coefficient was used to determine the relationship between different variables. All analyses were carried out by using SPSS version 14 (Statistical package for Social Science, Chicago, USA).

RESULTS

The waist circumference (WC) and waist to hip ratio (WHR) were represented in Table (1). The results showed a very high significant ($p<0.05$) increase in WC and WHR in group I as compared to group II.

The levels of CRP, ApoB and Ferritin were very highly significant ($p<0.05$) increased in group I when compared to group II as represented in Table (2). In addition, there was a high positive significant ($p<0.05$) correlation between CRP and both of ApoB and Ferritin at $r=0.895$ and $r=0.618$ respectively and positive significant ($p<0.05$) correlation between ApoB and Ferritin at $r=0.818$ in group I.

A very high significant correlation was found between WHR and the CRP at $r=0.766$,$p<0.05$ as in Fig (1); ApoB at $r=0.650$, $p<0.05$ as in Fig (2) and Ferritin at $r=0.442$, $p<0.05$ as in Fig (3).

Table 1: The difference between group I and group II for WC and WHR

Variables	Group I (n=45)	Group II (n=45)	P
Age	13-18	13-18	-
WC (cm)	101.95±17.60	79.31±4.96	0.05
WHR	0.87 ± 0.11	0.74±0.02	0.05

Data represented as mean±SD p<0.05 significant

Table 2: The levels of CRP, ApoB and Ferritin in group I compared to group II.

Variables	Group I (n=45)	Group II (n=45)	P
CRP (mg/l)	14.03±5.78	4.68±1.61	0.05
ApoB (ng/ml)	9.04±0.85	5.78±1.06	0.05
Ferritin (ng/ml)	84.02±37.75	57.28±1.38	0.05

Data represented as mean ±SD p<0.05 significant.

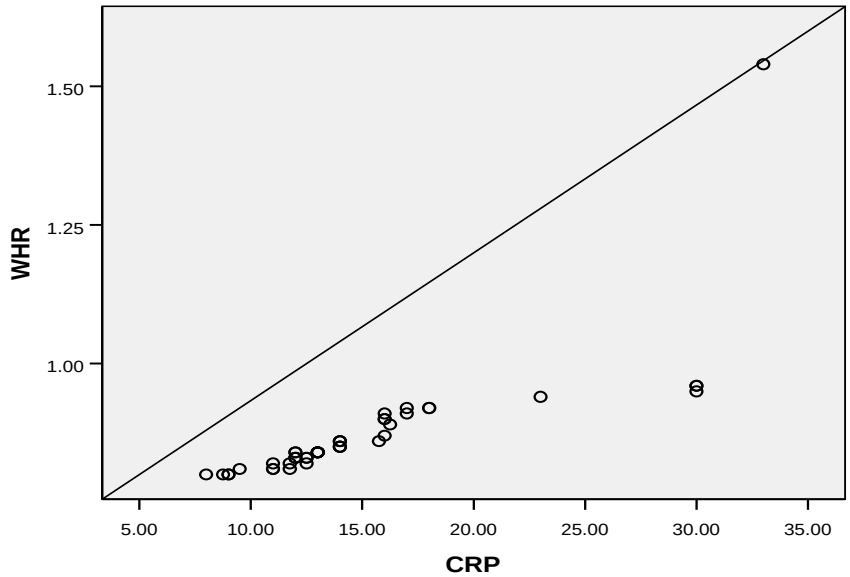

Fig. 1: Correlation between WHR ratio and CRP in group I.

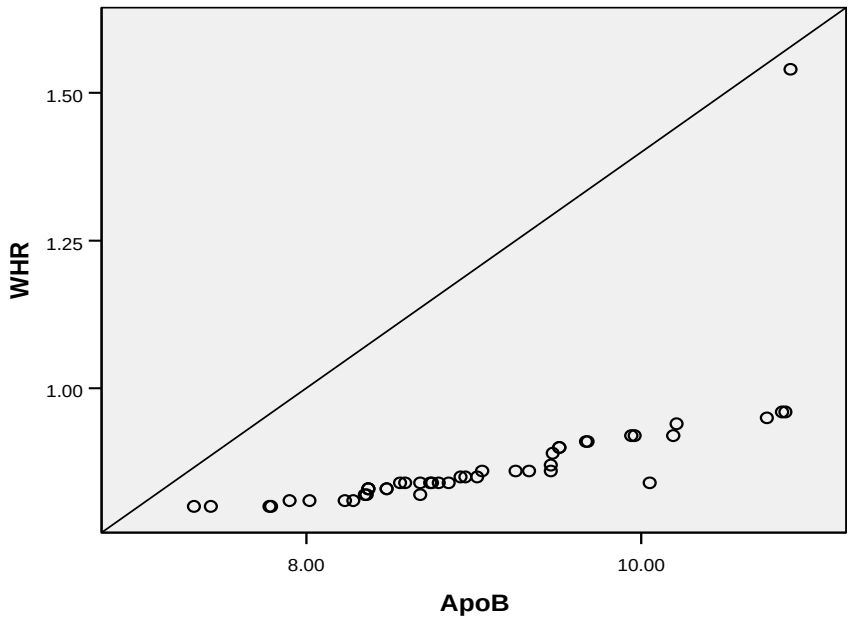

Fig. 2: Correlation between WHR ratio and ApoB in group I.

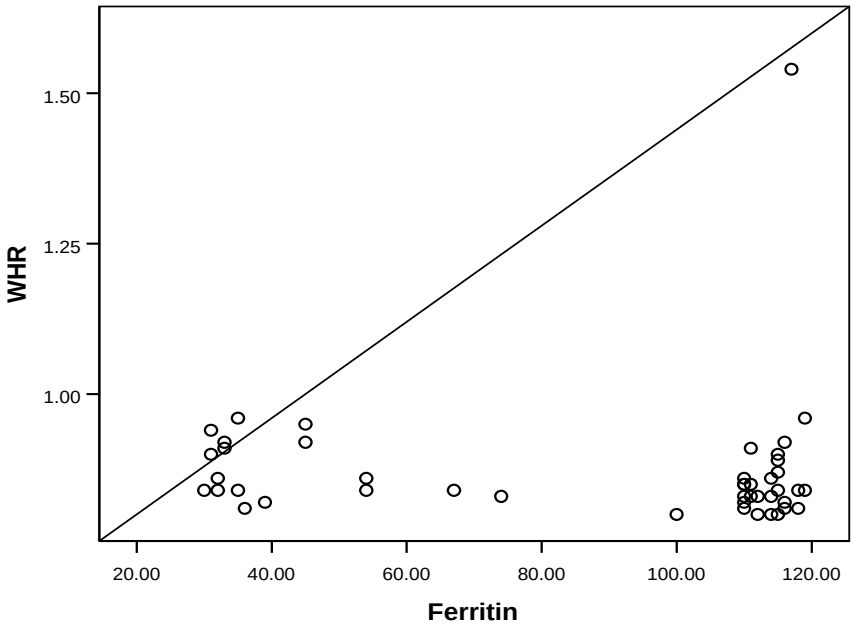

Fig. 3: Correlation between WHR ratio and Ferritin in group I.

DISCUSION

The prevalence of obesity and diabetes has reached pandemic proportion. Obesity, particularly in assocition with high waist circumference and high BMI, is independent risk factor for diabetes (19). Subclinical inflammation is an early complication of childhood obesity and may foreshadow an increased burden of CVD and type 2 diabetes in the future (20).

Chronic subclinical inflammation may be one of the pathophysiological mechanism explaining the increased risk of diabetes and other complications associated with obesity. Adipose tissue expresses inflammatory cytokine and stimulates the release of inflammatory markers such as CRP (21). The regulatory mechanisms of CRP synthesis by the liver include interleukin-6 as a potent inducer of its expression in humans (22). (23) showed that, TNF-α and IL-6 is the main proinflammatory cytokines secreated by the adiposetissue. (24) Stated that IL-6 which stimulate the hepatic production of fibrinogen and CRP is synthesized in adipose tissue, particularly by visceral adipose tissue. (20) determined the positive relation between waist circumference and CRP concentration. Moreover, they stated that increasing CRP was associated with higher insulin resistance, higher Apolipoprotein B, LDL, Triglycerides and total cholesterol(25) found positive correlation between fasting insulin level and CRP, this consistent with the established pattern of onset in middle and late adulthood of glucose intolerance.

[26,27]In epidemiological studies, prove that CRP levels significantly predict the risk of type 2 diabetes. CRP was strongly related to total and central obesity, hypertension, hyperglycemia and dyslipidemia,these relations are likely to contribute significantly to prospective associations between CRP and type 2 diabetes (28).Chronic systemic inflammation can induce insulin resistance

and is a key mechanism linking obesity and diabetes, CRP acts as a nonspecific marker of systemic inflammation (29).

Our study identify a very high significant ($p<0.05$) increase in CRP level in very obese group I (WHR>0.8) whencompared to group II (WHR<0.8)with a very high significant correlation with WHR. Possible explanation for higher CRP value in these group include a very high prevalence of central obesitysince high WHR is associated with elevated levels of CRP (30, 31). The elevated CRP also have several explanations, obesity is a state of chronic low–grade inflammation that activate macrophage to produceinterleukin (IL)-1 andtumer necrosis factor (TNF)-α and increase oxidative stress (32). The biological mechanisms through which CRP increases the risk of type 2 diabetes are not well understood.CRP is a marker of low-grade inflammation and may have indirect influence on insulin resistance and insulin secretion through altered innate immune response due to heightened systemic inflammation (19, 33). Elevated CRP also stimulate endothelial production of E-selection, intercellular adhesion molecules (ICAM-1 and VCAM-1), the important mediators of impaired vascular reactivity, reduced insulin secretion and increased peripheral insulin resistance (34, 35).

ApoB is a key structural component of all atherogenic lipoprotein particles.The total ApoB level represents the total number of circulating atherogenic lipoprotein particles and found to be risk factor in the development of diabetes (7). It was considered to be a better risk predictor than traditional lipid variables in subjects with high prevalence of obesity and impaired glucose tolerance (8).

(36) Stated that, ApoB is a significant predictor of diabetes and metabolic syndrome independent of waist circumference and CRP.The increase in ApoB level was associated with the incidence of obesity, in particular, central obesity (37, 38). Central obesity has been associated with insulin resistance, which leads to a defect in the ability of insulin to suppress free fatty acids, and this defect in insulin action has been associated with increased ApoB and may contribute to the development of type 2 diabetes (39). (40) stated that, the increased ApoB level may be from insulin resistant that is commonly characterized by a profound metabolic dyslipidemia which appears to result from hepatic and intestinal overproduction ofatherogenic lipoprotein particles. In addition, increased fatty acids have been shown to decrease the uptake of glucose by peripheral tissues, to reduce hepatic insulin clearance, and to hepatic gluconeogenesis (41).

Along with aforementioned studies, the present study showed a very high significant ($p<0.05$) increase in ApoB level in group I when compared to group II with a very high significant ($p<0.05$) correlation with WHR and CRP and these results also are in agreement with (42) who found that ApoB was associated with incidenttype 2 diabetes among subjects with highincidence of obesity and impairedglucose tolerance. Moreover, subjects with hyper ApoBin this population had elevated levels of CRP, compared to the subjects with normal ApoB, independent of body weight, fat distribution, insulin sensitivity and blood pressure. Aselevated levels of these inflammatory markers are independent risk factors for the development of type 2 diabetes, hyper ApoB subjects had a greater risk than normal ApoBsubjects of developing not only chronic heart diseases but also type 2 diabetes. Accordingly, the dyslipidemia of the metabolic syndrome should be redefined to include ApoB.

Ferritin is a protein involved in regulating iron homeostasis.Iron is a catalyst in the formation of hydroxyl radicals. In animals model, iron excess might result in B-cell oxidative stress and decreased insulin secretory capacity (43). Oxidative stress, also increases Ferritin synthesis, partly to avoid further oxidative damage, given that Ferritin neutralizes the highly toxic unbound iron (44).

Studies in patients with iron overload indicated that iron accumulation in the hepatocytes might cause impaired hepatic insulin extraction and metabolism (45). The mechanism linking iron over load and diabetes is yet to be established.Elevated iron stores,reflected in elevated plasma Ferritin concentration, frequently cluster with well-established risk factors of development of type 2 diabetes including obesity, metabolic syndrome, inflammation and lifestyle factors (46). Alternatively, elevated Ferritin may be just one of several metabolic abnormalities related to the undergoing process that ultimately results in diabetes rather than a causal factor for diabetes (44). Inflammation was suggested to regulate not only Ferritin mRNA and proteinslevels but also its secretion (47). As a result, elevated Ferritin concentration might reflect systemic inflammation in addition to elevated body iron stores (48). Meanwhile, inflammation was postulated to be involved in the physiopathological mechanisms behind metabolic syndrome and diabetes (49).

The results of this work showed a very high significant ($p<0.05$) increase in Ferritin level in group I when compared to group IIwith a very high significant ($p<0.05$) correlation with WHR. These results are in consistent with the previous studies that summarized by (50) who showed an increase in serum Ferritin levels in obese group compered to overweight group. (51) explained this increase by the presence of obesity-related inflammation that would be expected to cause an increase in serum Ferritin,a well known acute-phase reactant. The role of serum Ferritin in this setting is unclear; it may reduce oxidative stress by binding freeredox-active iron.

In our study, Ferritin level was positively correlated with CRP in group I, this observation was consistent with the previous finding by (46) who found the same correlation between Ferritin and CRP and the association of diabetes with them tended to be independent of each other but after adjusting for CRP in the multivariante models, no substantial change was observed in the association of Ferritin and type 2 diabetes or metabolic syndrome. Ferritin also showed to predict the onset of hyperglycemia independent of CRP concentration (13). Therefore, it is possible that Ferritin may increase the risk of type 2 diabetes or metabolic syndrome through a pathway not greatly overlapping with CRP and other inflammatory markers.Furthermore, Ferritin is produced in macrophages, hepatocytes and adipocytes in conditions associated with inflammation not only because it is an acute-phase reactant,but also induced by the presenceof inflammatory cytokines such asinterlukin (IL)-β andtumer necrosis factor (TNF)-α (52).

This deserves additional researches that should determine if inflammation results in a cascade that over many years leads to sever damages.If such processes were confirmed, inflammation may transform the adolescent obesity into a future incidence of diabetes in adults.

Modification of unhealthy diet, lifestyle factors and avoiding obesity and being overweight, fundamental causes of heightenedinflammatory response, and type 2 diabetes should remain the cornerstone for the prevention and management of diabetes. Pharmacological agents with anti-inflammatory properties may also have a role in diabetes prevention and treatment.There is an urgent need for increased public awareness of the risks associated with obesity and greater efforts should be made to overcome the dangerous effects of obesity and development of type 2 diabetes.

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