Interactive Role of Obesity and Other Risk Factors in Egyptian Subjects with Coronary Artery Disease

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Abstract: Coronary artery disease (CAD) is a leading cause of morbidity and mortality worldwide. Obesity has been suggested as a major risk factor for this disease. This study aims to assess the relation between obesity and CAD in a selected group of Egyptian population. Other risk factors, including blood pressure, blood glucose, and lipids have also been investigated. The study included **80** patients with CAD (**mean age**: 47.86 years, males / females: 43/37), and **40** healthy controls (**mean age**: 46.15 years, males / females: 13/27). CAD patients were divided according to their body mass index (BMI) into 2 main groups: normal weigh group (BMI: 18.5–24.9, n=**40**) and abnormal weight group (BMI≥25, n= **40**), the latter group was further sub-divided into overweight group (BMI: 25.0–29.9, n= **20**) and obese group (BMI≥ 30, n= **20**).The study revealed marked increase in systolic blood pressure (SBP), and diastolic blood pressure (DBP) among CAD patients compared to normal subjects. Significant increase in serum lipids [total cholesterol (TC), triglycerides (TGs), low density lipoprotein cholesterol (LDL-C)] and glucose, as well as blood glycosylated hemoglobin (HbA1c) % were also recorded. This goes in parallel with a reduction in high density lipoprotein cholesterol (HDL-C) and NO level in all CAD patients. However, these changes together seemed to be more drastic in the obese patients comparing with control and CAD patients with normal and overweight profile. So, it can conclude that obesity confers independent risk factor for CAD, probably through influencing interaction with the traditional risk factors, such as hypertension, dyslipidemia and hyperglycemia.

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1. Introduction

Coronary artery disease (CAD) is a slow, progressive disease affecting walls of the coronary arteries (Ootaki *et al.,* 2006). It is an important health public problem in many developed nations (Yusuf*et al.,* 2004) and is also increasing in developing countries to an alarming rate (Hackam &Anand, 2003). According to global and regional projections of mortality and burden of disease, CAD will remain the leading cause of death for the next 20 years (Mathers & Loncar, 2006).

In the second half of the 20th century, Egypt has undergone dramatic socio-economic changes which resulted from a great tide of urbanization and a rise in living standards. This is reflected by a rise in the average age for both men and women and a change in the pattern of diseases. Therefore, Egypt is experiencing a tidal rise in CAD, hypertension, and diabetes (Ibrahim, 2003), while there is a decline in infectious and rheumatic heart disease prevalence. The direct assessments of CAD have shown several factors that interact together, causing development of this disease. Among these risk factors, obesity has attracted attention as a major risk factor for CAD. Obesity may affect the heart through its influence on other risk factors such as dyslipidemia, hypertension, glucose intolerance, and endothelial dysfunction which is coupled with decrease in nitric oxide (NO) secretion (Mathiassen *et al.,* 2007).

Given the above observations, the present study was undertaken to further understand the interactive role of obesity and other risk factors in the development of CAD in a number of Egyptian subjects, which may provide a new strategies for monitoring and managing this disease.

2. Subjects and Methods

Subjects

This study was composed of 80 patients with coronary artery disease (CAD) (mean age: 47.86± 0.34 years, males / females: 43/37), and 40 healthy controls (mean age: 46.15± 0.56 years, males / females: 13/27). Subjects diagnosed with stenosis 50% or more by coronary angiography in any of the coronary arteries or their branches were classified as CAD patients. CAD patients were divided according to their body mass index (BMI) into 2 main groups: normal weigh group (BMI: 18.5–24.9, n=40) and abnormal weight group (BMI ≥25, n= 40), the latter group was further sub-divided into overweight group (BMI: 25.0–29.9, n= 20) and obese group (BMI ≥ 30, n= 20).This classification was defined according to the world

health organization (WHO) recommendations, as described by Low *et al.*(2009). BMI was determined by dividing the subject's mass by the square height, typically expressed in metric units. BMI = kilograms / meters^2 (WHO, 2000). CAD patients were recruited from health insurance and private polyclinics (Mansoura), as well as, Naser institute, and Cardiology National institute, Cairo, Egypt. Control subjects were proven to have no history of cardiac disease, diabetes, hypertension and they were normal weight individuals. Hypertension was defined as having blood pressure ≥140/90 mm Hg (Chobanian *et al.,*2003).Diabetic patients was defined as having fasting blood glucose value ≥126 mg/dl (Suresh *et al.,*2008). Subjects who had smoking habits were excluded from the study. The biochemical measurements were done in the laboratories of the Genetics Unit, Children Hospital, Mansoura University, Egypt.

Methods

Clinical investigations

For all participants, echocardiography (Echo) and electrocardiography (ECG) were performed at rest and/or stress in order to define the presence, distribution, and functional status of CAD. Segmental Wall Motion Abnormalities (SWMA) has been used to define myocardial ischemia, detect coronary artery perfusion impairment, and assess cardiac function. Coronary angiography was performed in CAD patients for the assessment of the extent and severity of CAD (Christus *et al.,* 2011).

Samples collection:

Venous blood samples were collected from each examined subject after overnight fasting in two separate fractions: (a) The first blood fraction (about 3ml) was collected in polypropylene tube without anticoagulant and left to clot at 25° C for 30 min then centrifuged at 860g for 15 min to separate serum for biochemical analysis.(b)Second blood fraction (about 1ml) was collected in polyethylene tube containing 0.1% ethylene diamine tetracetic acid (EDTA) solution as an anticoagulant for determination of glycosylated hemoglobin (HbA1c)%.

Biochemical investigations

All biochemical investigations were carried out using readymade chemicals (kits) supplied by the Egyptian Company for Biotechnology (Spectrum, Egypt), according to the following methods. Fasting serum glucose was measured by the GOD-PAP enzymatic colorimetric method (Tietz, 1995). Serum cholesterol was measured by the CHOD-PAP enzymatic colorimetric method (Young *et al.,* 1975). Serum triglyceride was measured by the CPO-PAP enzymatic colorimetric method (Stein, 1987).Serum HDL-C was measured by the precipitation method (Lopez-Virella *et al.,* 1977). HbA1c % in blood was measured by the colorimetric method using Kit supplied by Cal-Tech Diagnostics, Inc (CDI, USA) (Gonen and Rubenstein, 1978). Total lipids were quantified by using kit supplied by the ABC Diagnostics, Egypt (Tietz,1976).Serum nitrite concentration (as an indicator of nitric oxide "NO" production) was measured by the colorimetric method, using Kit supplied by Biodiagnositic, Egypt (Montgomery and Dymock ,1961).Serum low-density lipoprotein cholesterol (LDL-C) was calculated according to formula applied by Ahmedi *et al.*(2008).

Statistical analysis:

Data were statistically analyzed using SPSS statistical computer package, version 17 software (SPSS 17, 2008). Quantitative variables were expressed as mean ± SE, while the qualitative variables were presented as numbers and percentages. Comparison of qualitative data was done using chi-square test ($\chi 2$). Quantitative data were compared using Independent- Samples T test or One Way ANOVA test. Statistical significance was set at $p \leq 0.05$ (Snedecor and Cochran, 1980).

3. Results

Clinical characteristics of the study subjects

Analysis of clinical characteristics of the study subjects (Tables 1 a & b), generally indicated that there was no significant difference in the mean age on comparing CAD patient to control subjects. Also, there was no significant difference when obese & overweight CAD patient groups compared with the normal weight patient group (Table 1b).

Higher prevalence of the traditional risk factor, male gender was observed in the CAD patient group when compared with the control group (32.5% vs. 53.75%). Also, there was increase but not significant in male gender prevalence on comparing overweight CAD patient group to normal weight groups. For the obese CAD patients significant increase was detected in the prevalence of females when compared with normal weight patient group. This is may be due to the susceptibility of Egyptian females to be obese more than males.

BMI tended to be significantly higher in the CAD patient when compared to control group. It was noticed that obese and overweight patient groups are characterized by significantly higher BMI relative to the normal weight patients.

CAD patient group was observed to have elevated blood pressure (DBP and SBP)which tended to be significant when compared to control group. Significant variation was also detected when the obese and overweight CAD patient groups compared to the normal weight patient group.

For the other risk factor; diabetes mellitus it was exhibited only in the CAD patient groups, the

prevalence of which was higher but non-significant in overweight and obese patient groups when compared to normal weight group (40% vs. 27.5%).

Biochemical investigations of the study subjects

As shown in Tables (2 a & b), CAD patient groups exhibited marked increases in serum total cholesterol, triglycerides, total lipid and LDL-C levels which were significant when compared to control group .On the other hand, HDL-C showed reverse behavior where decreased values were observed in patient group that tended to be significant when compared to control group. Further statistical analysis showed that serum total cholesterol, triglycerides, total lipid and LDL-C levels were significantly higher in the overweight & obese CAD patient groups when compared to normal weight patient group, while HDL-C showed significantly decreased values in these groups on comparison to normal weight patient group. Obese patients were the worst ones according these parameters.

Serum glucose was significantly increased in the patient group when compared to control subjects. At the same time, patient group showed significantly increased levels of glycosylated hemoglobin (HbA1c) % when compared to control group. For the two studied variables; serum glucose and HbA1c%; statistically significant increases were detected on comparing overweight and obese CAD patient groups with normal weight patients (Tables 2 a & b).The obese patients were the highest regarding these two parameters.

CAD patient group showed significantly decreased serum total nitric oxide levels when compared with control group. Similarly, further statistical analysis exhibited significant decreases of serum NO levels in overweight and obese CAD patient groups if compared to normal weight patient group. The lowest NO values were shown in the obese patients.

Table 1(a). Clinical characteristics of the study subjects

		Control (n=40)	CAD (n=80)
Age (years)		46.15± 0.56	47.86± 0.34
Gender	Male, n (%)	13(32.5%)	43(53.75%)[a]
	Female, n (%)	27(67.5%)	37(46.25%)[a]
BMI(Kg/m2)		23.57± 0.36	27.39± 0.54[a]
SBP(mm/Hg)		120.88±1.06	133.25 ±1.45[a]
DBP(mm/Hg)		76.00±1.05	86.19±0.94[a]
Diabetic, n (%)		0(0%)	27(33.75%)[a]

Data are presented as mean± SEM. n: number of cases, (%): percentage of cases. CAD: Coronary artery Disease; BMI: Body mass index, SBP= Systolic blood pressure, DBP=Diastolic blood pressure. $p \leq 0.05$ (significant). a=significant difference if comparing CAD patients with control subjects.

Table 1 (b). Clinical characteristics of CAD patients

		CAD (n=80)		
		Normal weight (n=40)	overweight (n=20)	Obese (n=20)
Age(years)		47.75± 0.53	47.60± 0.65	48.35± 0.54
Gender	Male, n (%)	23(57.5%)	16(80%)	4(20%)[b]
	Female, n (%)	17(42.5%)	4(20%)	16(80%)[b]
BMI(Kg/m2)		23.92± 0.39	27.76± 0.50[a]	33.97± 0.80[b]
SBP(mm/Hg)		131.50± 1.7	133.00±3.37[a]	137.00±3.27[b]
DBP(mm/Hg)		79.50± 0.62	91.25± 1.53[a]	94.50± 1.08[b]
Diabetic, n (%)		11(27.5%)	8(40%)	8(40%)

Data are presented as mean± SEM. n: number of cases, (%): percentage of cases. CAD: Coronary artery Disease; BMI: Body mass index, SBP= Systolic blood pressure, DBP=Diastolic blood pressure.$p \leq 0.05$ (significant). a=significant difference if comparing overweight patients with normal weight patients. b=significant difference if comparing obese patients with normal weight patients.

Table 2(a). Biochemical characteristics of the study subjects

	Control (n=40)	CAD (n=80)
Total lipids (g %)	628.13±11.69	1034.58±3.15[a]
Total cholesterol (mg/dl)	171.40±1.21	204.04±1.22[a]
Triglycerides (mg/dl)	90.93±3.68	140.35±1.55[a]
HDL-C (mg/dl)	43.25±0.69	39.54±1.01[a]
LDL-C (mg/dl)	89.14±1.29	137.47±1.38[a]
Glucose (mg/dl)	84.73±1.51	125.60±3.78[a]
HbA1c (%)	4.94± 0.09	7.56± 0.16[a]
NO (µmol/L)	33.33± 0.35	26.25± 0.64[a]

Data are presented as mean± SEM. n: number of cases, (%): percentage of cases. CAD: Coronary artery Disease; NO: Total nitric oxide; HbA1c%: Glycosylated hemoglobin; HDL-C: high density lipoprotein Cholesterol; LDL-C: low density lipoprotein cholesterol. $p \leq 0.05$ (significant). a=significant difference if comparing CAD patients with control subjects.

Table 2(b). Biochemical characteristics of CAD patients

	CAD (n=80)		
	Normal weight (n=40)	Overweight (n=20)	Obese (n=20)
Total lipids (g %)	1017.55±4.68	1047.75±3.44[a]	1053.45±2.90[b]
Total cholesterol (mg/dl)	199.93± 0.98	204.35±3.33[a]	211.95±2.14[b]
Triglycerides (mg/dl)	131.85± 1.39	147.55±2.91[a]	150.15±2.84[b]
HDL-C (mg/dl)	41.50± 1.71	38.70± 1.28[a]	36.45± 1.59[b]
LDL-C (mg/dl)	132.30± 2.21	140.47± 1.96[a]	144.82±1.22[b]
Glucose (mg/dl)	111.80± 3.42	134.95± 9.81[a]	148.15±3.23[b]
HbA1c (%)	6.53± 0.14	8.14± 0.27[a]	9.05± 0.13[b]
NO (µmol/L)	27.21± 1.12	25.67± 1.12[a]	24.92± 0.34[b]

Data are presented as mean± SEM. n: number of cases, (%): percentage of cases. CAD: Coronary artery Disease; NO: Total nitric oxide; HbA1c%: Glycosylated hemoglobin; HDL-C: high density lipoprotein Cholesterol; LDL-C: low density lipoprotein cholesterol. $p \leq 0.05$ (significant). a=significant difference if comparing overweight patients with normal weight patients. b=significant difference if comparing obese patients with normal weight patients.

4. Discussion

Coronary artery disease (CAD) is one of the major causes of mortality worldwide (Kim *et al.,* 2007). However, there are marked variations in the epidemic of CAD among regions of the world, nations, and even between regions within a country. Certainty, a number of risk factors including dyslipidemia, diabetes mellitus (DM), hypertension, smoking, immobility and obesity may influence these variations (Allender *et al.,* 2007). Apart from these metabolic and life style risk factors, sex difference may also be considered as a contributory factor, where CAD is more common in men than in women. Among middle-aged people, CAD is 2 to 5 times more common in men than in women (Jousilahti *et al.,* 1999).In the present study, the sex distribution for the CAD patients were 53.75% males, and 46.25% females. The study was predominantly male oriented. There is evidence that difference in the level and activity of endogenous sex hormones may play a role. Among women, estrogen is the predominant sex hormone; which may have protective effects through influencing glucose and lipid metabolism and hemostatic system (Masood *et al.,* 2010). Moreover, it may have a direct effect on improving endothelial cell function (Jousilahti *et al.,* 1999). So, it is important to consider the protective effect of estrogen regarding the less common CAD among female subjects in the present study.

Another factor to keep in consideration is obesity which is rapidly becoming a serious health problem throughout the world during the last few decades .In Egypt; it becomes an increasingly important public health concern. An estimated 35 % of Egyptian adults (18.7 % males & 48.1 % females) are considered to be obese (National Nutrition Institute, 2004) .In the present study, obesity was found to have significantly higher prevalence among females when compared with normal weight patients. This is probably due to increased susceptibility of Egyptian females to be obese more than males. In support, it has reported that the prevalence of obesity in adults is very high in Egypt, particularly among women, and that the prevalence of diabetes and hypertension parallels that of obesity (Galal, 2002). Such findings are in agreement with those of the present study that may be attributed to sociocultural factors in Egyptian communities, such as high unemployment, restricted outdoor activities and the high illiteracy rate among females (National Nutrition Institute, 2004).

Obesity can affect cardiovascular system through several ways. Indeed, a relation exists between obesity and impaired endothelial function has been suggested (Mathiassen*et al.,* 2007). Obesity can affect the cardiovascular system through its influence on endothelial function, coupled with a decrease in nitric oxide (NO) level (Poirier, *et al.,* 2006).

NO normally functions to maintain vascular homeostasis through a number of physiologic processes. One prevalent action involves the activation of soluble guanylcyclase, which then produces cyclic guanisine monophosphate (cGMP) being responsible for vasorelaxation (Dhir and Kulkarni, 2007). NO can also act directly on calcium dependent potassium channels, leading to relaxation of smooth muscle cells (SMC) .Moreover, the vasoprotective effect of NO includes promotion of endothelial proliferation and protection of endothelial cells (ECs) from apoptosis and adherence of inflammatory cells (Hengartner, 2000) thus serves to limit endothelial inflammation. A decrease in the function of NO would result in vasoconstriction and an increase in vascular resistance that may predispose to CAD. In support, the present study showed significantly decreased serum NO levels in CAD patients, particularly the obese group.

CAD is characterized by systemic endothelial dysfunction, not only of atherosclerotic vessels but also of vessels usually not prone to atherosclerosis. Due to special anatomical position of the vascular endothelium (between circulation and vascular wall) it is a primary target for a number of risk factors, which in turn cause endothelial dysfunction (Nozaki *et al.,* 2009). Dysfunction of vascular endothelium appears to be a key event in initiation, progression and complications of atherosclerosis (Vallance and Chan,

2001). One of the principal mechanisms underlying endothelial dysfunction is through increased generation of reactive oxygen species (ROS) with consequent oxidative stress (Hassanabad *et al*., 2010).

Increased ROS is suggested to play a role in coronary atherosclerosis by inducing endothelial dysfunction characterized by impaired production of NO (Balakumar *et al.,* 2009). ROS including superoxide anion (O^{2-}) can react with NO to form the reactive species peroxynitrite ($OONO^-$), thus inactivating NO and directly decreased endothelium synthesis of NO (Perona*et al.,* 2006). Consistent with this, it was reported that patients with developed coronary atherosclerosis have reduced NO bioavailability in both coronary and peripheral vasculature (Barbato and Tzeng, 2004).

It is well known that the risk of CAD is higher in diabetic patients. Diabetes mellitus (DM) is associated with a significantly higher morbidity and mortality of cardiovascular disease (CVD), with a 2–4 fold increased incidence of CAD (Raza and Movahed, 2003). Although this study was not designed to estimate the relation between CAD and diabetes, the observation of high proportion of diabetes in subjects with CAD (33.75% vs. 0 %,) has indicated that there is a high CAD risk affected by diabetes. Although DM is not itself a vascular disease; the pathophysiologic mechanisms behind development of vascular disease are accentuated in diabetics. So, they have a more aggressive form of arterial disease than do their counterparts without diabetes.

Recent trials have demonstrated that reversing the metabolic derangements of diabetes, including hyperglycemia and hyperlipidemia can reduce cardiovascular complications by as much as 50% (Joel *et al.,* 2004). In the present study, serum glucose was significantly increased in all patient subjects when compared to controls. These findings are in accordance with those of Quadros*et al.* (2007) who found that hyperglycemia was associated with CAD. Additionally, the present study showed that all patient groups have significantly increased levels of glycosylated hemoglobin (HbA1c) % when compared to control subjects.HbA1c% is an indicator of average glycemia over the previous 6 to 8 weeks, and the level of HbA1c% has been suggested as a diagnostic or screening tool for diabetes .High levels of HbA1c% were associated with raised atherosclerotic lesions and more extensive fatty streaks in the coronary artery (McGill *et al.,* 1995).

The rise in obesity triggers a parallel rise in DM, where the risk of diabetes increases between 4.5 and 9 %, for every kilogram of weight gain. Zimmet *et al.* (2001) coined the term 'diabesity' to illustrate the interdependence between these two diseases. Many studies indicated a link between obesity and the increased risk for developing diabetes (Resnick *et al.,* 1998). In the present study, the prevalence of diabetic patients was greater in overweight and obese group when compared to normal weight group (40% &40% vs. 27.5 %, respectively).Thus, indicating a positive correlation between BMI and blood sugar, as in agreement with other studies (Adamu *et al.,*2006).

Hypertension is now a global epidemic affecting 1.5 billion people worldwide and claiming about 7 million lives every year (Abubakar *et al.,* 2009). In this study, blood pressure (DBP and SBP) tended to be significantly higher in CAD patient group when compared to healthy subjects. This is in agreement with previously reported data showing a link between blood pressure levels, both systolic and diastolic and risk of cardiovascular disease (CVD) (WHO, 1999).

Hypertension is strongly correlated with BMI; it seems that with the increase in BMI, blood pressure rises in both females and males. The causal association between obesity and elevated blood pressure has been demonstrated by large population based studies .The majority of patients with high blood pressure are overweight, and hypertension is about 6 times more frequent in obese subjects than in lean men and women (Rangaswamy *et al.,* 1997).

Dyslipidemia is also an important comorbidity of obesity associated with a very high incidence of coronary and vascular events (Lamarche *et al.,*1999).One study indicated that dyslipidemia of obesity is characterized by elevated TC, TGs , LDL-C and decreased HDL-C and that dyslipidemia is associated with increased risk of CAD (Walldius *et al.,*2001). In the present study, these relations have confirmed where CAD patients exhibited marked increase in serum TC, TGs, total lipid and LDL-C levels, which were significant when compared to control group. However, HDL-C showed reverse behavior, where decreased values were observed; indicating an association between decreased HDL-C and CAD.

Recent studies demonstrated that high level of TGs is a prominent predictor for CAD independent of other cardiovascular risk factors (Imke *et al.,* 2005). High TGs levels are also associated with increased insulin resistance, and increased blood leukocyte count .Both of them may contribute to atherosclerosis and thrombosis (Tseng *et al.,* 2006). Other risk factor is the increased serum cholesterol which is causally associated with risk of CAD. Specifically, a 10% increase in serum cholesterol is associated with a 20% to 30% increased risk of CAD and elevations earlier in life may be associated with higher risk of CAD (Lo Rosa, 1990).The increased risk of CAD in association with high serum TC levels in the present study was consistent with this finding. Other studies have identified low levels of HDL-C as an independent risk

factor of CAD beside the other traditional risk factors (Weissglas and Pajukanta, 2010).

Apart from this , Glass and Witztum, (2001) have indicated that elevated level LDL-C is unique in being sufficient to drive development of atherosclerosis and vascular disease even in the absence of other known risk factors. A number of studies suggested oxidative modification of LDL-C as a key mediator in this process (Covas, 2007).Oxidative modification of LDL-C not only results in formation of oxidized LDL-C (Ox-LDL-C), but also of free radicals which may interact directly with NO reducing its bioavailability. While LDL-C has essential physiological role as a vehicle for the delivery of cholesterol to peripheral tissues, increased LDL-C levels are associated with increased risk of CVD (Glass and Witztum, 2001). On the other hand, HDL-C can be protective by reversing cholesterol transport, inhibiting the oxidation of LDL-C and neutralizing atherogenic effect of Ox-LDL-C (Yang *et al*., 2008). A greater increase of LDL-C may cause a greater decrease of HDL-C, as there is reciprocal relation between the concentration of LDL-C and HDL-C. Under hypercholesterolemic conditions, LDL-C can be oxidized through peroxidation of lipid components of this lipoprotein, leading to production of Ox-LDL-C (Covas , 2007). Such particles are not bound by LDL-C receptors, but instead taken by scavenger receptors on macrophages present in the vascular subendothelial space. Thus, intracellular cholesterol accumulates, converting macrophages into lipid laden foam cells, characteristic of early atherosclerotic lesions (Hansson, 2009). However, Ox-LDL-C was suggested also to produce other actions that promote atherosclerosis. In this respect, Zwan *et al.*(2009) reported that Ox-LDL-C may directly damage the endothelium and contribute to atheroma and plaque formation in association with vascular disease.

In conclusion, the present study provided more proof about the relation between obesity and CAD. The study also indicated a relation between obesity and other risk factors (diabetes, hypertension and dyslipidemia) whose deleterious effects are synergistically involved in the development of CAD.

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