Is It Possible to Predict the Atherosclerosis in Aorta by the Patients Lipids Panel?

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Abstract

Background and Aim: Atherosclerosis is a chronic inflammatory event that characterized by stiffness and thickening of the vascular walls. In our daily practice, we assume the atherosclerotic potential of the patient by following the total cholesterol, HDL, LDL and triglyceride levels (Lipids panel). We aimed to understand the relation between the HDL, LDL, cholesterol levels and the atherosclerosis in large vascular structures such as ascending aorta.

Methods: We have searched for atherosclerosis in the aortic tissue samples with 48 patients. It is a study in which we examine the correlation of preoperative cholesterol values (HDL, LDL, triglyceride, total cholesterol) by dividing the patients into two groups according to the presence of plaque.

Results: 43 males (89.6%), and 5 females (10.4%) patients between 39 and 81 years of age were included in the study. There was no statistically significant difference between the patients' preoperative cardiovascular risk assessments. The free T3 values were within the normal range with of all patients, however there was a difference that patients in the non-atherosclerosis group have lower values. There was no statistically significant difference between two groups' HDL, LDL, total cholesterol, triglyceride parameters.

Conclusion: As a result, in our study, no significant difference was found between HDL-C, LDL-C, triglyceride, total cholesterol values and the pathological process of aortic atherosclerosis. As a result of this study, we believe that it was necessary to correct the error margins of these parameters. In addition, it required the need for a clearer laboratory parameter to demonstrate atherosclerosis.

Introduction

There are many reasons among cardiovascular risk factors (CVRF), and the most important of these are diabetes mellitus (DM), smoking, high body mass index (BMI), high blood pressure and atherosclerosis. The actual number of patients with atherosclerosis and cardiovascular disease is quite high, even if their cardiovascular risk are resulted low. Atherosclerosis remains as an important risk factor with coronary artery disease and peripheral vascular diseases in middle-age asymptomatic patient groups where there are no other risk factors mentioned. In middle-age group patients with low CVRF, it is seen that if they are classified by coronary artery classification or carotid ultrasound, approximately 60% of them have subclinical atherosclerosis.

Atherosclerosis is a chronic inflammatory event that characterized by stiffness and thickening of the vascular walls. Local vascular damage, inflammation and oxidative stress are the basis of its pathology. Vascular endothelial damage can be count as the first step of this process. Platelet and leukocyte adhesion and lipid accumulation occur in this damaged area. These adhesive cells release endothelial-induced growth factor and therefore cause smooth muscle cell proliferation. Atherosclerotic plaque has content rich in cholesterol and fatty acid. Besides, lipoproteins responsible with carrying cholesterol and fatty acid which makes it significantly important for plaque build-up. Relationship between atherosclerosis and low-density lipoproteins (LDL) was described in the study of Austin et al. for the first time. LDL is a cholesterol-rich triglyceride-poor molecule. Goldstein at al. defined the LDL receptors, thus we now have more detailed information about LDL. It is known that there is an inverse proportional relationship between triglyceride and high density lipoprotein (HDL) levels. It is considered that HDL does its work by moving cholesterol in the opposite direction. Indeed, HDL reduces atherosclerotic plaque build-up by protecting the LDL from oxidation. Also, triglyceride (TG) has an effect on atherosclerosis independently from HDL and LDL. Increase in TG level causes a decrease in serum HDL level and an increase in LDL. Under normal circumstances, TG does not accumulate in the vascular wall normally, but it tends to pass to the sub-endothelial cavity through the damaged endothelium when TG-rich lipoprotein levels increase in blood. This pathologic accumulation increases oxidation and smooth muscle proliferation, and
contributes to the formation of atheroma plaques. In the light of these, in our daily practice, we assume the atherosclerotic potential of the patient by following the total cholesterol, HDL, LDL and triglyceride levels (Lipids panel). According to the patients' laboratory results, we determine our anti-atherosclerotic treatment so as to reduce cardiovascular risk. In this study, we aimed to understand the relation between the HDL, LDL, cholesterol levels and the atherosclerosis in large vascular structures such as ascending aorta.

**Methods And Materials**

**Study Design**

For 10 weeks starting in June 2019, we evaluated the patients who underwent coronary artery bypass grafting due to isolated coronary artery disease. Only elective cases with patients over 18 years of age were included in the study. Emergency cases and patients who had full arterial grafts were excluded from the study. HDL, LDL, triglyceride and total cholesterol levels were checked preoperatively. We have searched for atherosclerosis in the aortic tissue samples with 48 patients. It is a study in which we examine the correlation of preoperative cholesterol values (HDL, LDL, triglyceride, total cholesterol) by dividing the patients into two groups according to the presence of plaque.

**Laboratory Evaluation**

Venous 8 milliliters (ml) of blood was drew from each patient into tubes without anticoagulants. These blood samples were left for clot formation for 20 minutes before centrifugation for a minimum of 10 minutes at 4000 rpm within total 30 minutes. Total cholesterol, triglyceride, HDL-cholesterol (HDL-C) plasma concentrations of the serum samples were evaluated with enzymatic chemical cleaning method using Cobas 6000 (Roche Diagnostics GmbH, Mannheim, Germany). LDL cholesterol(LDL-C) values were calculated by the Friedewald formula. The threshold value for HDL-C is 45 mg / dl, 70 mg / dl for LDL-C (for high-risk patients), 200 mg / dl for triglyceride, 200 mg / dl for total cholesterol. Accepted values for LDL should be < 100 mg / dl in moderate risk group, and < 70 mg / dl for high risk groups. Since all of our patients were at high risk, our threshold value in LDL is also 70 mg / dl.

**Sampling the ascending aortic tissue**

The proximal anastomoses of saphenous vein grafts are performed on the aorta while coronary artery bypass grafting (CABG). We chose the correct region for anastomoses after manual examining the presence or absence of hard plaque in the aortic tissue. While aortic side or cross-clamping during the CABG, a small incision was made on the aorta using No: 11 scalpels. After that, aortic tissue samples were taken by using aortic punch (IBC Aortic Punch size: 4.0 mm / 4.4 mm ®) (Fig. 1)

**Pathology Evaluation**

The aortic tissue samples stored with gluteraldehyde solutions under sterile conditions and taken to the pathology laboratory. Tissue samples were processed by routine clinical laboratory methods, being fixed in 10% formaldehyde and embedded in paraffin wax. Tissue sections were cut, using a microtome, at 5 micrometer thickness, placed onto glass slides, and the sections were stained with hematoxylin and eosin(H&E) and examined under the light microscope. Histochemical evaluation was done with orcein.

Vascular atherosclerosis were classified as AHA lesion type I, II, III, IV, V or VI plaques by two independent reviewers blinded to histopathology. Figure-2) (Table-1) In histopathologic examination, the evaluation of type 3,4,5 and 6 was considered significant in terms of atherosclerosis in our study and was selected into atherosclerosis group.
Type 1  
Initial lesion (isolated macrophage foam cells)

Type 2a  
type prone to progression of atherosclerosis (mainly intracellular lipid accumulation)

Type 2b  
type resistant to progression of atherosclerosis

Type 3  
Pre-Atheroma (type 2 + small extracellular lipids pool)

Type 4  
Atheroma (type 2 + core of extracellular lipid)

Type 5a  
Fibro atheroma (lipid core + fibrotic layer or multiple lipid core)

Type 5b  
Calcific lesion (fibrotic layer, mainly calcific)

Type 5c  
Fibrotic lesion (fibrotic layer, mainly fibrotic)

Type 6  
Lesion with surface defect, and/or hematoma-hemorrhage, and/or thrombotic deposit (surface defect, hematoma-hemorrhage, thrombus)

Table 1
Atherosclerotic Lesions in Histological Classification (Appearance With the Eyes)

**Statistical Analysis**

SPSS v21.0 and Microsoft Office Excel 2016 were used for data collection and analysis. Categorical variables are expressed in frequency (n) and percentage (%), while continuous variables were expressed as mean ± standard deviation and median (smallest-largest value). The suitability of the data to normal distribution was evaluated by the coefficient of variation, histogram curves and Shapiro Wilk Test. While chi-square test and fisher's exact test are used to evaluate the difference between groups for categorical variables; Independent groups t test was used if normal distribution conditions were provided in evaluating the difference between two independent groups for continuous variables. In cases where normal distribution conditions are not met, Mann Whitney U test was used. Statistical significance value was taken as p < 0.05 in the analyzes.

**Results:**

| No Atherosclerosis | Atherosclerosis | P value |
|--------------------|-----------------|---------|
|                    | Mean ± std      | Median  | Mean ± std | Median  |         |
| Age                | 64.91 ± 8.91    | 65(48-83)| 59.50 ± 10.54| 58.5(39-76) | 0.076‡  |
| Smoking (Pack-year)| 27.44 ± 27.57   | 25(0-100)| 21.57 ± 18.23| 18.5(0-55)  | 0.755*  |
|                      | ECO (EF%)          | Ascending Aorta | BMI (Kg/m²)         | WBC                  | Lymphocyte           | Neutrophils         | Hematocrit           | Creatinine           | TSH                   | Free T3               | HbA1c(%)            | Total Cholesterol    | HDL (mg/dl)          | LDL (mg/dl)          | Triglycerides (mg/dl) | Albumin               | CRP                   | Total Bilirubin      | Direct Bilirubin     |
|----------------------|-------------------|----------------|---------------------|-----------------------|----------------------|---------------------|---------------------|---------------------|----------------------|----------------------|---------------------|----------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
|                      | 52.53 ± 9.18      | 35.35 ± 3.47   | 26.88 ± 4.74        | 8.27 ± 2.32           | 1.99 ± 0.92          | 5.30 ± 2.10         | 38.49 ± 4.18        | 0.91 ± 0.21          | 1.98 ± 1.87          | 2.94 ± 0.38           | 5.4 ± 0.3            | 173.91 ± 41.36       | 41.42 ± 12.53        | 115.24 ± 40.44       | 167.61 ± 105.06      | 4.20 ± 1.03           | 11.71 ± 17.48        | 0.63 ± 0.29          | 0.22 ± 0.09          |
|                      | 57.5(32–60)       | 35(30–45)      | 26.55(20.2–40.4)    | 8.15(4.6–14.6)        | 1.8(0.9–5.7)         | 4.95(1.2–12.5)      | 39.35(28.8–46.4)    | 0.9(0.5–1.69)        | 1.55(0.03–10.47)     | 2.97(2.03–3.58)       | 5.3 (5.0–5.8)        | 165(109–276)         | 40(21–80)           | 109(59–210)          | 144(53–528)          | 4.14(3.13–9.54)      | 4.5(0.5–63)           | 0.57(0.23–1.42)      | 0.21(0.09–0.44)      |
|                      | 55.07 ± 6.12      | 35.07 ± 4.78   | 27.47 ± 3.12        | 8.12 ± 2.35           | 2.21 ± 0.82          | 5.43 ± 2.03         | 37.35 ± 3.85        | 0.90 ± 0.34          | 1.53 ± 0.75          | 3.28 ± 0.54           | 5.6 ± 0.2            | 156.79 ± 36.36       | 42.57 ± 15.41        | 99.64 ± 29.95        | 148.21 ± 89.68       | 4.25 ± 0.43           | 7.16 ± 6.06          | 0.65 ± 0.35          | 0.26 ± 0.11          |
|                      | 57.5(42–60)       | 36(28–47)      | 27.38(22.77–33.06)  | 7.9(5.1–13)           | 1.9(1.5–4.2)         | 4.85(2.7–9.4)       | 37.7(30.44–44.3)    | 0.82(0.54–1.8)       | 1.59(0.7–3.53)       | 3.3(2.22–4.45)        | 5.4 (5.0–5.9)        | 149(107–223)         | 36(22–67)           | 99.5(53–143)         | 127(58–420)          | 4.19(3.62–5.01)      | 7.4(1.1–22)          | 0.53 ± 0.35          | 0.28(0.06–0.46)      |
|                      | 0.535*            | 0.820‡         | 0.460*              | 0.733*                | 0.270*               | 0.981*              | 0.383‡              | 0.266*              | 0.517*               | 0.018‡               | 0.518*              | 0.186‡              | 0.735*              | 0.221*              | 0.537*              | 0.266*              | 0.785*              | 0.916*              | 0.226‡              |

(*: Chi-square test was applied. Fisher exact test was performed. ECO: Echocardiography, BMI: Body mass index, WBC: white blood cell)

Table 2

Preoperative baseline values according to the presence of atherosclerotic plaque.

There were 48 cases in our study. All of these patients had an elective isolated CABG. And then, all of them were
in the high-risk patient group according to the 2019 ESC / EAS dyslipidemia guidelines for the management of dyslipemias. 43 males (89.6%), and 5 females (10.4%) patients between 39 and 81 years of age were included in the study. There was no statistically significant difference between the patients' preoperative cardiovascular risk assessments. (Table-2). The free T3 values were within the normal range with of all patients, however there was a difference that patients in the non-atherosclerosis group have lower values. There was no statistically significant difference between two groups' HDL, LDL, total cholesterol, triglyceride parameters. All other preoperative results are presented in Table-2. 9 (18.75%) patients have a two-vessels bypass, 26 (54.2%) of them three-vessels, 8 (16.7%) of them four-vessels, 5 (10, 4%) of them five-vessels bypass. We took tissue samples from one side or both sides of the ascending aorta. 40 tissue samples were taken from the right side of the ascending aorta, and 12 of them resulted in atherosclerosis group. Another 44 samples were taken from the left side, and 4 had atherosclerosis. With two patients, atherosclerosis was observed in both the left and right side of the aorta.

|                               | No Atherosclerosis | Atherosclerosis | p value |
|-------------------------------|-------------------|-----------------|---------|
|                               | n     | %    | n     | %    |
| Gender                        |       |      |       |      |
| Male                          | 31    | 72.09| 12    | 27.91| 0.621‡ |
| Female                        | 3     | 60   | 2     | 40   |
| Diabetes Mellitus             |       |      |       |      |
| (-)                           | 18    | 66.67| 9     | 33.33| 0.471* |
| (+)                           | 16    | 76.19| 5     | 23.81|        |
| Hypertension                  |       |      |       |      |
| (-)                           | 13    | 68.42| 6     | 31.58| 0.766* |
| (+)                           | 21    | 72.41| 8     | 27.59|        |
| Total Cholesterol             |       |      |       |      |
| < 200 mg/dl                   | 24    | 66.67| 12    | 33.33| 0.336* |
| > 200 mg/dl                   | 9     | 81.82| 2     | 18.18|        |
| HDL Cholesterol               |       |      |       |      |
| > 45 mg/dl                    | 10    | 71.43| 4     | 28.57| 0.906* |
| < 45 mg/dl                    | 23    | 69.7 | 10    | 30.3 |
| LDL Cholesterol               |       |      |       |      |
| < 70 mg/dl                    | 13    | 65   | 7     | 35   | 0.501* |
| > 70 mg/dl                    | 20    | 74.07| 7     | 25.93|        |
| Triglycerides                 |       |      |       |      |
| < 200 mg/dl                   | 24    | 66.67| 12    | 33.33| 0.336* |
| > 200 mg/dl                   | 9     | 81.82| 2     | 18.18|        |

(*:Chi-square test was applied. ‡:Fisher exact test was performed.)

Table 3
Comparison of Risk Classes and HDL, LDL, Total Cholesterol, Triglyceride according to the 2019 ESC/EAS dyslipidemia guidelines for the management of dyslipidemias.

There was no statistically significant difference between two groups in favor of cardiovascular risk factors. 19 patients were using statin due to hyperlipidemia history. 4 of them were in the atherosclerosis group and there was no statistically significant difference in both groups. There was no statistically significant difference in the presence of atherosclerosis in any lipid panel (HDL-C, LDL-C, Total cholesterol and triglyceride) (Table-3).

Discussion

According to the LDL-C hypothesis, LDL-C is a causative factor in atherosclerosis. Although the hypothesis is generally accepted, controversy continues about its validity. Evidences supporting this hypothesis emerge from experimental models, epidemiological cohorts, and cholesterol-lowering (mainly statin-based) clinical studies. However, the remaining conflicts should be considered.

Many studies have shown us that there is an important link between LDL-C and atherosclerotic cardiovascular disease. Therefore, we consider the LDL values as we are choosing the adequate treatment. Many clinical trials recommend statin therapy to manage LDL levels. We also aim to maintain the HDL in adequately higher levels. In fact, since rosuvastatin and simvastatin are thought to have the effect on increasing HDL-C, we also prefer these statins in our patient groups. Therefore, that it is important to determine which of these laboratory parameters play a role in the process of artery atherosclerosis. In this study, we aimed to understand the relation between the HDL, LDL, cholesterol levels and the atherosclerosis in large vascular structures such as ascending aorta.

American Diabetes Association (ADA) and the American College of Cardiology (ACC) arrived at a consensus and published that non-HDL-K is a better indicator for identifying patients with high cardio-metabolic risk factors. Srinivasan et al. reported that non-HDL-K levels may be useful for the determination of lipoprotein-related risks. In our study, we investigated LDL and HDL values during the follow-up periods. 7 of 27 patients with LDL > 100 mg/dl and 10 of 33 patients with HDL < 45 mg/dl were in the atherosclerosis group but there was no statistically significant difference in these groups. The non-HDL-C which was used in the Srinivasan et al. study was not used in our study. There might be a statistically difference between the atherosclerosis and the non-atherosclerosis group, if it was used. In subsequent studies, non-HDL-C will be used along with the other lipid markers. Despite the importance of LDL-C, it may not be that cost-effective. There are many studies investigating for an easy and reliable methodology for its routine use. Since it is affordable and easy to use, Friedewald Formula (FF) is an easy and widely used method. However, while using this formula, if triglyceride is over 400 mg / dl, it causes the very low density lipoprotein (VLDL) to be over calculated and the LDL to be under calculated. This miscalculation raises doubts about if LDL is truly related with atherosclerosis. In our study, there were 1 patient with triglyceride over 400 in the atherosclerosis group and 2 patients in the non-atherosclerosis, which was not statistically significant.

Youn et al. examined the carotid intima media layers thickness in 1700 subjects and it appeared to be associated with increased body mass index (BMI) and high LDL cholesterol in healthy individuals. The LDL value was 113.1 ± 31.9 mg/dl in the male patients and 117.3 ± 32.2 mg/dl in the female. In our study, LDL mean ± std value was 99.64 ± 29.95 mg/dl in the group with atherosclerosis and 115.24 ± 40.44 mg/dl in non-atherosclerosis. No statistically significant difference was found between both LDL and BMI values and presence of atherosclerosis. (p: 0.221)

In a PESA study with 1779 subjects by L.Fernández-Friera et al., patients were examined by Doppler USG or CT. More than 0.5 mm thickening in the intima media or 1.5 mm intima thickness towards the lumen in the
carotid arteries or infrarenal aorta was considered as atherosclerosis. BMI was 24.5 ± 3.3 kg/m² in the non-atherosclerosis group and 25.3 ± 3.4 kg/m² in the group with atherosclerosis. There was no statistical difference. Total cholesterol values were 187.0 ± 24.4 mg/dl in the non-atherosclerosis group and 194.6 ± 22.9 mg/dl in the group with atherosclerosis. The LDL was 125.7 ± 20.1 mg/dl versus 117.4 ± 21.7 mg/dl. The HDL value was 53.5 ± 10.1 mg/dl versus 55.4 ± 10.6 mg/dl. The triglyceride was 63 (50-83) mg/dl versus 68 (53-92) mg/dl. In our study, the triglyceride was 167.61 ± 105.06 mg/dl in the non-atherosclerosis group, while it was 148.21 ± 89.68 mg/dl in atherosclerosis group. Total cholesterol was 173.91 ± 41.36 mg/dl versus 156.79 ± 36.36 mg/dl. LDL value was 115.24 ± 40.44 mg/dl in the non-atherosclerosis group and it was 99.64 ± 29.95 mg/dl in the atherosclerosis group. HDL was 41.42 ± 12.53 mg/dl versus 42.57 ± 15.41 mg/dl. In our study, no statistically significant difference was found.

There are studies showing that there is a relationship between HbA1c and subclinical atherosclerosis. In 2,340 non-diabetic individuals, higher HbA1c concentrations (between 5.7% and 6.4%) were associated with increased carotid intima-media thickness. In another prospective series (n = 2,652) with non-diabetic patients, HbA1c which in the near-highest level (> 5.7%) was associated with progression of both carotid intima-media thickness and cardiovascular events. In our study, the HbA1c was 5.4 ± 0.3 in the group without atherosclerosis and 5.6 ± 0.2 in the group with atherosclerosis. No statistically significant difference was found.

In a study with 91 patients, the relationship between LDL-K and ascending aorta was examined. LDL-K was observed to have a linear relationship with the ascending aorta diameter which was measured as 40.5 ± 7.3 mm. In our study, it was measured as 35.35 ± 3.47 mm in the group without atherosclerosis and 35.07 ± 4.78 mm in the group with atherosclerosis. However, it was not statistically significant.

The shortcomings of our study are; insufficient number of patients and taking tissue samples from plaque free areas of ascending aorta, as its required in CABG procedure. Therefore, since this region (calcific/fibrotic plaque) is avoided, the plaque load may be considered less.

As a result, in our study, no significant difference was found between HDL-C, LDL-C, triglyceride, total cholesterol values and the pathological process of aortic atherosclerosis. As a result of this study, we believe that it was necessary to correct the error margins of these parameters. In addition, it required the need for a clearer laboratory parameter to demonstrate atherosclerosis.

Declarations

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Ethics Committee Approval:

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Informed Consent:

Informed consent was obtained from the participants.

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Conflict of Interest:

No conflict of interest was declared by the authors.
Availability of data and material:
Due to the legal system in our country and the law of protection of personal data, we cannot share patient data in detail.

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No competing of interest was declared by the authors.

Authors' contributions:
All authors read and approved the final manuscript

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Figure 1
Aortic tissue sampling from ascending aorta with 4.0mm aortic punch while CABG

Figure 2
Dense foam cells. x100)