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Original Article

Effect of Meal Size on Postprandial Lipid Profile and Endothelial Changes in Healthy Subjects

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Abstract

Background: A well balanced diet is important for normal function of endothelial cells. Diets high in fat and/or calories can lead to hypertriglyceridemia and postprandial lipidemia and thus are considered a risk factor for the development of atherosclerosis. Big meals may result in chronic elevations in the level of atherogenic lipoproteins as well as evoking chronic inflammatory response. Both may lead to pathological changes on the arterial vessel wall and myocardium.
Objective(s): To study the effect of the size of a well-balanced meal on the lipid profile in the post prandial state and its effect on the endothelial function, ventricular filling and diastolic function.
Methods: one group pretest-posttest study was carried out on 40 young healthy lean volunteers aged 30 to 39 years who after overnight fast were invited to eat a big breakfast meal. Postprandial blood samples were then drawn after 3-4 hours to determine changes induced by the big meal in the blood. On the following day, the same procedure was adopted but with a breakfast meal which contains only one third of the size of the big meal (small meal). The items of comparison between the two meals included: The changes induced by both types of meals on the lipid profile of the blood by assessing the postprandial levels of TG, TC, LDL-C, HDL-C and FFAs; assessment of the inflammatory response by assessing postprandial levels of CRP; The changes induced on endothelial cell functions by assessing the postprandial levels of ET1 and NO; and the changes induced by the two types of meals on the left ventricular function as determined by echo Doppler as well as tissue Doppler imaging (TDI).
Results: The big meal was associated with elevations in TG, TC, LDL-C, CRP, ET1 and NO (P=0.001, 0.021, 0.057, 0.110, 0.002, 0.001respectively). The small meal showed significant increase in levels of HDL-C (P=0.001) and FFAs (P=0.048). The diastolic function of the left ventricle showed significant reduction after the ingestion of the big meal versus the small meal.
Conclusions: The study concluded that big meal size negatively impact lipid homeostasis and endothelial function and the recognition of this possible danger of big meals can lead to the possibility of prevention of atherosclerosis through controlling of the meal size.

***Keywords*:** Meal size, postprandial, Lipid profile, CRP, endothelin 1, nitric oxide, diastolic function, ventricular filling

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INTRODUCTION

Cardiovascular disease (CVD) is now recognized as the leading cause of death and disability worldwide.(1) According to the latest WHO data published in May 2014 CVD deaths in Egypt reached 46% of total deaths.(2) Although CVD is a complex multi factorial disease, it is considered by some a postprandial phenomenon.(3) It has been shown that postprandial triglycerides (TG) is associated with increased remnants of apoB-48 carrying chylomicrons of intestinal origin and apoB-100 carrying very low density lipoproteins of hepatic origin in the postprandial state.(4) Postprandial TG and remnant lipoproteins are known to attain their highest concentrations 3–6 h after food intake.(5–7) Remnants are atherogenic, consistent with the idea that the progression of atherosclerotic lesions can occur in the postprandial state, a potential contributor to morbidity not assessed by current practices that focus on the measurement of fasting lipoproteins.(8) Postprandial hypertriglyceridemia, exaggerated elevations in blood glucose and free fatty

acids following a high caloric meal generates excess free radicals and oxidative stress which in turn induce inflammation and endothelial dysfunction even in healthy subjects, contributing to early stages of atherosclerosis. [9,10] Elevated postprandial TG levels have been shown to independently increase the incidence of myocardial infarction by 40% per 100 mg/dl increase.[11] Angiographic progression of coronary atherosclerosis and carotid artery intimal thickness were found to be related proportionally to postprandial TG levels.[12] Furthermore, postprandial TG levels can lead to increased vascular superoxide anion production and a subsequent decrease in the key endothelium-derived relaxing factor Nitric oxide (NO) that plays a pivotal role in the maintenance of vascular tone and reactivity bioavailability.[13] In addition, it has been reported that leukocytes, and especially monocytes, adhesion to the endothelial surface is stimulated by triglyceride- rich lipoproteins (TRLPs).[14]

The National Cholesterol Education Program Adult Treatment Panel III guidelines recommend that dietary interventions should be the first line of treatment to reduce CVD risk.[15] A well balanced diet is important for normal function of endothelial cells.[16] In this context, one form of diet therapy often suggested to improve health is altering meal frequency. Eating smaller frequent meals may reduce CVD risk more so than larger, less frequent meals.[17] However, the evidence thus far relating to the effects of meal size alone on lipid responses is lacking.

The recognition of the impact of big meals on lipoprotein homeostasis and endothelial function once established may lead to the possibility of prevention or reversal of the process of atherosclerosis through controlling the size of the meal. To shed some light on this possibility, the present work aimed at studying the effect of the size of a well-balanced meal on lipid profile in the post prandial state and its effect on the endothelial function, ventricular filling and diastolic function.

METHODS

This one group pretest posttest study comprised 40 healthy male aged 30-40 years, who agreed to participate in the study and attended the main University Hospital; Faculty of Medicine, Alexandria University with the following inclusion criteria: non-obese, free of any endocrinological, cardiovascular, hepatic or renal disease, not on medications that are known to affect blood hormones or lipid profile and non-smokers.All participants in the present study were subjected to the following:

1-Thorough history taking with special stress on eating habits, present or past history of medical illness or medications that might affect the interpretation of this study and family history of diabetes mellitus or other medical conditions.

2-Full physical examination including weight, height, waist circumference which was carried out according to criteria described by Gibson (2005)[18], body mass index (BMI) was calculated according to the formula (weight) in Kg/ (height)2 in meters and blood pressure was recorded.

3-Pre challenge laboratory tests: Complete blood picture was assessed using a Coulter automated hematological analyser [19], fasting (8-10 hours) blood glucose (FBG), 2-hours postprandial blood glucose,[20] serum TC and TG (after 14 hours fasting) were determined by standard spectrophotometric methods.[21] A modified heparin-MnCl2 method was used to determine HDL-C concentrations.[22] A modified Friedewald equation was used to determine serum LDL-C concentrations as this equation was shown to be the most accurate for determining postprandial LDL-C concentrations.[23]

4-Challenge meal: After an overnight fast, all participants were invited to eat a well-balanced low cost big breakfast meal which essentially contains carbohydrates, fats, proteins, fibers, vitamins and minerals. The meal's caloric value was 830 kcal that represents about 32% of the total caloric needs of healthy moderately active male subjects (2600 kcal/day) , the macronutrients distribution was as follow 60% carbohydrates, 15% proteins and 25% fats (Table 1).[24]

Table (1): A model of low cost big breakfast meal (test meal)

Item	Weight (g)	Conventional amount	kcal
Bread	180	One and half loaf	420
Triangular cheese	20	One	80
Cooked beans	160	Full 3 table spoons	105
Vegetable oil	15	One table spoon	135
Lemon juice	10	Half a lemon	
Arugula	60		15
Orange	150	One of medium size	75
Total Calories			830

On the next day the same subjects were invited again to eat a small breakfast meal which was only one third of the size of the big meal eaten on the day before.

5-Post challenge laboratory tests: 2-hours postprandial blood sugar level was estimated to exclude impaired glucose tolerance patients. After three to four hours of having the challenge meals blood samples were obtained for the estimation of: serum TC, TG, HDL-C, LDL-C, high sensitivity CRP level was determined by high sensitivity CRP enzyme immunoassay test kit from Biocheck [25], NO (total) detection was done using kit from ENZO Life Sciences[26], ET-1 by enzyme immunoassay for quantitative

determination of human endothelin in serum from Biomedical group[27], and Free fatty acids by Human free fatty acids ELISA for in vitro quantitative determination of human FFA concentration in serum from Biovision.[28]

6-An echo cardiogram graphic assessment of the ventricular diastolic function was done to each subject four hours after the challenge meal in 2 dimensional mode; M mode and pulsed wave Doppler to record trans mitral velocity pattern during the rapid filling phase (E wave deflection) and during the A wave deflection arising from atrial contraction. From the pulsed Doppler spectrum of the mitral flow, the following measurements were calculated: Peak velocity of early filling (E), peak velocity of atrial filling (A) and ratio E/A which represents the diastolic function of the left ventricle. Subjects were allowed to be ambulant prior and after sampling without strenuous exercise. Besides they will be prohibited from smoking, or eating while drinking water will be allowed.[29] Doppler signals from the myocardial wall were also displayed by tissue Doppler imaging (TDI) to calculate: Peak velocity of early filling (E), Peak velocity of atrial filling (A), Ratio E/A.[30]

Statistical Analysis

Data were analyzed with statistical software SPSS version 20. For descriptive statistics mean and standard deviation were used. Student's t test was used to evaluate the significance of the difference between means, a P value less than or equal to 0.05 was considered to be significant.

Ethical Considerations

This study was conducted according to the guidelines laid down for medical research involving human subjects and was approved by the ethics committee of the faculty of medicine, Alexandria University, Egypt. All measurements were taken in full privacy and the collected data were kept confidential. All participants were informed about the objective of the study and they had the right to accept or refuse to participate in the study, then their written consent was obtained.

RESULTS

The clinico-demographic characteristics of the participants are presented in (Table 2), mean age of the participants were 35.38± 2.46 years, their mean BMI, waist circumference, clinical and pre challenge laboratory values were all within normal ranges. Table (3) illustrates the postprandial response of the post challenge selected variables. The mean postprandial levels of both TG and TC were significantly higher (P=0,001), while mean HDL-C level (32.78 ± 4.70 mg/dl) was significantly lower (P=0.001) after the ingestion of the big meal. The same table also reveals that there was a significant decrease of mean FFAs after the ingestion of the big meal 1,05 ± 424 mmol/L compared to 1.94 ± 3.98 mmol/L after the ingestion of the small meal (p =0.048). As regards the effect of the diet on the level of the inflammatory marker CRP, the results obtained showed that the postprandial level of CRP after the ingestion of the big meal was higher than that obtained after the ingestion of the small meal. Although the statistical value is non significant (p=0.110) but this does not deny that there was a tendency of the big meal to result in an increase in the level of inflammatory markers in the plasma in the postprandial period. Concerning ET1and NO, the results obtained revealed that the postprandial level of both after the ingestion of the big meal were significantly higher than that obtained after the ingestion of the small meal (p=0.002 and 0.001respectivly). In the present study, the assessment of cardiac function by blood flow Doppler showed that the postprandial mean value of the velocity of blood in the early filling phase (E) after the ingestion of the big meal was significantly lower (p=0.12) than the value obtained after the ingestion of the small meal. The mean value of the velocity of blood in the late or atrial filling phase (A) after the ingestion of the big meal was nearly the same value as that obtained after the ingestion of the small meal.fig.(1)

Table (2): The clinico-demographic characteristics of the participants

Variable	Range	Mean ± SD
Age (years)	30-39	35.38±2.46
Weight (kg)	80-100	92.3±7.62
Height (cm)	169-185	182.3±12.6
BMI (kg/m2)	20.31-25.85	23.55± 1.57
Waist circumference (cm)	70-100	85.15±8.67
Systolic BP (mmHg)	100-140	123±9.58
Diastolic BP (mmHg)	70-90	80.24±6.80
FBG (mg/dl)	70-100	84.38±8.61
2 hr. postprandial BG(mg/dl)	100-140	120.55±12.09
Basal TC(mg/dl)	99-210	159.93130.58
Basal TG (mg/dl)	30-155	99.63±33.84
Hb (g/dl)	13.5- 16.1	14.55±0.80
WBC (x109/L)	4.8-6.5	5.78+0.48
Platelets (x109/L)	160-290	237.65±34.60

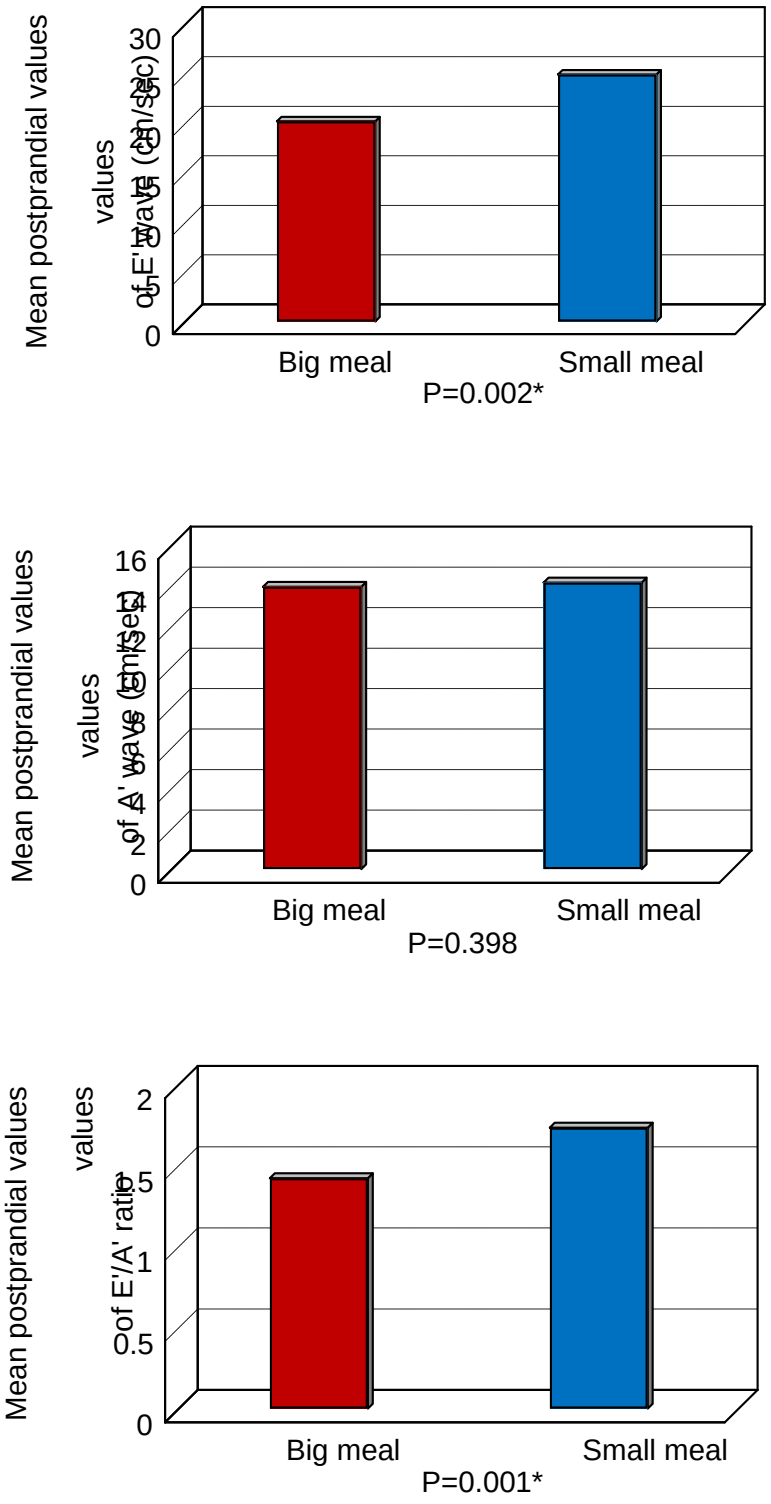

Figure (1): Comparison between postprandial tissue Doppler imaging after big and small meals

Tables (3): Postprandial response of the post challenge selected variables

Parameter	Big meal Mean ±SD	Small meal Mean ±SD	P value
Laboratory Profile			
TG mg/dl	158.28±32.51	122.58±31.37	0.001*
TC mg/dl	184.33±27.82	170.98±29.65	0.021*
LDL-C mg/dl	119.58±30.13	109.5±50±26.13	0.057
HDL-C mg/dl	32.78±4.70	38.05±5.22	0.001*
FFAs mmol/L	1,05±424	1.94±3.98	0.048*
NO mol/L	23.10±8.85	17.26±6.08	0.001*
ET1 fmol/L	1.24±0.80	0.83±0.33	0.002*
CRP mg/dl	0.04±0.04	0.03+0.04	0.110
Echo			
E (cm/sec)	72.63±14.06	79.81+13.99	0.012*
A (cm/sec)	53.06±10.57	52.58±8.93	0.413
E/A	1.38± 0.20	1.55±0.29	0.001*

*significant, P value less than or equal to 0.05

The comparison of early filling (E) and atrial filling (A) wave ratios E/A which is suggestive of diastolic function, the mean value after the ingestion of the big meal was significantly lower (p=0.001) than that obtained after the ingestion of the small meal. These results denote that the big meal resulted in significant reduction in diastolic function. Diastolic filling patterns (E' and A') studied by TDI were found to resemble those obtained by mitral inflow (E and A) patterns obtained by blood flow Doppler (Figure 1).

DISCUSSION

Postprandial state refers to that period after meal ingestion and it lasts about 3-4 hours. Many years before, the medical hazards during this period were reported especially in relation to cardiovascular system.With the cultural habit of eating three meals per day, it seems that human beings are in the postprandial state for about one third of their life spans. So, this period should take more attention to prevent the medical hazards that may occur during that time.[3] This study aimed to investigate the metabolic changes that may occur during this period specially lipid profile which is related to many cardiovascular diseases as well as what is behind these metabolic changes that may share in these cardiovascular risks as endothelial cytokine changes and lastly the impact of these changes on cardiac performance.

Our study showed that the postprandial levels of TG and TC were significantly elevated after the ingestion of the big meal versus the small meal. The increased level obtained in the big meal may be due to the postprandial increase in VLDL secretion by the liver in response to the high carbohydrate and cholesterol content of the big meal. It was found that the level of TG once elevated by a big meal in the postprandial period will be further stimulated by the next meal, therefore repeated diets high in carbohydrates may lead to continuous high TG plasma levels in healthy subjects which may represent a continuous threat of damage of the endothelial lining of the arterial tree.[31] The effect of a big meal becomes exaggerated when there is lack of insulin secretion or non response of the adipose tissue and the liver to secreted insulin. In such cases big meals may raise the postprandial triglyceride levels to as much as three folds more than that in healthy subjects.[32] In addition high levels of TG can exaggerate the procoagulant activity of the blood which can lead to thrombus formation.[33]

The postprandial higher levels of LDL-C reported in our study after the ingestion of the big meal is probably due to the higher levels of LDL-C precursors lipoprotein VLDL produced by the liver after the ingestion of the big meal. Pathological high levels of LDL-C can occur when excess of LDL-C particles production is accompanied by a defect in LDL-C degradation by peripheral tissues. The latter can occur if there is a defect in lipoprotein B 100 receptor expression in the liver and peripheral tissues. The resultant high level of LDL-C becomes a major factor in the genesis, progression and complications of atherosclerosis in these individuals.[34]

In contrast, the mean value of HDL after the ingestion of the big meal was 32.78 ± 4.70 mg/dl which is considered risky because it is lower than the borderline level (35mg/dl). On the other hand the mean value of HDL after ingestion of the small meal was 38.05 ± 5.22 mg/dl which is above 35mg/dl and is considered as desirable level. HDL particles interact with excess cholesterol deposited in peripheral cells and macrophages and transport it to the liver to be excreted in bile. Therefore HDL particles are protective to endothelial cells from deposited LDL-C cholesterol.[35] As small meals are associated with significantly high levels of HDL, they are considered as an important factor guarding against endothelial damage from excess LDL-C cholesterol and may lead

to regression of already developed atherosclerotic lesions.

Postprandial levels of free fatty acids were significantly higher after the ingestion of the small meal versus the big meal. Plasma free fatty acids concentrations are at the highest level after overnight fast during which the body needs to draw upon its stored fat as the only source of energy. Their levels increase as a result of activity of hormone sensitive lipase (HSL) enzyme on intracellular TG. The activity of this enzyme is enhanced in the fasting state when insulin secretion is minimal.[36] After the ingestion of the big meal there is significant increase in the secretion of insulin more than that produced by the small meal, therefore there is less suppression of the activity of HSL after ingestion of the small meal than after ingestion of the big meal. As a result small meals are associated with more lipolytic activity and on the long term may be effective in the reduction of body weight.

Regarding the effect of meal size on the level of the inflammatory marker CRP, the results obtained revealed that the mean postprandial level of CRP after the ingestion of the big meal was higher than that obtained after the ingestion of the small meal. It is now generally accepted that each meal provokes an inflammatory response which is transient in duration and of low intensity compared with a classical inflammatory disease.[37] Its importance is derived from the fact that most of the population is in almost constant postprandial state.[38] The quantity and quality of the diet plays a central role in the physiology and pathophysiology of the postprandial inflammatory response.[37] LDL-C taken up by macrophages represents the link between hyper cholesterol level and endothelial vascular inflammation through the release of inflammatory mediators by the immune cells. The inflamed endothelial cells secrete cellular adhesive molecules CAM which is the first step in penetration of macrophages into the vessel wall that starts the process of atherosclerosis.[39] Macrophages laden with LDL-C represent a major contributor to generation of reactive oxygen species ROS which is responsible for oxidation of LDL-C and the resultant oxidized LDL-C is 10 times more atherogenic than LDL-C.[40]

The significantly higher level of ET1 reported in our study after ingestion of the big meal may be due to excess expression of inflammatory cytokines produced by the big meal. This denotes that the big meal can lead to generalized vasoconstriction, expression of inflammatory cytokines, increasing smooth muscle cell proliferation and may be a contributing factor in development of essential hypertension and on the long run may induce myocardial hypertrophy.[41] The significant elevation of NO levels after ingestion of the big meal is the natural mechanism by which the blood vessels are protected against the injurious effects of ET1 and against other metabolic derangement which can be produced by the big meal. Shear force has been established as the most important regulatory factor of NO production.[42] NO is considered the major atheroprotective element as it is involved in the regulation of LDL-C uptake and metabolism, prevents inflammation of the vessel wall and it is involved in the reduction of the overall intracellular oxidative stress.[43]

The effect of the big meal on diastolic function of the left ventricle was not studied before. The present study showed that the postprandial values of early diastolic filling E as studied by Doppler flow and E' as studied by TDI were significantly lower after the ingestion of the big meal than that obtained after ingestion of the small meal denoting that the bigger the meal size of the diet, the lower the relaxation rate of the left ventricle. This result is important if we consider it in the light of other factors which influence the rate of relaxation of the left ventricle. Studies in world literature proved that the earliest dysfunction of the human heart affects the early filling phase of diastolic function. It was found that the E wave decreases with increasing age and this contributes significantly to symptoms in this age group who show normal or nearly normal systolic function.[44] The exact mechanism by which the big meal size results in decrease in the relaxation rate of the left ventricle and the mechanism by which the low caloric meal results in significant improvement in the relaxation rate of the left ventricle is explained by the fact that the relaxation phase of the myocardium is an active energy dependent process. The dislodgment of the actin and myosin proteins in the myocardium that occurs during the relaxation phase needs more blood supply and more energy. And it is known that during the postprandial state there is shift of blood flow from the systemic to the portal circulation. This is in addition to the endothelial changes that involve significant release of ET1 after the big meal which is important vasoconstrictor.[45]

CONCLUSION & RECOMMENDATIONS

The authors concluded that the final impact of the big meal on the human being health status includes a significant decrease in the left ventricular diastolic function which is an early era of frank left ventricular failure. Big meal size negatively impact lipid homeostasis and endothelial function, additionally it promotes a state of lipogenesis contributing to the increased prevalence of obesity with its well-known risk for cardiovascular diseases. The recognition of this possible danger of big meals can lead to the possibility of prevention of atherosclerosis through controlling of the meal size.

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Conflicts of Interest

None to declare.

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