Hypercholesterolemia enhances the release of proinflammatory cytokines in obese Egyptian adolescents

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Abstract: The interrelation between hypercholesterolemia, proinflammatory cytokines, C-reactive protein (CRP) and body mass index (BMI) were not yet established in obese Egyptian adolescents .The aim of this work is to study the relation between hypercholesterolemia; as a major determinant of serum inflammatory cardiovascular risk marker; TNF- α and IL-1 β as proinflammatory cytokines; and CRP with body mass index (BMI); as indicator for obesity and waist circumference; as indicator for central obesity . The study was carried out on obese Egyptian adolescents with high lipid profile levels (Group I) and obese one with lipid profile within normal levels (Group II) from both sexes. TNF –α, IL- 1β and CRP were significantly higher in Group I than Group II ($p<0.001$). There were positive highly significant correlations between cholesterol, and each of BMI, IL1-β, TNF-α and CRP ($p<0. 001$) with a negative significant correlation between it and HDL ($p<0.029$). A significant negative correlation between HDL and both LDL ($p<0.001$), and TNF-α ($p<0.01$) was recorded. LDL have shown a significantly positive correlation with TNF-α, IL-1B and CRP ($p<0.001$). There were significant positive correlations between waist circumference (central obesity) with TNF-α, IL-1β and CRP ($p<0.001$). Conclusion: The positive association of obesity with elevated cytokines levels suggests the importance of reducing obesity to prevent elevation in cytokines levels which are risk factors for future cardiovascular diseases. [Journal of American Science 2010;6(8):428-435]. (ISSN: 1545-1003).

Keywords: hypercholesterolemia, obesity, CRP, Proinflammatory cytokines, cardiovascular risk factor, adolescents.

1. Introduction

Obesity is a pathological condition accompanied by an excessive fat deposition as compared to expected values for a given stature, sex and age which is often estimated by a body mass index (BMI) (kg⁄m2) , BMI percentiles equal to or more than 95% considered obese . The best way to estimate obesity in clinical practice is to measure waist circumference (central obesity) this is because an excess of abdominal fat is most tightly associated with the metabolic risk factor, (National institute of health., 1998). According to the obesity and health risk, 2000**,** obesity has been related to hypercholesterolemia, hypertension and cardiovascular disease. Three of the most proinflammatory cytokines, Tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β) and C-reactive protein (CRP), have been implicated in atherogenesis (Cesari et al., 2003).

The immunological process involved in the collaborative defense of organisms are affected by nutritional state (Marti et al., 2001), thus a positive chronic imbalance between energy intake and expenditure leads to situations of obesity (Ulizaszek, 2008). Coppack (2001), stated that the importance of the immune system in whole body energy balance and in providing a rationale for the links between cytokines and adipose tissue which could be a major contributor to the biochemical and clinical features of the metabolic syndrome and central obesity. Fain (2006), reported that the white adipose tissue especially of humans is recognized as the central player in the proinflammatory state .As the adipose tissue was primarily a reservoir for excess calories that were stored in the adipocytes the expansion of adipose tissue seen in obesity results in more blood vessels, more connective tissue fibroblasts, and especially more macrophages. These proliferate and amplify the inflammatory response through the secretion of numerous growth factors and cytokines including tumor necrosis factor alpha (TNF-α) and interleukin (IL-1β) (Swirski et al.,2007, and Tacke et al., 2007).

IL-1β is a multipotent proinflammatory cytokines that affects most cell type and cooperates with other cytokines chemokines and a variety of cellular mediators.IL-1β is produced by a variety of inflammatory cells that release a cascade of inflammatory signals (Dinarello, 2005). Eizirik and his colleagues, 2001; stated that IL1-β is proatherogenic and appears to have procoagulant activity, stimulates monocytes-endothelial cell adhesion and cholesterol esterification in

macrophages. Blake and Ridker (2003), showed that CRP is an important marker of vascular inflammation and a predictor of atherosclerosis . A recent study of Ridker (2009) revealed also that an increase in the concentration of CRP indicate a greater risk for acute coronary syndrome .This finding showed that evaluation of CRP carry predictive power for the development of major cardiovascular events, led to the concept that advanced and unstable atherosclerotic plaques are in an even higher state of inflammation than stable plaque.

Tzoulaki and others, 2008, demonstrated that obese persons have elevated levels of CRP, which is the most sensitive circulating marker for cytokines in obese subjects. This finding let, Harris and his colleagues, 2008, to suggest that obesity is a proinflammatory state and is somehow connected with the development of unstable atherosclerotic plaques . Pai (2008) stated that CRP as an acute phase reactant and marker of inflammation has been shown to predict risk of incident cardiovascular events.

TNF- α is a multifunctional circulating proinflammatory cytokine derived from endothelial and smooth muscle cells, as well as macrophages .TNF-α plays a major role in the cytokine cascade as it stimulates the synthesis of other cytokines like interleukin 6 (IL-6) which is a central mediator of the acute phase response and the primary determinant of C-reactive protein (CRP) production (Heinrich,Castell and Andus.,1990;Van Snick .,1990). Thereby, it contribute to the maintenance of chronic low grade –inflammation state involved in the progression of obesity and its associated co-morbidities (Harris et al., 2008).

The aim of this work is to study the relation between hypercholesterolemia; as a major determinant of serum inflammatory cardiovascular risk marker; TNF- α and IL-1 β as proinflammatory cytokines; and CRP with body mass index (BMI); as indicator for obesity and waist circumference; as indicator for central obesity.

2. Material and Methods

This study was conducted by the National Research Centre, Egypt, to estimate the prevalence of obesity and metabolic syndrome among school children and adolescents, and the potential risk factors for these diseases**.** It was a cross-sectional survey. Four local public schools situated in Giza governorate were enrolled in this study regarding adolescents (two secondary schools and two high schools). The study included boys and girls during the period of October, 2007 to April 2009. 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".

Of the total sample, one hundred and three adolescents (32 boys and 81 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.

These adolescents were required to meet the following inclusion criteria: age, 13–18 years and BMI, greater than the 95th percentile for age and gender based on the Egyptian Growth Reference Charts 2002 (2008). Adolescents were excluded if they had a prior major illness, including type 1 or 2 diabetes, took medications or had a condition known to influence body composition, insulin action or insulin secretion (e.g. glucocorticoid therapy, hypothyroidism and Cushing's disease).

Method:

Each adolescent underwent a complete physical examination, including anthropometric measures. The height and the weight were measured. 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 (in kilograms) divided by height (in meters) squared. Waist circumference was measured at the level of the umbilicus and the superior iliac crests at the end of normal expiration with patient standing and breathing normally using non-stretchable plastic tape to the nearest 0.1 cm. Each measurement was taken as the mean of three consecutive readings following the recommendations of the International Biological program (Hiernaux and Tanner 1969). After a verified 10- hour fast, subject had a blood draw for laboratory assays. According to their lipid profile results the participating adolescents were divided into two groups; Group I: with high triglycerides [>110 mg/dL], low HDL-cholesterol [<40 mg/dL], high total cholesterol [>210 mg/dL] or High LDL–Cholesterol [> 130 mg/dL] (defined according to modified WHO criteria adapted for children); Group II: with normal lipid profile.

Biochemical assays:

Serum CRP levels were determined with an enzyme- linked immunosorbant assay (Eliza) method using commercial kits (BioCheck, Inc 323 Vintage Park Drive Foster City, CA 94404) and the sensitivity of detection level was 0.1 mg\l. Serum concentrations of cytokines , IL-1 β and TNF- α were measured using commercially available Elisa kits (Ani Biotech

Oy Orgenium Laboratories Business Unit Finland; Bender MedSystems GmbH Campus Vienna Biocenter and the sensitivity of detection for IL-1β and TNF-α was <4 pg⁄ml and 2.3 pg⁄ml respectively. Triglycerides, Total cholesterol, HDL, were measured using Quantitative- Enzymatic – Colorimetric Determination in serum (STANBIO laboratory.1261 North Main Street. Boerne Texas 78006 U.S.A

LDL was calculated as follow: LDL=Total Cholesterol-HDL-TG/5.

Statistical analysis

All values are expressed as mean±SD. Differences among the two groups were calculated by student´s t test, correlation were done between different parameters using pearson correlation. A p value ‹ 0.05 was considered significant. All analyses were carried out using SPSS 9.0 statistical software.

3. Results

Serum level of Cholesterol, low density lipoprotein(LDL) and triglycerides (TG) were used to classify obese adolescent into two groups .The levels of serum cholesterol, LDL and TG were very high significantly increased (P<0.001) in obese subjects group I, as compared to group II while the level of HDL was significantly decreased (P<0.01) as shown in table(1).

The level of proinflamatory cytokines; TNF-α and IL-1β, and CRP were all significantly higher in the obese Egyptian adolescents group I in comparison with the obese adolescents group II with p<0.001, table (2) fig (2).

There were significant positive correlations between each of BMI and waist circumference with TNF-α , IL-1β, and CRP (p<0.001) as shown in table(3).

Table (1) Comparison of lipid profile between Group I and Group II

Lipid profile	**Group I (N=35) Mean ±SD**	**Group** II **(N=78) Mean ±SD**
Triglycerides mg\dl	161.27±44.45	131.79±37.84***
Cholesterol mg\dl	255.65±35.86	150.10±34.56***
HDL mg\dl	40.19±19.35	49.23±32.04**
LDL mg\dl	178.3±54.7	81.64±34.7***

p<0.01= highly significant difference;*p<0.001= very highly significant difference

Table (2) Comparison of proinflammatory cytokines between Group I and Group II

Proinflammatory cytokines	**Group I (N=35) Mean ±SD**	**Group** II **(N=78) Mean ±SD**
TNF- α pg/ml	15.11±9.95	0.72±3.83***
IL-1 β pg/ml	51.24±38.77	10.68±17.7***
CRPμg/dl	8.49±3.49	1.68±0.90***

***p<0.001= very highly significant difference

Table (3): Correlation between anthropometric parameters, and TNF-α,IL-1B ,CRP of obese group I

Proinflammatory cytokines⁄ Anthropometric measurements	TNF-α pg⁄ml	IL-1β pg⁄ml	CRP μg/dl
Waist circumference	r=0.773**	r=0.901**	r=0.822**
Body mass index (BMI)	r=0.925**	r=0.901**	r=0.901**

**p<0.01= highly significant difference

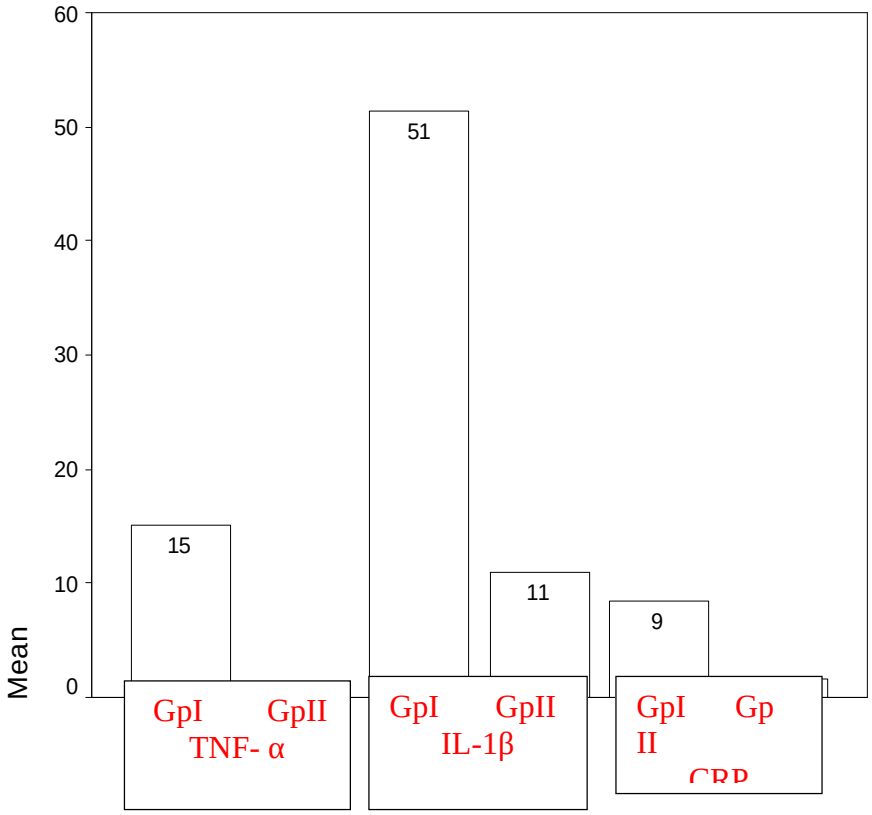

Fig :(2) Histogram of proinflammatory cytokines showing the comparison between Group I and Group II

The results of the current work also, illustrated the following: There was a highly significant positive correlation between each of BMI and waist circumference, with cholesterol, LDL ($p<0.001$), but such correlation was not found with triglycerides and no correlation between HDL and waist circumference. Moreover, BMI has recorded negative correlation with HDL ($p<0.04$). There was very highly significant positive correlation between cholesterol and TNF-α, IL-1β and CRP ($p<0.001$), a negative correlation between cholesterol and HDL at ($p<0.029$) have also been shown with no significant correlation between cholesterol and triglycerides. Negative significant correlations were found between HDL and both LDL, and TNF-α ($p<0.001$, $p<0.01$; respectively), with no significant correlation between HDL and either IL-1β or CRP was observed. LDL has shown a very highly significant positive correlation with TNF-α, IL-1B and CRP at ($p<0.001$) table (4).

Table (4): Correlations Between The Different Variables

	waist	BMI	Triglyceridesmg\dl	Cholesterol mg\dl	HDLmg\dl	LDLmg\dl	TNF-α pg\ml	IL-1β pg\ml	CRP
Waist		r=0.796** a***	r=0.031 a NS	r=0.826 a***	r=-0.091 a NS	r=0.602** a***	r=0.773** a***	r=0.901** a***	r=0.822** a***
BMI			r=0.037 a NS	r=0.935** a***	r=-0.221* a=0.041	r=0.731** a***	r=0.925** a***	r=0.901** a***	r=0.901** a***
Triglyceridesmg\dl				r=0.080 a NS	r=0.010 a NS	r=-0.123 a NS	r=0.101 a NS	r=0.025 a NS	r=0.104 a*

Cholesterol mg\dl	r=0.826 a***	r=0.935** a***			r=-0.236* a*	r=0.763** a***	r=0.979** a***	r=0.912 a***	r=0.982** a***
HDL mg\dl	r=-0.091 a NS	r=-0.221* a=0.041	r=0.010 a NS			r=-0.708** a***	r=-0.271* a**	r=-0.141 a NS	r=-0.160 a NS
LDL mg\dl	r=0.602** a***	r=0.731** a***	r=-0.123 a NS	r=0.763** a***			r=0.770** a***	r=0.681** a***	r=0.688** a***
TNF-α pg\ml	r=0.773** a***	r=0.925** a***	r=0.101 a NS	r=0.979** a***	r=-0.271* a=0.011			r=0.862** a***	r=0.969** a***
IL-1 β pg\ml	r=0.901** a***	r=0.901** a***	r=0.025 a NS	r=0.912 a***	r=-0.141 a NS	r=0.681** a***			r=0.876** a***
CRP	r=0.822** a***	r=0.901** a***	r=0.104 a NS	r=0.982** a***	r=-0.160 a NS	r=0.688** a***	r=0.969** a***		

a** Correlation is significant at 0.01 level (2 tailed),a*Correlation is significant at 0.05 level (2 tailed),aNS=non significant

4. Discussions

Because the prevalence of obesity has increased dramatically in recent years, one of the key targets of public health is obesity and its associated pathological conditions. Obesity occurs as a result of white adipose tissue enlargement, caused by adipocyte hyperplasia and/or hypertrophy. Recently, endocrine aspects of adipose tissue have become an active research area and these adipose tissue-derived factors are referred to as adipokines. These adipokines interact with a range of processes in many different organ systems and influence a various systemic phenomena (Inadera, 2008)Obesity leads to increased circulating levels of proinflammatory cytokines that are secreted by adipocytes thus increasing cardiovascular risk (Ikeoka et al., 2010).

In this study we have shown that in Group I there is a strong interrelation between hypercholesterolemia and the increased levels in proinflammatory cytokine TNF-α , IL-1β and CRP which are risk factors of cardiovascular disease.High cholesterol levels are frequently associated with increased soluble markers of systemic inflammation(Ferroni et al., 2003) such as CRP (Ridker et al., 2009) and IL-1β (Ferroni et al., 2003), which support our results. Gomes and his colleagues (2009) reported that hypercholesterolemia is associated with peripheral blood (PB) leucocytes and increased platelet levels , generally attributed to cholesterol – induced circulating proinflammatory cytokines and increased soluble markers of systemic inflammation such as IL-1 β (Ferroni et al.,2003). Studies also done by Domenico and his team (2000) suggested that cholesterol biosynthesis is associated with proinflammatory cytokines formation and that adipose tissue is acknowledged to be a source of cytokines such as TNF-α (Hostamisliglil et al.,1993.) The current work has shown that CRP concentration was higher in Group I than Group II .In obese Egyptian adolescent with high lipid profile obesity measured by BMI was significantly correlated with CRP concentration which was previously reported by (Park and co- workers 2005) and coincide with the studies of (Rexrode et al., 2003 and Tzoulaki et al., 2008) who found that BMI was the adiposity parameter that is strongly correlated with CRP concentration. Such acute phase reactant (CRP), suggest that obesity may be a state of low grade inflammation (Ikeoka et al., 2010) that indicates a greater risk for acute coronary syndrome (Ridker et al., 2009). These results may be related to the finding that adipose tissue is a dynamic endocrine organ that secretes a number of factors that contributes to systemic inflammation (Lyon et al., 2003).

The significant correlation between BMI and proinflammatory cytokines can be interpreted by the suggestion of Cousin et al., 1999, that preadipocytes could function as macrophages like cells supporting the idea of a direct involvement of adipose tissue in inflammatory process and that inflammatory cytokines as TNF –α seem to be produced by the infiltrating macrophage in the adipose tissue (Weisberg et al., 2003). These events may perpetuate a vicious cycle of macrophage recruitment and production of proinflammatory cytokines (Janeway et al., 2005).

In addition the study of Fain (2006) revealed that obesity markedly elevates the total release of TNF- α which was explained by Landry et al., (1997) as TNF-α activates the transcription factor nuclear factor kβ which organize inflammatory changes in vascular tissue . The increased TNF- α mRNA expression in adipose tissue from obese humans (Hostamisliglil., 1993)causing increase in circulating concentration of TNF-α in such people (Hostamisliglil et al.,1995). In our study the increase in TNF- α and IL-1β in Group I in comparison with Group II can be explained by the fact that adipocytes

can synthesize both TNF-α and several interleukins notably IL-1β (Fain ., 2006 ; Swirski et al., 2007,Tacke et al., 2007).

IL-1β is one of the major proinflammatory cytokines that is produced by monocytes and macrophages (Martin and Wesche., 2002). Expression of both IL-1β and its receptor is increased in visceral adipose tissue of obese subjects (Juge –Aubry et al., 2004) an observation that we confirmed in this study as we found a positive correlation between central obesity and IL-1β .

Previous studies of (Festa et al., 2001 , Pannecciulli et al., 2001) have shown a positive association between CRP and obesity.The strong correlation between serum levels of CRP and TNF-α in our study can be understood by the explanation that the increase in the concentration of TNF-α induce IL-6 secretion which promotes the production of CRP which is raised in obese individuals with high lipid profile (Petersen and Pedersen ., 2005) this fact may explain the positive association between CRP and obesity .

In this study there was also a strong correlation between CRP and lipid profile and this was in agreement with (Tamakoski et al., 2003) who found that hypertriglyceridemia, hypo- HDL cholesterolemia, hyper LDL cholesterolemia were significantly associated with elevated CRP and there is a strong association of CRP with obesity. The addition of CRP with traditional cholesterol enhances cardiovascular risk prediction independently of LDL concentration (Ridker et al .,2009) suggesting that increased CRP concentration in particular may identify asymptomatic individuals with average cholesterol concentrations at high risk for future cardiovascular events.

To sum up we agreed with the concept that obesity leads to increased circulating levels of proinflammatory cytokines that are secreted by adipocytes thus increasing cardiovascular risk (Ikeoka et al., 2010). Moreover, circulating levels of adipokines can be used as high-throughput biomarkers to assess the obesity-related health problems, including low grade inflammation.

In conclusion: Obesity is recognized as a worldwide public health problem that contributes to a wide range of disease conditions. The development of a method for convenient prediction of obesity-related health problems represents a major challenge for public policy makers facing the epidemic of obesity. We believe that Markers of inflammation have been proposed for use in clinical practice to aid in the identification of asymptomatic patients at high risk for CVD. Thus, measurement of inflammatory markers could be used to assess the risk of developing CVD. Elucidation of the significance of circulating cytokines may provide a therapeutic target for adipokine-based pharmacological and/or interventional therapies in obesity and related complications.

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