Wilma González[1], Pablo I. Altieri[1,2]*, Héctor Banchs[1,2], Diego Iravedra[1], Rafael Calderón[2], Iván González-Cancel[2], Carmen Gurrea[2], Nelson Escobales[1] and Maria Crespo[1]

[1]Department of Medicine and Physiology, University of Puerto Rico, Medical Sciences Campus, Pablo I. Altieri

[2]Cardiovascular Center of Puerto Rico and the Caribbean, Pablo I. Altieri

Research Article

HDL as a Biomarker of Rejection in Heart Transplant

Abstract

Background: One hundred once patients underwent heart transplants due to multiple causes. These patients included 36 females and 65 males whose mean age was 51 years.

Objective: To study metabolic and lipid changes after heart transplantation with emphasis on HDL in rejected and non rejected hearts.

Methods: The metabolic changes pre and post transplant were analyzed.

Results:

1. Body mass index (BMI): 25 ± 4 - 28 ± 5 kg/ m^2 ($P<0.05$)

2. Systolic blood pressure (sBP): 107 ± 17 - 131 ± 20mmHg ($P<0.05$)

3. Diastolic blood pressure (dBP): 70 ± 13 - 81 ± 10 mmHg($P<0.05$)

4. Fasting blood sugar (FBS): 107 ± 37- 117 ± 55 mg%(0.164) (non significant)

5. Cholesterol: 170 ± 55 - 189 ± 32 mg/dl($P<0.05$)

6. High density lipoprotein (HDL): 38 ± 16 - 52 ± 17 mg/dl ($P<0.05$)

7. Low density lipoprotein (LDL): 99 ± 20- 83 ± 15 mg/dl (0.34).

8. Triglycerides: 163 ± 10 -188 ± 12 mg/dl (0.144).

Conclusions: The heart transplant patients developed metabolic syndrome (MetS). The elevated HDL levels observed after transplantation are indicative of role of immunologic reaction to chronic rejection processes. The patients who died of rejection (19) exhibited greater elevations in HDL that those who did not (47 ± 22 − 71 ± 40 mg/dl, P<0.05). Seven autopsies were performed and revealed severe atherosclerotic changes in the aorta and coronary arteries that were likely related to dysfunctional HDL. The transplanted hearts were 21 years old. The high levels and persistent elevation of HDL observed in the rejected group can be used as a biomarker of rejection and this will help to change the anti-rejection protocol to try to avoid the rejection of the implanted heart. LDL was found to be a factor in the progressive atherosclerotic process because the level was reduced post transplant.

Abbreviations

BMI: Body Mass Index; dBP: Diastolic Blood Pressure; FBS: Fasting Blood Sugar; HDL: High Density Lipoprotein; HT: Heart Transplant; LDL: Low Density Lipoprotein; MetS: Metabolic Syndrome; sBP: Systolic Blood Pressure; HDL-C= High Density Lipopoprotein Cholesterol; BP: Blood Pressure; T2D: Type 2 Diabetes; apoCIII: Apolipoprotein C-III; Lp-PLA2: Lipoprotein associated phospholipase A2; p38-MAPK: Inhibitor of Mitogen Activated Protein Kinase; SAA: Serum Amyloid A; SA-A1: Serum Amyloid A-1; MCP-1= Monocyte Chemoattractant Protein-1; Ox-PL= Oxidized Phospholipids; PON1= Paraxonase 1; SD= Standard Deviation

Introduction and Background

The incidence of metabolic syndrome (MetS) is growing each year; approximately one third of the population suffers from MetS [1]. MetSis an important issue to study because it emerges as a novel risk in cardiovascular disease events due to endothelial dysfunctions, diabetes mellitus, hypertension and dyslipidemia [2].

MetS is a risk factor related with cardiovascular diseases, insulin resistance, post-transplantation complications, and late morbidity and mortality [3,4]. MetS is described as by a clustering of cardiovascular risk factors that are correlated with pathophysiological defects that are indicative of metabolic burden associated with disturbances in adipose tissue, including diabetes, obesity, dyslipidemia and hypertension [3,5]. MetS is defined according to ethnicity/race, specific waist circumference and the presence of two of the following: [6]

a. triglycerides: >150 mg/dl

b. high density lipoprotein- cholesterol (HDL-C): < 40 mg/dl for males

c. HDL-C: <50 mg/dl for females

d. blood pressure: >130/85 mmHg

e. fasting blood sugar:>100 mg/dl

The prevalence of MetS has been strongly associated with obesity due to its fundamental control of the distribution of free fatty acids disorders including dyslipidemia and insulin resistance preceding type 2 diabetes [6]. Visceral adipose tissue is highly susceptible to catecholamine-induced lipolysis compared to subcutaneous tissue [7]. This visceral fat produced in patients with MetS is related to insulin sensibility, which moderates angiogenic proteins, metabolic regulators and inflammatory mediators that produced hypertension, inflammation, endothelial dysfunction and the production of atheromas [2,5]. Heart transplant patients tend to develop MetS while also presenting with dysfunctional levels of high density lipoprotein-cholesterol [8]. This manuscript describes the changes in our population (Table 1) that lead to MetS and the consequences of MetS. Moreover, the importance of functional and dysfunctional HDL will be discussed, because changes in both are extremely important for the survival of transplanted patients (Table 2). Also, the importance of a marked and persistent elevation of HDL can be used as a biomarker of an impending rejection process (Figure 1). The HDL-C of 70 mg/dl was not chosen as a cut-off, it was the mean value of the evaluation of HDL-C in the rejected patients who died. This will lead to an aggressive change in the rejection protocol to avoid this disaster. This last observation is the main point, we want to stress in this paper-HDL levels as a biomarker in heart transplant pathophysiology.

Material and Methods

The records of 101 heart transplant patients were reviewed in the Cardiovascular Center of Puerto Rico and the Caribbean, to determine the incidence of Met Sin the transplant population and the body mass index (BMI), systolic blood pressure, diastolic blood pressure, fasting blood sugar, total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides and drugs in the congestive heart failure patients before and after heart transplantation, were monitored. Seven autopsies specimens of rejected hearts were evaluated, and emphasis was given to the amount of atherosclerosis in the coronary arteries and aorta. The data were examined with Student's t-test with p-values, and the levels are expressed as the mean values ± SD's. The autopsies were performed according to a standard protocol. Emphasis was given to the transplanted heart including the aorta and coronary arteries.

We evaluated 101 patients whose mean age was 51 years. Sixty patients were males and 41 were females. Nineteen deaths were due to rejection; 81.0% of the deaths were females and 19.0% were males. Only seven autopsies were performed; autopsies were not performed on all the deceased patients because some of the relatives objected. The age of the transplanted hearts were 21 years, and all hearts were from healthy patients without any metabolic or lipid abnormalities.

Results

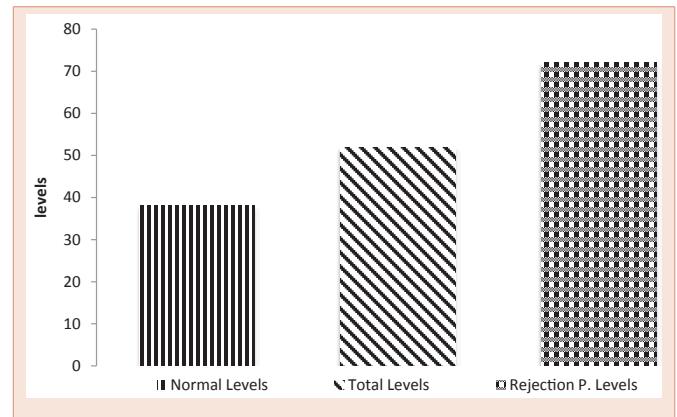One hundred one patients with heart transplant were studied.

Figure 1: HDL-C Results compared to normal controls (mg/dl). HDL: High Density Lipoprotein Cholesterol; P: Patients

Sixty-five patients were males and 36 were female. The mean age was 51 years (Table 1). The observed pre- and post-transplant metabolic changes were as follows (Table 2):

1. BMI: 25 ± 4 – 28 ± Kg/m^2 (P < 0.05).

2. sBP: 107 ± 13 – 131 ± 20 mmHg (P <0.05).

3. dBP: 70 ± 13 – 81 ± 10 mmHg. (P <0.05).

4. FBS: 107 ± 37 – 117 ± 55 mg% (< 0.164).

5. Total cholesterol: 170 ± 55 – 189 ± 32 mg/dl (P < 0.05).

6. Total HDL: 38 ± 16 – 52 ± 17 mg/dl (P < 0.05).

7. Total LDL: 99 ± 20 – 83 ± 15 mg/dl (< 0.34).

8. Triglycerides: 163 ± 10 – 188 ± 12 mg/dl (< 0.144).

Our data shows that all of the patients developed Mets. The HDL of the entire group increased from 38 mg/dl to 52 mg/dl (Figure 1). These changes cannot be solely attributed to the immunosuppressive treatment. Nineteen of the patients died due to rejection. The HDL's of patients who exhibited rejection increased from 47 ± 22 to 71 ± 40 mg/dl (P< .005). This increase persisted through the course of the rejection period (Figure 1).

The mean age of the transplanted hearts was 21 years; 81% of the donors were females and 19% were male. The rejections occurred inless than five years (3.5 years). Only seven autopsies were performed. Four of the autopsies revealed severe atherosclerotic changes in the coronary arteries and aorta, and these findings are likely attributable to dysfunctional HDL. The LDL levels were reduced post transplant. Due to this LDL was not considered to be a factor in this aggressive atherosclerotic process.

Discussion

MetS represents a common interaction between genetic tendencies, metabolic factors, nutrition, physical activities, and environmental factors that affect allograft patients [9]. MetS is accompanied by risk factors that are associated with cardiovascular disease, primarily, ischemic heart disease, which is an important predictor of post-transplantation complications [3,10]. Several studies

Table 1: Sample Data.

Patients	N=101
Males	60
Females	41
Mean Age	51 ± 3 years
Deaths due rejection	16
Males	19.0%
Females	81.0%

Table 2: Results.

	Pre HT*	Post HT*	P-Value & Significance
[1]BMI (kg/m^2)	24±4	28±5	<.05
[2]sBP (mmHg)	107±17	131±20	<.05
[3]dBP (mmHg)	70±13	81±10	< .05
[4]FBS (mg%)	107±37	117±55	0.164
Total cholesterol (mg/dl)	170±55	189±32	<.05
[5]HDL (mg/dl)	38±16	52±17	<.05
[6]LDL (mg/dl)	99±20	83±15	0.34
Triglycerides (mg/dl)	163±10	188±12	0.144

[1]BMI: Body Mass Index; [2]Systolic BP: Systolic Blood Pressure; [3]Diastolic BP: Diastolic Blood Pressure; [4]FBS: Fasting Blood Sugar; [5]HDL: High Density Lipoprotein; [6]LDL: Low Density Lipoprotein; *HT: Heart Transplant

have shown that insulin resistance and visceral obesity are main factors in MetS, which causes post-transplantation abnormalities between muscles and adipose tissue in patients who tend to be obese, or overweight or develop abdominal obesity [5,10].

In patients with type 2 diabetes and MetS, there are predispositions for elevation of Angiotensin II and endothelin I due to the activation of the neuro-hormonal system by systemic inflammation. These elevations results in inflammatory cytokines, endothelin I and smooth muscle proliferation, which initiates the atherosclerotic process [9,10]. The incidence of atherosclerosis in MetS is related to pathogenesis of insulin resistance, which tends to produce abnormalities in fat storage. The accumulation of triglycerides by visceral fat provokes a reduction in energy intake reduction and free fatty acids release, which discharge cytokines, fatty tissue and inflammatory cells that affects adipokines and increase the risk factors for cadiovascular disease [11]. Visceral adiposity has been associated with excess of free fatty acids release and suppression, increased hyper triglyceridemia and the production of alterations in HDL-C levels [11]. Doubts regarding HDL functionality have been proposed and correlated with the post-transplantation incidence. Higher levels have been associated with reduction in cardiovascular disease risk factors, but recent studies and drugs effects suggest that an elevation is not necessarily beneficial [12]. We propose that a marked elevation of HLD-C to levels of around 70 mg/dl is a warning that a severe chronic rejection process is active. We think that those changes can be used as a biomarker of a severe rejection process.

HDL particle compositions are critical to biological maintenance and functionality. This functionality has been strongly suggested to be better indicators that levels that assess cardio-protection. To maintain body homeostasis, this functionality tempers endothelial function and cholesterol efflux function, regulates pro-inflammatory and promigratory factors, oxidation and prevents thrombotic activity related to platelets [13]. Conversely, the disfunctionallity has been associated with certain genetic variants, and this association is corroborated by some drug results that have demonstrate opposite, inflammatory, thrombotic, oxidative and cholesterol influx-increasing results.

HDL is composed principally of apolipoprotein A-1 (apoA1) and apolipoprotein A-2 (apoA2), and interaction with ABCA1 gene expression regulates efflux capacity via reverse cholesterol transport. Mutations in this pathway are associated with greater incidence of atherosclerotic burden [13-15,19]. Although higher levels had been suggested to diminish cardiovascular disease risk, we proposed abnormal levels affect influx and efflux activity. The aforementioned finding supports our results of higher levels of HDL post-transplantation, particularly in the rejected hearts and severe atherosclerotic activity upon the autopsies.

The pathophysiologies of cardiovascular diseases are influenced by apoptotic endothelial activities, which are controlled by HDL function. However, anti-apoptotic effects vary according to the dysfunctional activity [13,20]. Disruptions of endothelial monolayer can lead to apoptotic pathways and enhance cardiovascular disease risk factors. Cell death has been associated with intracellular Ca^{2+}, which is caused by oxidized LDL and reversed by HDL particle functions [13]. Moreover, growth factors and deprivation-related apoptosis are related. The association with lysophospholipid sphingosylphorycholine inhibits apoptotic pathways by signaling, and, nitric oxide synthase is as a paracrine mediator in dietary fats that induces insuline resistance [11,13,20,21]. In contrast to these findings, some authors have proposed that chronic and inflammatory diseases reduce the atheroprotective functions of HDL, which is strongly associated with the acute phase due to loss of function in reverse cholesterol transport [12,17,20-22].

The relation between HDL elevation and protein response strong during the acute phase and leads to pathological consequences [22]. Recent studies have proposed differences in HDL protein cargos [22] and have suggested that not all particles are equal. Abnormal levels of HDL proteins in the acute phase have been reported. Reduced clusterin levels and elevations in apolipoprotein-CIII (apoCIII) elevation, serum amyloid A-1 (SA-A1) and lipoprotein-associated phospholipase A2 (Lp-PLA2) are biomarkers due to their vascular endothelial cell contribution to inflammation and atherogenesis [18,20,23-24]. Probably a marked and persistent elevation of HDL can be proposed as a biomarker or rejection.

Riwanto et al. [20] proposed that higher levels of clusterin are related to the mechanism of HDL in apoptotic pathways that are mediated by phoinostide 3-kinase/Akt (PI3/Akt) functioning in healthy subjects and that this mechanism is not activated in coronary artery disease subjects. The BCL2 class of proteins are crucial mediators of apoptosis, and HDL modulates the BCLXL protein via PI3K/Akt activation [25,27]. In contrast, lower levels of clusterin protein lead toproapoptotic effects that are specific to HDL and not the serum by activating tBid [20,26] and, induce apoptosis related to the release of

cytochrome c in mitocilin-deficient mitochondria [27]. Furthermore, Riwanto [20] demonstrated that the inhibition of mitogen-activated protein kinase (p38-MAPK) phosphorylation increases tBid expression by blocking apoCIII. Relations between apoCIII and cardiovascular disease risk factors, MetS and T2D patients have been proposed based on findings that reduction in plasma apoCIII are paralleled by elevated plasma triglycerides [28]. The acute phase of inflammation is accompanied by elevated levels of serum amyloid A(SAA) family proteins, which are principal non-invasive biomarker of allograft rejection due to their G-protein receptor-mediated pro inflammatory and atherosclerotic activities [29,30]. Töle et al. [30] recently demonstrated that the cardio-protective properties of HDL are lost during inflammatory diseases with high triglyceride levels in end stage renal disease patients. The recruitment of monocytes in the subendothelium is preceded by monocyte chemo attractant protein-1 (MCP-1), which leads to an increased incidence of atherosclerotic activity. Töle [30] found that the capacity of HDL is reduced by the inhibition of MCP-1 production in end stage renal disease patients, and that this process is related to higher levels of protein fraction that are highly enriched with SAA protein. These authors also proposed that MCP-1 with the formyl-peptide receptor 2 is produced; similar proposals have been made in other studies that have found produced effluxes of HDL activity in end stage renal disease patients, especially whose with diabetes Type 2 [18].

In the present study, we reviewed the different factors related to cardiovascular disease that contribute to MetS in heart transplant patients. We presented a trend suggesting that BMI is related to the predisposition for being obese or to the development of post-transplantation obesity, which is correlated with higher levels of cholesterol and strongly related to moderate to severe atherosclerotic activity on autopsy. Due to the resistance of donor patients to autopsies after heart transplant, we performed seven autopsies that exhibited this atherosclerotic activity. These finding are likely due to post-transplantation HDL dysfunctionality. We proposed a dysfunctional activity that involves structure, function and density that will reverse the efflux activity of cholesterol to create an influx activity into the heart cells. This observation has been supported and proposed in other studies and has been related to the use of HDL protein cargos, such as apoA1, apoCIII, clusterin, SA-AI and Lp-Pla2, as potential biomarkers of cardiovascular disease. Thus, HDL capacity in the endothelial activity plays the important role for those patients after heart transplantation. The disruption of HDL proteins and enzymes might lead to changes in the injury process by altering or inhibiting the inflammatory response that is related to helper T cell responses through the degradation of the endothelial functions [15-17]. We don't think LDL is a factor because there was a reduction instead of an elevation.

The development of MetS following heart transplant might be related to the permanent use of prednisone and the implications of that use rather than the immune system overreacting to a chronic rejection process by elevating HDL levels. Future research should be performed in this group of patients to determine the reasons for this phenomenon and to review the protocol to avoid further damage to the allograft.

Atherosclerotic activity stimulates monocyte adhesion, and these monocytes differentiate into macrophages and oxidized LDL, which produced foam cells that are involved in the inflammatory process. Cytokine production, reactive oxygen species and monocytes are related in the inflammatory process [17-19]. Changes in oxidative activities and proinflammatory gene expression occur due to activating platelets, monocytes adhesion and plaque formation [31].

Ostadal et al. [32] proposed that the abnormal levels related to Lp-PLA2 worsening cardiovascular events, especially in acute coronary syndrome patients, and can thus be used as biomarkers. A higher incidence of oxidative platelest (Ox-PL) than Lp-PLA2 in the artery walls leads to proinflammatory activity that produces bioactive lipid mediators that are chemo attractants for monocytes that impair endothelial function and the plasma membrane by inducing apoptotic pathways [31]. Navab et al. [17] proposed that normal HDL levels are related to Ox-Pl. In this proposed relation, the HDL-associated enzyme paraoxonase 1 (PON1), which inhibits the endothelial cell responses to Ox-Pl and apolipoprotein m, increased the anti-oxidative properties of HDL. Decreased levels of PON1 result in higher levels of lipid hydroperoxide in the HDL while reducing HDL-C and increasing the molecular weight of apoA1. Navab [17] proposed that a greater molecular weight in the HDL content of apoA1 antibodies that recognize Ox-Pl is a form of genetic control over the anti atherogenic properties of HDL.

The HDL levels observe in the patients that died due to rejection are related to disfunctionallity. The disruption of the endothelium leads to altered homeostasis and increases the risk of thrombosis, which places the arterial walls at risk [13]. The vascular injury activates the platelets during the acute phase, which results in greater atherosclerotic activity and triggers coagulation and platelet-rich thrombi [33].

Increased incidence of chronic rejection has been evaluated and related to metabolic disorders in patients with insulin resistance. These disorders include pathophysiological factors, such as oxidative stress, nitric oxide bioavailability, growth factors and abnormal cell signaling [22]. Dysfunctional HDL elevation in chronic rejection is related to severe atherosclerotic activity and has been linked to with glycosphingolipids in recent studies due to is modulation of the immune system and T-lymphocyte differentiation [34]. Atherosclerotic activity is produced through foam cell formation; these cells mature by accumulating inflammatory T cell subsets that are activated and produce chemokines, cytokines and growth factors by degrading the subendothelium, which influences the atherosclerotic lesion and protein response [35]. These findings explain the possible relationship between proteins concentrations in the HDL and atherosclerotic activity in the acute phase due to T cell subtype imbalances. The importance of this higher HDL-C level in the rejected group should be studied further and find out which sub factors of HDL is the one elevated and why, to alter the rejection protocol and avoid this fatal process. Studies with proteonics are planned to try to clarify which particle of HDL is responsible for its dysfunctionality. This marked elevation of HDL in the rejected heart, starting at the beginning of the procedure suggests that this elevation may be used as a biomarker of rejection. Also this abnormal

statistically significant (P<0.05) elevation of HDL up to levels of 70 mg/dl, probably is due to a dysfuntional HDL which produces severe deposition of lipids in the aorta and coronaries, producing early death of the patients. Further studies should be done in HDL structure to find which particle of HDL is responsible for this abnormality of being transformed to a dysfunctional HDL and in this way being used as a biomarker.

Conclusions

Importantly, among the seven autopsies that were performed, five patients exhibited severe atherosclerotic changes. The mean age of the transplanted hearts was only 21 years. As observed, the HDL of the patients who exhibited rejection averaged 71 ± 40 mg/dl, while that of the patients who did not, averaged 47 ± 22 mg/dl (Figure 1). We believe these finding are due to increases in dysfunctional HDL. Moreover, we propose that this significant increase in HDL can be used as a biomarker of rejection. These findings serve as a warning that changes to the immune suppression protocol should be done to try to revert the rejection process.

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Citation: González W, Altieri PI, Banchs H, Iravedra D, Calderón R, et al. (2014) HDL as a Biomarker of Rejection in Heart Transplant. Glob J Obes Diabetes Metab Syndr 1(1): 001-006.

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