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ScienceDirect
Metabolism Clinical and Experimental 59 (2010) 1642 – 1648
Metabolism
Clinical and Experimental
www.metabolismjournal.com

Serum glucose and lipid levels in adult congenital heart disease patients

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Received 13 November 2009; accepted 19 March 2010

Abstract

Atherosclerosis has been correlated with known cardiovascular risk factors such as serum glucose or lipid levels. Because congenital heart disease patients tend to survive until adulthood, atherosclerosis has also become a matter of concern in these patients. One hundred fifty-eight congenital heart disease patients and 152 patients selected at random from the population were studied and compared to determine serum glucose, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein cholesterol, and triglycerides levels. Both groups had similar socioeconomic status levels and the same environmental influences. Significant differences were seen between congenital heart disease patients and the control group, after sex, age, and body mass index adjustment, in fasting plasma glucose (97.7 [94.2-101.2] vs 86.9 [83.2-90.7], $P < .001$), total cholesterol (171.5 [165.7-177.3] vs 199.8 [90.7-206.0], $P < .001$), LDL cholesterol (103.9 [98.8-108.8] vs 123.8 [118.5-129.1], $P < .001$), and high-density lipoprotein cholesterol (48.1 [46.2-50.0] vs 54.2 [52.1-56.2], $P < .001$) levels. Nonsignificant differences were seen in triglycerides concentrations. Those patients with ventricular septal defect, coarctation of the aorta, and cyanosis had the lowest total cholesterol and LDL cholesterol concentrations. Congenital heart disease patients have lower plasma cholesterol concentrations and higher serum glucose levels than noncongenital ones.

1. Introduction

Early lesions of coronary heart disease patients have been correlated with known cardiovascular risk factors such as concentrations of total cholesterol, low-density lipoprotein (LDL) cholesterol, or impaired glucose tolerance [1,2]. Prevention and early diagnosis of atherosclerotic disease are the essential objectives in the field of cardiovascular disease because it is the main cause of mortality in developed countries.

Although a few decades ago only a minority of patients, particularly those with complex congenital heart disease and cyanosis, reached adulthood, progress in pediatric cardiology and cardiac surgery has allowed a larger survival of the majority. That is why lipid levels and serum glucose concentrations have also become a matter of concern in these patients.

Although other studies have focused to some extent on serum glucose [3] and lipid concentrations [4,5] in congenital heart disease patients, none of them has compared congenital patients with a general population of similar socioeconomic conditions.

The aim of the study is to estimate and compare serum glucose and lipid levels in congenital heart disease patients and an age-stratified random sample of the community with similar socioeconomic status levels and the same environmental influences.

This manuscript has not been submitted for publication, nor has it been published in whole or in part elsewhere. We attest to the fact that all authors listed on the title page have contributed significantly to the work, have read the manuscript, and attest to the validity and legitimacy of the data and its interpretation. The authors of this manuscript have also certified that they comply with the Principles of Ethical Publishing.

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doi:10.1016/j.metabol.2010.03.014

2. Methods

One hundred fifty-eight congenital heart disease patients (cases) and 152 patients selected at random from the same area of Gran Canaria Island (Spain) (controls) were studied and compared.

Case patients were obtained from the Adult Congenital Heart Disease Unit of the Complejo Hospitalario Universitario Insular-Materno Infantil of Gran Canaria. Inclusion criteria were being older than 14 years and having a structural congenital heart disease. All patients were white, and all of them or their parents gave their informed consent for participation in the study.

Control patients were selected from the Telde study population [6] at random according to year strata and sex, proportionally to the population. The city of Telde was chosen for the survey because its population was deemed to be representative of that of the entire Canarian community. Names and addresses were provided by the Canarian Institute of Statistics. The selected individuals received personalized letters informing them about the objectives of the study. Later, they were visited at home by a field worker. After providing informed consent, all the people who agreed to participate completed a survey questionnaire and were informed about the site and procedural details of the physical examination and blood sampling. Although the initial target population was adults older than 30 years, we only included those between 30 and 35 years old as an age-stratified random sample of the community in our study.

Congenital heart disease patients were studied as a whole and according to the most frequent types of congenital malformations (atrial septal defect, ventricular septal defect, partial and complete atrioventricular septal defect, coarctation of the aorta, pulmonary stenosis, tetralogy of Fallot, and dextro- and levo-transposition of the great arteries). In addition, 4 groups of congenital heart disease patients were made in relation to the existence of cyanosis or acyanosis with or without operation (group A, cyanotic patients not operated on; group B, cyanotic patients rendered acyanotic by operation; group C, acyanotic patients not operated on; and group D, acyanotic patients before and after operation).

After an overnight fast of at least 10 hours, blood samples were drawn for the measurements (in milligrams per deciliter) of plasma glucose, total cholesterol, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides (TG). Serum glucose and lipid levels were determined by spectrophotometric methods using an Olympus AU 2700 (Olympus Diagnostic, Hamburg, Germany) in congenital heart disease patients and a Dimension RxL autoanalyzer (Dade-Behring, Liederbach, Germany) in the control group. Serum glucose and lipid levels were measured and compared with both analyzers, with no significant

Table 1
Types of congenital heart diseases

Type of congenital malformations	n (%)	Cyanosis		Acyanosis	
		A	B	C	D
Ventricular septal defect	25 (15.8)	5	1	17	2
Tetralogy of Fallot	17 (10.8)		17		
Coarctation of the aorta	16 (10.1)			3	13
Partial atrioventricular septal defect	12 (7.6)			1	11
Pulmonary stenosis	12 (7.6)			5	7
Atrial septal defect	11 (7.0)			5	6
Univentricular heart	8 (5.1)	5	3		
D-Transposition of the great arteries	8 (5.1)	1	7		
Aortic stenosis	6 (3.8)			3	3
L-Transposition of the great arteries	6 (3.8)	2		4	
Bicuspid aortic valve	4 (2.5)			4	
Pulmonary atresia	4 (2.5)	1	3		
Ebstein anomaly	4 (2.5)			4	
Double outlet right ventricle	4 (2.5)	1	3		
Hypertrophic myocardiopathy	4 (2.5)			4	
Ductus	3 (1.9)			2	1
Mitral regurgitation	3 (1.9)				3
Mitral valve prolapse	3 (1.9)			3	
Complete atrioventricular septal defect	2 (1.3)	1			1
Systemic venous anomaly	1 (0.6)			1	
Tricuspid atresia	1 (0.6)	1			
Aortic regurgitation	1 (0.6)			1	
Subaortic stenosis	1 (0.6)			1	
Idiopathic pulmonary artery aneurysm	1 (0.6)			1	
Anomalous pulmonary venous connection	1 (0.6)				1
Total	158 (100)	17	34	59	48

A, cyanotic patients not operated; B, cyanotic patients rendered acyanotic by operation; C, acyanotic patients not operated; D, acyanotic patients before and after operation.

Table 2
Demographic, clinical, and analytical data of congenital heart disease patients (cases) and the control population

	Cases (158)	Controls (152)	*P*
Age (y)	28.3 (16.4-51.6)	33 (30-35)	.000
Sex (male)	94 (59.5)	49 (32.2)	.000
Height (cm)	167.34 ± 12.06	167.62 ± 8.58	.821
Weight (kg)	69.46 ± 19.18	74.74 ± 17.41	.015
BMI	24.66 ± 5.60	26.44 ± 5.07	.005
Diabetes	5 (3.16)	5 (3.28)	.948
Serum glucose (mg/dL)	97.06 (78.90-121.25)	86.85 (72.65-107.00)	.000
Total cholesterol (mg/dL)	169.28 ± 37.26	199.86 ± 35.43	.000
LDL cholesterol (mg/dL)	101.67 ± 30.59	123.94 ± 32.47	.000
HDL cholesterol (mg/dL)	47.83 ± 11.73	55.61 ± 13.82	.000
TG (mg/dL)	98.49 ± 49.11	99.32 ± 77.66	.991

The values are expressed as mean ± standard deviation or median and quartile values (5-95); and qualitative variables, as percentages of the total.

differences between either of them and with both instruments keeping the same reference values. The LDL cholesterol (in milligrams per deciliter) was determined with the Friedewald formula (LDL = total cholesterol − [HDL + TG/5]).

Weight and height were measured without shoes and in light clothing. Body mass index (BMI) was determined as weight/height^2. Congenital heart disease patients were classified as cyanotic when basal oxygen hemoglobin

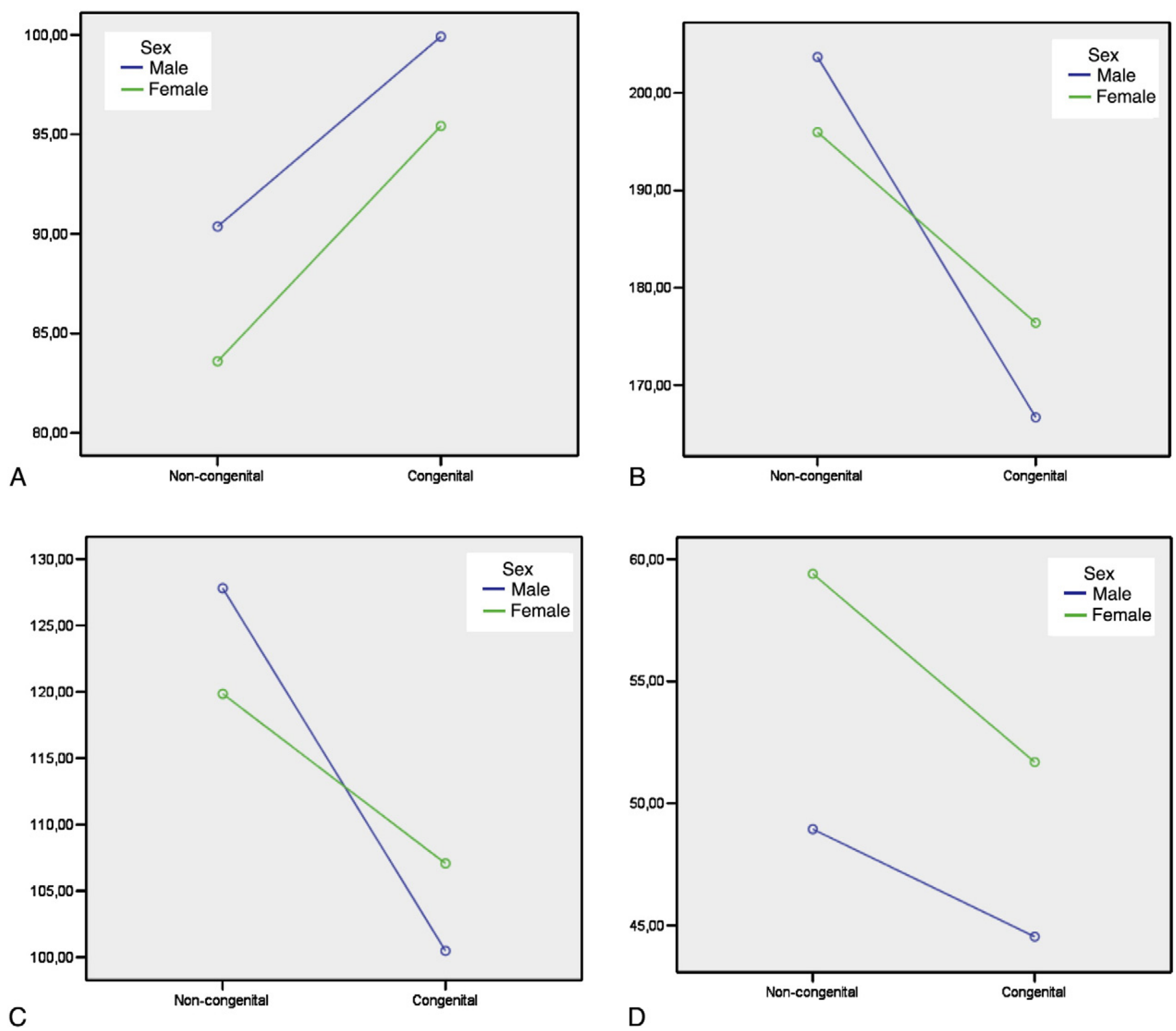

Fig. 1. Analysis of covariance, adjusted for age and sex, in congenital heart disease patients and the control population (noncongenital). Data are expressed in milligrams per deciliter. A, Serum glucose. B, Total cholesterol. C, Low-density lipoprotein cholesterol. D, High-density lipoprotein cholesterol.

Table 3
Glucose and lipid levels in male and female congenital heart disease patients and the control population

Type (n)	Sex	Glucose	Total cholesterol	LDL cholesterol	HDL cholesterol	TG
Congenital	Male (94)	99.91 (95.47-104.35)	166.68 (159.35-174.02)	100.49 (94.17-106.80)	44.54 (42.08-47.00)	108.29 (95.56-121.03)
	Female (64)	95.42 (90.05-100.78)	176.39 (167.52-185.26)	107.07 (99.44-114.70)	51.69 (48.72-54.66)	87.52 (72.13-102.91)
	Total (158)	97.66 (94.16- 101.17)	171.54 (165.74-177.33)	103.78 (98.79-108.76)	48.11 (46.17-50.05)	97.90 (87.85-117.44)
Control	Male (49)	90.37 (84.24-96.49)	203.70 (193.57-213.83)	127.80 (119.08-136.51)	48.94 (45.55-52.33)	131.45 (113.87-149.02)
	Female (103)	83.60 (79.35-87.84)	195.98 (188.96-203.00)	119.84 (113.80-125.88)	59.40 (57.04-61.75)	81.91 (69.73-94.09)
	Total (152)	86.98 (83.23-90.73)	199.84 (90.73-206.04)	123.82 (118.48-129.15)	54.17 (52.09-56.24)	106.68 (95.92-117.44)

Congenital heart disease patients had higher glucose concentration and lower total cholesterol, LDL cholesterol, and HDL cholesterol levels than control patients ($P < .001$). Male congenital heart disease patients had lower HDL cholesterol ($P < .001$) and higher TG ($P = .008$) levels than female congenital patients. Male control patients had higher glucose ($P = .022$) and TG levels ($P < .001$) and lower HDL cholesterol ($P < .001$) than female control patients. Covariates in multivariate ANCOVA are evaluated for an age of 30.77 years and a BMI of 25.58. The values are expressed as mean and 95% confidence intervals. Data are expressed in milligrams per deciliter.

saturation was less than or equal to 90%. *Diabetes* was defined by patients receiving oral hypoglycemic agents or insulin for the control of hyperglycemia.

The values are expressed as mean ± standard deviation or median and quartile values (5-95); and qualitative variables, as percentages of the total. The association between categorical variables was evaluated using the Pearson χ^2 test and the Student t test for continuous data. The Mann-Whitney U nonparametric test was used to compare 2 nonrelated samples when the assumption of normality or equality of variance was not met. Serum glucose, total cholesterol, LDL cholesterol, HDL cholesterol, and TG values were evaluated using a multivariate general lineal model analysis of covariance (ANCOVA), adjusted for a P value level of .05. Case vs controls, the different types of congenital abnormalities, sex, age, and BMI were used as independent variables. Data were expressed as mean and 95% confidence interval. Significance was established as $P < .05$. The data analyses were performed with SPSS 15.0 (Chicago, IL).

3. Results

One hundred fifty-eight consecutive congenital heart disease patients seen in the Adult Congenital Heart Disease Unit at the Complejo Hospitalario Universitario Insular-Materno Infantil of Gran Canaria between September 2008 and November 2009 and 152 patients from the Telde study population were studied and compared.

Table 1 shows the different types of congenital abnormalities, those who were cyanotic or acyanotic at birth, or those who had cardiac surgical intervention. Table 2 shows demographic, clinical, and analytical data of case and control patients. Eleven patients had Down syndrome associated with a congenital heart disease: 7 patients had atrioventricular septal defect, 3 patients had ventricular septal defect, and 1 patient had a mitral valve prolapse. Five patients in the case group developed diabetes: 4 patients had type 2 diabetes mellitus, 3 patients were taking oral antidiabetic agents, and 1 patient was undergoing insulin treatment because of a severe pancreatitis. Another patient with Down syndrome and a ventricular septal defect developed type 1 diabetes mellitus. No congenital heart disease patients were under hypercholesterolemic treatment.

Case patients had higher glucose concentration and lower total cholesterol, LDL cholesterol, and HDL cholesterol levels than control ones ($P < .001$) after sex, age, and BMI adjustment (Fig. 1). In the case group, male patients had lower HDL cholesterol concentrations ($P < .001$) and higher TG levels ($P = .008$) than female patients. Similarly, in the control group, male patients had higher glucose ($P = .022$)

Table 4
Glucose and lipid levels of the different types of congenital abnormalities

Type (n)	Glucose	Total cholesterol	LDL cholesterol	HDL cholesterol	TG
ASD (11)	100.72 (79.22-122.21)	184.23 (159.58-208.88)	107.42 (86.58-128.26)	54.66 (46.88-62.43)	110.43 (79.50-141.369
VSD (25)	103.50 (90.95-116.06)	165.98 (151.59-180.38)	100.73 (88.57-112.90)	47.27 (42.73-51.81)	90.02 (71.96-108.08)
AVSD (14)	96.43 (79.29-113.56)	182.68 (163.03-202.33)	111.79 (95.18-128.40)	42.03 (35.84-48.23)*	141.67 (117.02-166.33)†
PE (12)	92.98 (74.13-111.84)	171.05 (149.42-192.67)	105.00 (86.72-123.28)	50.15 (43.33-56.97)	79.45 (52.31-106.59)
CoAo (16)	93.62 (77.21-110.03)	165.46 (146.64-184.28)	98.14 (82.23-114.05)	50.78 (44.85-56.71)	82.73 (59.12-106.35)
TGA (14)	102.79 (79.85-112.32)	186.54 (159.96-213.12)	113.49 (91.02-135.96)	49.32 (40.94-57.70)	118.71 (85.36-152.07)
TF (19)	96.08 (79.61-125.97)	171.97 (153.36-190.59)	103.55 (87.81-119.29)	50.07(44.20-55.94)	91.60 (68.23-114.96)

Covariates in multivariate ANCOVA are evaluated for an age of 29.44 years and a BMI of 24.40. The values are expressed as mean and 95% confidence intervals. Data are expressed in milligrams per deciliter. ASD indicates atrial septal defect; VSD, ventricular septal defect; AVSD, atrioventricular septal defect (partial and complete); PE, pulmonary stenosis; CoAo, coarctation of the aorta; TGA, transposition of the great arteries (D-TGA and L-TGA); TF, tetralogy of Fallot.

* AVSD patients had significantly lower HDL cholesterol levels than patients with ASD and CoAo ($P < .05$).

† AVSD patients had higher TG levels than VSD, PE, CoAo, and TF patients ($P \leq .005$).

Table 5
Glucose and lipid levels in cyanotic and noncyanotic congenital heart disease patients

Type (n)	Glucose	Total cholesterol	LDL cholesterol	HDL cholesterol	TG
A (17)	102.11 (89.40-114.83)	152.14 (135.13-169.15)*	89.94 (76.11-103.78)*	45.12 (39.77-50.47)*	85.05 (62.07-108.04)
B (34)	97.96 (88.57-107.36)	169.59 (157.01-182.16)	103.56 (93.34-113.79)	45.04 (41.09-49.00)	104.83 (87.85-121.82)
C (59)	95.34 (88.41-102.27)	171.70 (162.42-180.97)	103.53 (95.99-111.07)	50.36 (47.45-53.28)	88.99 (76.46-101.51)
D (48)	95.87 (88.44-103.30)	176.91 (166.97-186.85)	106.19 (98.11-114.28)	49.45 (46.32-52.58)	91.74 (91.74-118.61)
A + B (51)	99.03 (91.54-106.53)	162.88 (152.63-173.12)	98.29 (89.98-106.61)	44.86 (41.70-48.02)†	98.44 (84.51-112.38)
C + D (107)	95.56 (90.53-100.59)	173.70 (166.82-180.58)	104.44 (98.86-110.02)	49.96 (47.83-52.08)	95.91 (86.55-105.26)

Covariates in multivariate ANCOVA are evaluated for an age of 29.04 years. The values are expressed as mean and 95% confidence intervals. Data are expressed in milligrams per deciliter.

* A patients had significantly lower total cholesterol concentrations than C patients, lower LDL levels than D patients, and lower HDL cholesterol concentrations than C patients ($P < .05$).

† A + B patients had significantly lower HDL cholesterol levels than C + D patients ($P < .005$).

and TG concentrations ($P < .001$) and lower HDL cholesterol levels ($P < .001$) than female patients (Table 3).

In relation to serum glucose and lipid levels in the different types of congenital malformations, the only subgroup that obtained significant differences when compared with the rest, after sex, age, and BMI adjustment, was the atrioventricular septal defect one. Atrioventricular septal defect patients had significantly lower HDL cholesterol levels than patients with atria septal defect ($P = .015$) and coarctation of the aorta ($P = .044$) and higher TG levels than ventricular septal defect ($P = .001$), pulmonary stenosis ($P = .001$), coarctation of the aorta ($P = .001$), and tetralogy of Fallot ($P = .005$) patients (Table 4).

In cyanotic and noncyanotic patients, after sex and age adjustment, those in group A had significantly lower total cholesterol ($P = .049$) and HDL cholesterol concentrations ($P = .034$) than those in group C and lower LDL cholesterol levels ($P = .047$) than those in group D. When A and B groups were taken together, this new group had significantly lower HDL cholesterol levels than group C plus D ($P = .009$) (Table 5). In relation to sex, male patients in groups A, B, C, and D had lower HDL cholesterol levels (44.90 [42.1-47.34] vs 50.10 [47.03-53.10], $P = .010$) and higher TG concentrations (105.77 [95.12-116.42] vs 86.25 [73.09-99.42], $P = .024$) than female patients. Similarly, this occurred when groups A and B were compared with groups C and D. In group A, 14 patients had pulmonary hypertension with Eisenmenger syndrome.

4. Discussion

Congenital heart disease, with its incidence of approximately 6 to 8 per 1000 live births, is the single most common major congenital abnormality. Although some years ago congenital heart disease patients did not survive until adulthood, the situation has now been transformed by advances in medical and surgical care during childhood; and a majority can expect to survive into adulthood.

Compelling evidence shows that the atherosclerotic process begins in childhood and progresses slowly into adulthood, being closely related with cholesterol concentrations. That is why lipid levels have also become a potential matter of concern in congenital heart disease patients. Many factors have been involved in lipid concentrations.

Overweight during childhood has been proposed as one of the mechanisms related to raised lipid levels, weight gain up to adulthood being associated positively with total cholesterol and negatively with HDL cholesterol. In this context, Kajantie et al [7] reported that weight gain during infancy was associated with higher total cholesterol and LDL cholesterol concentrations in adulthood. In addition, other studies have found that there are critical periods in early childhood related to an atherogenic lipid profile [8]. Obesity has also been associated with an unfavorable effect on concentration of lipids [9]. In our series, although we had no information about weight gain, the existence of a lower BMI in our congenital patients associated with a lower weight gain usually seen during childhood [10,11] could explain why congenital patients have lower lipid levels. However, weight per se is unlikely to be a major variable in determining lipid concentrations.

Physical inactivity in adolescence has also been related to fat accumulation and development of metabolic changes. Vasconelos et al [12], for example, found that more active young men showed lower total cholesterol and TG levels in comparison with their moderately active and sedentary peers. Similarly, Barnard [13] reported that most adults can significantly reduce serum lipid values and the risk of atherosclerosis through lifestyle modification consisting of diet and exercise. Although congenital heart disease patients tend to limit exercise because of the belief that physical activity or training may have a negative impact on them [14,15], the sedentary lifestyle of the normal population could limit the exercise benefit effect in noncongenital patients [16].

Age and sex have also been associated with cholesterol levels in young and middle-aged adults. Rao and Sastry [17] determined that serum lipid levels increased gradually with age until the end of the fourth decade, remaining almost unchanged afterward. Similarly, sex has been related to lipid levels [18,19], although in our series, and as seen in other studies [20,21], we did not find significant differences in total cholesterol or LDL cholesterol levels between male and female patients of both groups studied.

In the group of congenital heart disease patients, the only subgroup that obtained a significant difference in lipid levels was the atrioventricular septal defect one. This could be explained by the high percentage of patients with Down syndrome seen with this congenital malformation. Similarly, other studies have obtained decreased serum HDL cholesterol concentrations [22] and increased TG levels [22,23] in Down syndrome patients.

In relation to cyanosis, and as seen in our series, previous studies have determined that cyanotic patients have significantly lower total cholesterol and LDL cholesterol levels than acyanotic ones, suggesting related variables that might account for hypocholesterolomia such as cyanosis, hypoxemia, erythrocytosis, and genetic determinants [4]. In addition to all these possible effects, the recent discovery of cholesterol's involvement in embryo- and morphogenesis through its role in protein signal transduction proteins seems also to provide an explanation for the clinical overlap in the pathogenesis of various malformation and cholesterol levels [24].

With regard to plasma glucose concentrations, previous studies have reported that patients with left to right shunt, such as atrial, ventricular, or atrioventricular septal defects, have higher serum glucose levels than control ones due to an excessive clearance of insulin by the lung [3]. Similarly, patients with Eisenmenger syndrome can develop higher glucose levels in this context. However, cyanotic patients can also have lower fasting glucose levels due to chronic increases in circulating catecholamines and impaired nutritional status [25]. In patients with Down syndrome, the prevalence rate of type 1 diabetes mellitus is thought to be more. Anwar et al [26] calculated that the prevalence of diabetes in Down syndrome patients could be between 1.4% and 10.6%, a prevalence considerably higher than that in the general population.

Although we had the limitation of using 2 different analyzers in the case and control groups, the existence of no significant differences in the samples of aliquots split measured by each instrument allows us to have an accurate and comparable determination of serum glucose and lipid levels in both populations. Furthermore, it is important to emphasize that the prevalence of diabetes and metabolic syndrome in the Canary Islands is greater than that observed in most other European populations [6,27].

Patients with congenital heart disease should be closely followed up because their congenital abnormalities make their hearts more vulnerable to both the development of atherosclerosis and the adverse sequelae of a cardiovascular event. A sedentary lifestyle and the propensity to obesity in our current obesogenic environment are risk factors for accelerated atherosclerosis. This is particularly true in patients with coarctation of the aorta who usually have related systemic hypertension that may persist after correction. That is why it seems prudent to be aggressive about the evaluation of their cardiovascular disease risk status [28].

Further investigation should be carried out to understand and explain serum glucose and lipid levels in congenital heart disease patients ruling out other clinical and genetic risk factors that could play an import role in these findings.

References

[1] McGill Jr HC, McMahan CA, Malcom GT, et al. Effects of serum lipoproteins and smoking on atherosclerosis in young men and women. The PDAY Research Group. Pathobiological Determinants of Atherosclerosis in Youth. Arterioscler Thromb Vasc Biol 1997;17:95-106.
[2] Berenson GS, Srinivasan SR, Bao W, et al. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. N Engl J Med 1998;338:1650-6.
[3] Hait G, Corpus M, Lamarre FR, et al. Alteration of glucose and insulin metabolism in congenital heart disease. Circulation 1972;46:333-46.
[4] Fyfe A, Perloff JK, Niwa K, et al. Cyanotic congenital heart disease and coronary artery atherogenesis. Am J Cardiol 2005;96:283-90.
[5] Perloff JK. The coronary circulation in cyanotic congenital heart disease. Int J Cardiol 2004;97(Suppl 1):79-86.
[6] Boronat M, Varillas VF, Saavedra P, et al. Diabetes mellitus and impaired glucose regulation in the Canary Islands (Spain): prevalence and associated factors in the adult population of Telde, Gran Canaria. Diabet Med 2006;23:148-55.
[7] Kajantie E, Barker DJ, Osmond C, et al. Growth before 2 years of age and serum lipids 60 years later: the Helsinki Birth Cohort study. Int J Epidemiol 2008;37:280-9.
[8] Horta BL, Victora CG, Lima RC, et al. Weight gain in childhood and blood lipids in adolescence. Acta Paediatr 2009;98:1024-8.
[9] Gidding SS, Bao W, Srinivasan SR, et al. Effects of secular trends in obesity on coronary risk factors in children: the Bogalusa Heart Study. J Pediatr 1995;127:868-74.
[10] Hirose Y, Ichida F, Oshima Y. Developmental status of young infants with congenital heart disease. Pediatr Int 2007;49:468-71.
[11] Chen CW, Li CY, Wang JK. Growth and development of children with congenital heart disease. J Adv Nurs 2004;47:260-9.
[12] Vasconcelos I.Q., Stabelini Neto A., Mascarenhas L.P., et al. Cardiovascular risk factors in adolescents with different levels of energy expenditure. Arq Bras Cardiol. 2008;91:207-12, 227-33
[13] Barnard RJ. Effects of life-style modification on serum lipids. Arch Intern Med 1991;151:1389-94.
[14] Trojnarska O, Gwizdała A, Katarzyński S, et al. Evaluation of exercise capacity with cardiopulmonary exercise test and B-type natriuretic peptide in adults with congenital heart disease. Cardiol J 2009;16:133-41.
[15] Reybrouck T, Mertens L. Physical performance and physical activity in grown-up congenital heart disease. Eur J Cardiovasc Prev Rehabil 2005;12:498-502.
[16] Lake AA, Townshend T, Alvanides S, et al. Diet, physical activity, sedentary behaviour and perceptions of the environment in young adults. J Hum Nutr Diet 2009;22:444-54.
[17] Rao PN, Sastry NS. Serum cholesterol levels of males and females in different age groups in South India. Am JClin Nutr 1980;33:181-2.
[18] Lauer RM, Connor WE, Leaverton PE, et al. Coronary heart disease risk factors in school children: the Muscatine study. J Pediatr 1975;86:697-706.
[19] Srinivasan SR, Frerichs RR, Webber LS, et al. Serum lipoprotein profile in children from a biracial community: the Bogalusa Heart Study. Circulation 1976;54:309-18.
[20] Hickman TB, Briefel RR, Carroll MD, et al. Distributions and trends of serum lipid levels among United States children and adolescents ages 4-19 years: data from the Third National Health and Nutrition Examination Survey. Prev Med 1998;27:879-90.

[21] Webber LS, Osganian V, Luepker RV, et al. Cardiovascular risk factors among third grade children in four regions of the United States. The CATCH Study. Child and Adolescent Trial for Cardiovascular Health. Am J Epidemiol 1995;141:428-39.

[22] Pueschel SM, Craig WY, Haddow JE. Lipids and lipoproteins in persons with Down's syndrome. J Intellect Disabil Res 1992;36(Pt 4):365-9.

[23] Salo MK, Solakivi-Jaakkola T, Kivimäki T, et al. Plasma lipids and lipoproteins in Down's syndrome. Scand J Clin Lab Invest 1979;39:485-90.

[24] Waterham HR. Inherited disorders of cholesterol biosynthesis. Clin Genet 2002;61:393-403.

[25] Lundell KH, Sabel KG, Eriksson BO, et al. Glucose metabolism and insulin secretion in children with cyanotic congenital heart disease. Acta Paediatr 1997;86:1082-4.

[26] Anwar AJ, Walker JD, Frier BM. Type 1 diabetes mellitus and Down's syndrome: prevalence, management and diabetic complications. Diabet Med 1998;15:160-3.

[27] Boronat M, Chirino R, Varillas VF, et al. Prevalence of the metabolic syndrome in the island of Gran Canaria: comparison of three major diagnostic proposals. Diabet Med 2005;22:1751-6.

[28] Kavey RE, Allada V, Daniels SR, et al. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. Circulation 2006;114:2710-38.