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The Relationship between Umbilical Obesity and Coronary Atherosclerosis Study in Monozygotic Goat Twins

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Abstract We have recently proved that; there is a close relationship between umbilical obesity and coronary atherosclerocalcifications. We have investigated 36 monozygotic male goat twins relationship between umbilical obesity and coronary atherosclerosis. Randomly selected 12 goats were left to graze in open pasture (B), and the remaining 24 were kept in stables and pens (A), and fed the identical feed. The A group goats were observed having all umbilical obesity and also after slaughter process, more prominent epicardial fat tissue were seen macroscopically. The remaining unslaughtered 12 goats of Group A were treated for atherosclerosis for 6 months, using a combination of drug. All of the Group A goats had indicators of obesity in their body and visible epicardial fat tissue was observed, atherosclerocalcific plaques were found in the coronary artery, and some narrowing was observed in artery lumens. Making a comparison between Group A and Group B was found statistically significant (p=00001) our results. The remaining 12 goats were treated for atherosclerosis for 6 months, using a combination of drugs. Following the treatments, very little epicardial fat tissue was observed, and 8 of the goats had perfectly normal coronary arteries with the remaining four having minimal atherosclerosis plaques. The Group A goats had significant obesity unlike Group B as well as epicardial fat tissue and significant coronary atherosclerocalcifications. Moreover, the unslaughtered ones of Group A were treated with ideal drugs, epicardial fat tissue and coronary atherosclerosis declined significantly compared to their co-twins that did not receive this treatment.

Keywords Umbilical obesity, Coronary atherosclerosis, Pericardial fat

1. Introduction

Despite the steady progress in the treatment of atherosclerotic and atherothrombotic cardiovascular diseases, coronary artery diseases and myocardial infarctions continue to be significant causes of morbidity and mortality, especially in industrialized countries. The term atherosclerosis refers to the thickened and hardened lesions, which have lipids and at the end calcifications in the intimae and media of elastic and muscular arteries. To date, the primary cause of arterial atherosclerotic calcifications has not yet been elucidated. It is generally accepted that atherosclerotic and calcified lesions first appear and develop within the innermost layer of the arteries (at the intimae) (Figure 1).

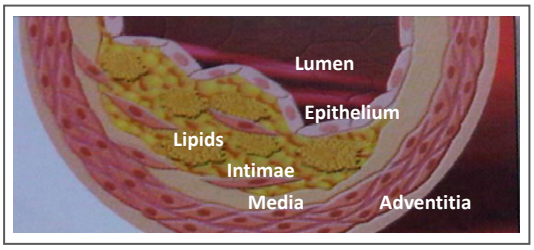

Figure 1. Classical pathway and accumulation of the lipids core in the intimae have been shown in this figure

Formation and progression of atherosclerotic plaques and calcifications in all arterial beds of intimae have been well documented by AHA (American Heart Association) and many authors, such as V. Fuster and E. Falk [1-4], who subdivided the formation and progression of these plaques into several phases. As known, atherosclerosis plays a major role in development of arterial calcification. Non-conjugated matrix GLA and osteonegrin proteins are also effective in the formation of this calcification [5-7]. Most lipids deposited in atherosclerotic lesions

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(atherosclerotic components) are derived from plasma low-density lipoproteins (LDLs) that enter the vessel wall through injured or dysfunctional endothelium. Within the normal population, fatty streaks often appear in the aorta and coronary arteries starting from the ages of 5 to 10; these are considered as the initial/starting points of plaque development. The classical pathway or famous well known cascade of the atherosclerosis brings about the formation of the atheroma in 1995 by AHA of atherosclerotic lesions [1-3]. This pathway of formation of atherosclerosis and calcifications almost universally were accepted in the intimae (under the endothelium). In spite of the fact that, there is no any doubt of this classical pathway or rule of the cascade of formation of atherosclerotic calcifications. Atherosclerosis is a focal disease in the intimae of large and medium sized systemic arteries. It has been well documented that, focal calcification in atherosclerotic plaques is very common in humans' arteries and nicely shown that coronary calcification in adults is almost always atherosclerosis related intimae until today [8, 9]. Arteries produce more than 250 active substances. These more than two hundred fifty factors can reach all tunicas of the arteries, as well as the adventitia, through the vasa vasorum and the neighborhood of epicardial lipid mass (Figure 2).

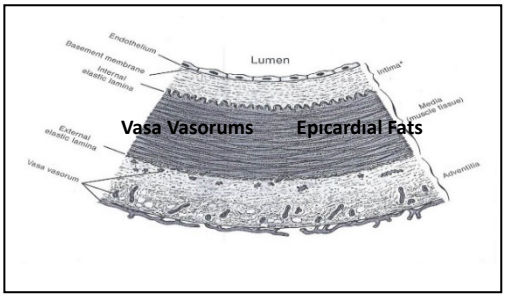

Figure 2. This figure shows epicardial fats tissue, vasa vasorums and tunicas of an artery (endothelium, intimae, tunica elastica interna, media, tunica elastica externa and adventitia)

In our recent studies, the adventitial calcifications develop more rapidly than the subendothelial (the intimae) calcified plaques. On the other hand, the medial calcifications develop far more frequently on the subendothelium of the aorta and its main branches, such as the carotid, vertebral, cerebral, renal, mesenteric, ilio-femoral, and peripheral arteries. Interestingly, the formation of calcified plaque begins more frequently beneath the subepithelium of the adventitia, and quickly develops towards to the lumen of arteries, following the same classical and accepted cascade on the coronary arteries. These calcifications mostly begin in the middle of the atheromatous component. Cholesterol (particularly oxLDL=oxidized low-density lipoproteins) and macrophage cells easily arrive to the adventitia by vasa vasorums of the coronary arteries from blood and/or through diffusion from epicardial fat accumulation around the heart appears in three different types: a) Intracellular in the heart, b) Epicardial and c) Pericardial adipose tissue around the heart. Intracellular fat is the microscopic lipid accumulation within the cytoplasm cardiac myocytes, and can result from myocardial ischemia, cell damage and/or cell death. The epicardial fat tissue is located between the outer wall of the myocardium and the visceral layer of pericardium, while the pericardial fat exists anterior to the epicardial fat layer and therefore located between visceral and parietal pericardium. Due to the close anatomic relation between myocardium and the epicardial fat, the two tissues share the same microcirculation. Through the vasa vasorums, diffusion way or potential interactions through paracrine and vasocrine mechanism between epicardial fat and adventitia of coronary arteries or myocardium are strongly suggested [10].

In our recent studies, we have shown that there is a statistical relation between umbilical obesity and adventitial atherosclerosis. This statistical calculations were performed by Dr Ozdemir by using SPSS [10, 11].

2. Subjects and Methods

This study was conducted with 36 monozygotic male goat twins older than 6 months, and lasted two years. At the beginning of the study (at age of 6 months), weights of the goats were between 25-40 kilograms and after 6 months (at the age of 1 year) between 45-65 kg. At the end of the study (after therapy) their means weights became between 45 and 55 kilograms same as non-prominent umbilical group (Table 1). Ethical committee approval was received from Istanbul University, Medical Faculty of the Advanced Research Laboratory.

Table 1. Before and after therapy change of measures

	Group A Means total weight	Group B Means total weight	Group A Means prominent umbilical weight, belly circumference and neck circumference	Group B Means non-prominent umbilical weight, belly circumference and neck circumference
Before therapy	At the beginning (age of 6 months) 30-40 kg After 6 months (age of 1 year) 50-65 kg	At the beginning (age of 6 months) 25-35 kg After 6 months (age of 1 year) 45-55 kg	At the beginning (age of 6 months) 1-2 kg 90-97 cm 27-34 cm After 6 months (age of 1 year) 2-4 kg 122-130 cm 40-47 cm	At the beginning (age of 6 months) 200-400 gram 85-92 cm 25-30 cm After 6 months (age of 1 year) 600-800 gram 117-122cm 36-40 cm
After therapy	45-55 kg	45-55 kg	600-800 gram 117-122cm 36-40 cm	600-800 gram 117-122cm 36-40 cm

All of the goats also underwent MSCT (multislice computerized tomography) by sedation for investigation of coronary arteries (Figure 3). All of the slaughtered goats' coronary arteries were investigated recurrent pathologically (macroscopically and microscopically). In the beginning of the study (at age of 1 year), the goats have weights of prominent umbilical obesity are between 2 and 4 kilograms (Group A) and the other group have weights of non-prominent umbilical obesity are between 600-800 grams (Group B). While means belly circumference of Group A were between 122 and 130 cm, means belly circumference of Group B were between 117 and 122 cm (Table 1). In addition, measurements of neck circumferences were given in Table 1.

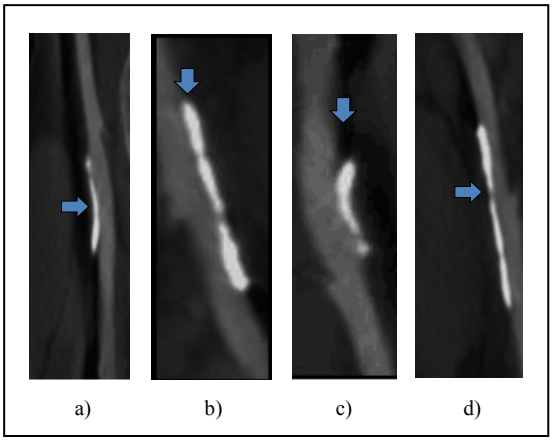

Figure 3. Adventitial atherosclerocalcifications (atheromatous components) of on the femoral arteries of a) Guinea pig, b) Rabbit, c) Goat, d) Mouse. The grey areas are soft plaque (lipids core), the white areas are calcified plaques

Randomly selected 12 goats were left to graze in open pasture (Group B), and the remaining 24 were kept in stables during winter and in pens during summer (Group A), and fed the identical feed (branches and grass) consumed by the grazing group for 6 months. All of the grazing goats and 12 of the stable goats were slaughtered at the end of six months (when they turned one).

These Group A goats were observed having all umbilical obesity and also after slaughter process, more prominent epicardial fat tissue were seen macroscopically all of them (Figure 4a-b).

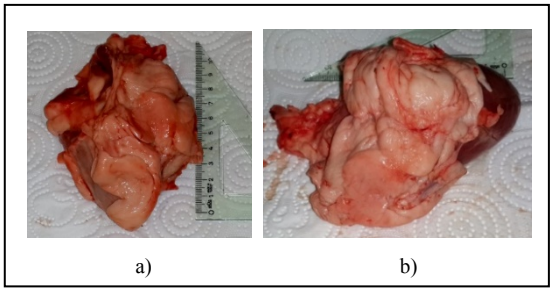

Figure 4a-b. These figures show more prominent epicardial fat tissue were seen goats having umbilical obesity

In addition to these, the remaining 12 of Group A goats which were kept in stables and had umbilical obesity, were treated for atherosclerosis for 6 months, using a combination of 4+3=7 drugs [(Menaquinone-7 50-100micg, Ubiquinol 100mg, Omega-3 1200mg, Plant Stanol Ester 2000mg, Atorvastatin 20mg, Clopidogrel 75mg, Acetylsalicylic Acid 100mg) (Table 2a-b)].

Table 2a. Erzengin's Polypill combination

Erzengin's Polypill is:

MENAQUINONE-7 (VIT. K 2), 50-100 micg. (Note: found in Soybeans and green lentils)
OMEGA 3 (Eicosapentaenoic Acid – EPA and Docosahexaenoic Acid - DHA), 1200 mg.
PLANT STANOL ESTERS, 2000 mgr.
COENZYME QH (Ubiquinol) or COENZYME Q10 (Ubiquinon10), 100 mg.

+

AGGRESSIVE ANTI-LIPIDS,
ANTI-AGGREGANTS or ANTI-PLATELLETS,

Table 2b. Usage of Erzengin's Polypill combination

Combination drugs	Dozages	Times
Menaquin-7 50-100micg	2micg/kg	Once a day
Ubiquinol 100mg	2mg/kg	Three times a day
Omega 3 1200mg	50mg/kg	Once a day
Plant sterenol ester 2000mg	100mg/kg	Once a day
Atorvastatin 20mg	1mg/kg	Once a day (night time)
Clopidogrel 75mg	3mg/kg	Once a day
Acetylsalicylic acid 100mg	4mg/kg	Once a day

Following the slaughter at the end of six months of treatment, very little epicardial fat tissue was observed, and properly conducted coronary artery cross sectional analysis showed that 8 of the goats had perfectly normal coronary arteries both in macroscopic and microscopic terms, with the remaining four having minimal atherosclerosis plaques (Figure 5a-b).

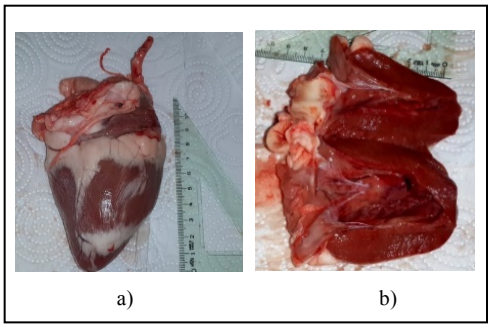

Figure 5a-b. This figures show no epicardial fat tissue were seen goats having less umbilical obesity treated with medically

3. Results

All of the grazing goats (Group B) and 12 of the stable goats (Group A) were slaughtered at the end of six months (when they turned one); none of the 12 goats in the grazing group (Group B) had any indicators of obesity in their waist, neck or abdominal regions, and no trace of epicardial fat was found in their hearts. In addition, during properly conducted coronary artery cross sectional analysis, macroscopic and microscopic inspection of the layers (Adventitia, Media, Intima) of the coronary artery showed that there were no atherosclerotic or calcific plaques in any of the layers, and the coronary arteries were found to be perfectly normal (Group B, Figure 5a-b).

All of the goats kept in stables and pens (Group A) had indicators of obesity in their waist, neck and abdominal regions, and in heart examinations following the slaughter of randomly selected 12 of these goats that turned one, visible epicardial fat tissue was observed, atherosclerocalcific plaques at various stages of development were found in the adventitia and Intima layers of the coronary artery, and significant (medium-advanced) narrowing was observed in artery lumens (Group A). The comparison between Group A and Group B showed that differences in epicardial fat tissue and coronary artery plaques were statistically very significant (p=00001).

The remaining 12 goats were treated for atherosclerosis for 6 months, using a combination of (4+3=7) drugs (Menaquinone-7 50-100micg, Ubiquinol 100mg, Omega-3 1200mg, Plant Stanol Ester 2000mg, Atorvastatin 20mg, Clopidogrel 75mg, Acetylsalicylic Acid 100mg) (Table 2a-b). Following the slaughter at the end of six months of treatment, very little epicardial fat tissue was observed, and properly conducted coronary artery cross sectional analysis showed that 8 of the goats had perfectly normal coronary arteries both in macroscopic and microscopic terms, with the remaining four having minimal atherosclerosis plaques. Significant narrowing was not observed in any of the goats in this group. The differences between the results from this group and the pasture grazing group were found to be statistically insignificant.

4. Discussion

Thus, our surprising findings were that the formation of the atherosclerotic and calcified plaques begin and develop not only in the intimae or media (Mönckeberg's Sclerosis), but also on the adventitia (Erzengin's Arterial Atherosclerotic Calcifications) of the coronary arteries and/or all of the medium and large arteries [11-12]. We suggest that the formation of the Adventitial Atherosclerotic calcifications is caused by vasa-vasorums and/or diffusion from the epicardial adipose tissues around the pericardium.

5. Conclusions

The main findings of this study, which was conducted over a two-year period with 36 (18 pairs) identical monozygotic goats, are as follows:

1) Twin subjects raised in stable and pen, had significant obesity in their bodies, unlike those raised in mobile conditions in open pasture, as well as epicardial fat tissue and significant coronary adventitial atherosclerosis.
2) It was found that when twins raised in stable and pen, were treated with ideal drugs, epicardial fat tissue and coronary atherosclerosis declined significantly compared to their co-twins that did not receive this treatment.
3) This study is the first in the literature which is conducted with monozygotic twins.
4) In this study, we couldn't assessed the other criteria of the Metabolic syndrome (such as blood pressure, blood cholesterol and sugar levels etc) (for that time being), but we can also assume that this study suggests the connection between Metabolic syndrome and atherosclerosis.

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