Abnormally high lipoprotein(a) levels in african-american communities from venezuela faced to other african-descending populations: are ethnic origins related?

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Abstract

Objective. Lipoprotein(a) is an independent risk factor for coronary artery disease. In Venezuela, Lipoprotein(a) concentration in African descending populations is unknown. Thus, the aim of this study was to determine Lipoprotein(a) levels and lipid profile behavior in an Afro-Venezuelan sample from Bobures, Santa María and San José de Heras, townships located at Sucre municipality, in Zulia State, Bolivarian Republic of Venezuela.

Materials and Methods. 311 healthy Afro-American individuals were chosen by stratified random sampling. Lipoprotein(a) was quantified by double antibody ELISA method. Kolmogorov-Smirnov test demonstrated an non-normal Lipoprotein(a) distribution, and results are shown as median. Comparisons were made by Mann-Whitney test or one factor ANOVA (previous logarithmic conversion), according to the case, considering significant a value of $p < 0.05$.

Results. Lipid profile in African-Americans was normal, with the exception of HDL-c levels, which were diminished in Bobures township (38.59 ± 11.65mg/dL) presenting significant differences with Santa María (51.38 ± 14.46mg/dL; p=0.001) and San José (46.15 ± 11.99mg/dL; p=0.03). Lipoprotein(a) concentration in Afro-Americans was unusually high (Bobures: 59.00mg/dL; Santa María: 47.00mg/dL; San José: 41.00mg/dL). Likewise, Bobures township had a significantly higher concentration of Lipoprotein(a) regarding Santa María (p=0,009) and San José (p=0.02).

Conclusions. Lipoprotein(a) levels in these Afro-American groups are even higher than those reported previously in other black populations of USA and Africa; although, the prevalence of coronary artery disease and stroke is not higher when compared to other municipalities in Zulia state, finding that would be explained by a possible predominance of Lipoprotein(a) high size isoforms in these townships.

Key words: Lipoprotein (a), risk factor, Apo(a), cardiovascular disease.

Introduction

Cardiovascular diseases are the main cause of death in the adult population of westernized countries. High serum concentrations of lipoproteins, especially low density lipoproteins (LDL's) are related to atherosclerosis development[1]. Nonetheless, in recent years there has been an increased interest in the study of other lipoproteins such as Lipoprotein(a) [Lp(a)].

Lp(a) possesses high structural similarity with low density lipoproteins (LDL's). Both have an esterified cholesterol nucleus surrounded by an outlying layer of non esterified cholesterol and phospholipids as well as apoprotein B-100. However, the difference among both lipoproteins resides in an additional glycoprotein known as Apoprotein(a), [Apo(a)], which is linked to Apo B-100 through a disulfide bridge.

Apo(a) has an 89% structural homology with the plasminogen molecule[2,3]. This leads to a competition of Lp(a) and plasminogen for binding sites on tissue plasminogen activator (t-PA) and fibrin, interfering with normal fibrinolysis processes and conferring prothrombotic properties to the Lp(a) molecule[4].

As a result of these special structural features, the study of the Lp(a) molecule has become of great interest in the last two decades, being recognized as an independent risk factor for the development of coronary artery disease due to its pro-atherogenic (LDL similarity) and pro-thrombotic (competition and inhibition of the t-PA) properties.

Lp(a) plasma concentration is mainly determined by genetic factors (90%) and in smaller proportion by environmental agents (10%)[5]. This correlates with the unusually low variability exhibited by the concentration of this lipoprotein when comparisons according to age and sex are made. However, it has been demonstrated that black individuals present a higher Lp(a) concentration than Caucasian and Asian groups, doubling[6] or tripling[7,8] its levels in some cases. This fact confirms that Lp(a) plasma concentration significantly varies according to ethnic origins, agreeing with the current tendency of accepting heritage as the main determining factor of Lp(a) levels[2].

On the basis of all the facts previously exposed and the lack of epidemiologic studies aimed to describe Lp(a) behavior in our African-American populations, the objective of this research was to determine Lp(a) levels and lipid profile behavior in a sample of African-American natives from Sucre County of Zulia State, Venezuela.

Materials and methods

Patient selection

311 Black-American subjects clinically healthy, with Negroid phenotype family members in first and second grade, all natives of three African-Venezuelan populations from South of Lake Maracaibo (Sucre Municipality): Bobures (n = 55), San José de Heras (n = 109) and Santa María (n = 147), were chosen by stratified random sampling. With previous informed consent, a complete clinical history to discard any acute or chronic pathologic process that could modify Lp(a) concentration was done since many investigations classify this lipoprotein as an acute phase reactant[2], although this has been recently debated in studies headed by D. J. Byrne[9] and H. J. Milionis[10].

The Bolivarian Republic of Venezuela is conformed by a Capital District and 23 states. One of this is Zulia State, which is conformed by 21 municipalities including Maracaibo (Capital) and Sucre Municipalities. Sucre covers many townships including Bobures (Capital), Santa María and San José de Heras (Figure 1).

Figure 1. Zulia State

• Maracaibo Municipality

⦿ Sucre Municipality: Bobures, Santa María and San José de Heras townships.

Blood tests

Blood samples were taken by antecubital venipuncture after a 12 hour fast and were processed to obtain serum in which the Lp(a) concentration

was quantified by an ELISA method, using a combination of an anti-apo(a) monoclonal antibody and an anti-apoB monoclonal antibody (Heber Biotech BioSCREEN™ Lp(a), Habana, Cuba). This method is based on a sandwich-type ELISA, in which the ribbons of sumps are recovered with specific mouse monoclonal antibodies against Apo(a), that do not cross-link with human plasminogen[11].

Total cholesterol, triacylglycerides and HDL-c levels were determined by the enzymatic-colorimetric method (Human Gesselshaft für Biochemica und Diagnostica mbH, Germany) and precipitation, respectively. LDL-c and VLDL-c levels were determined by the Friedewald[12] formula. If triacylglyceride levels were above 400mg/dL, LDL-c quantifying was made directly by ultracentrifugation.

Statistical analysis

Data from the studied variables was processed by SPSS for Windows ver.15.0. Lp(a) distribution behavior was evaluated by the Kolmogorov-Smirnov Z test, resulting in an non-normal distribution; therefore, results are shown as median. Remaining variables are presented as mean ± standard deviation (SD). Comparisons between groups were made by Mann-Whitney test or one factor ANOVA (previous logarithmic conversion and Tukey post hoc test) according to the case, considering $p<0.05$ as a statistically significant value.

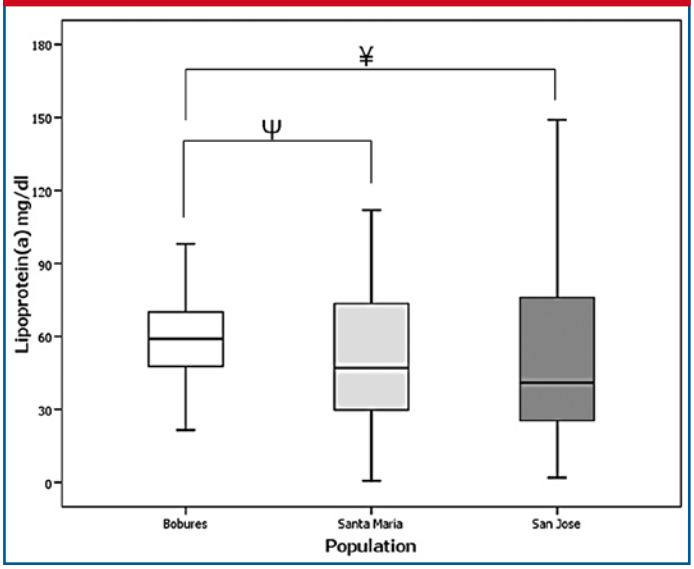
Lipoprotein(a) Behavior

Lp(a) levels were clearly high in African-descending groups from South Lake Maracaibo, presenting a median of 59.00mg/dL in the township of Bobures, 47.00mg/dL in Santa María and 41.00mg/dL in San José de Heras. Bobures presented lipoprotein(a) levels significantly higher than Santa María (p=0.009) and San José de Heras (p=0.02), (Graph 1). Lp(a) median was compared according to age (ten year ranges) and sex, finding statistically significant differences among gender in Santa Maria township, where women showed a median of 33.00mg/dl and men showed one of 57.00mg/dl (p=0.0002), (Graph 2).

Lipid Profile Behavior

Total cholesterol, triacilglycerides, VLDL-c and LDL-c levels were found normal according to the Adult Treatment Panel III (ATP III) guidelines[1]. HDL-c levels were significantly lower in the township of Bobures (38.59 ± 11.65mg/dl) compared with Santa María (51.38 ± 14.46mg/dL; p=0.001) and San José de Heras (46.15 ± 11.99mg/dL; p=0.03). Lipid profile values according to sex in the studied populations are illustrated in Table 1.

Graph 1. Median of serum Lipoprotein(a) concentration according to the studied population. It show significative differences in serum Lp(a) concentration to compare Bobures vs. Santa María (Ψ; p=0.009) and Bobures vs. San José (¥; p=0.02)



Graph 2. Median of serum Lp(a) concentration according to the population and sex. It shows significative differences in serum Lp(a) concentration according sex in Santa María townships. * = Significant difference (p=0.0002)

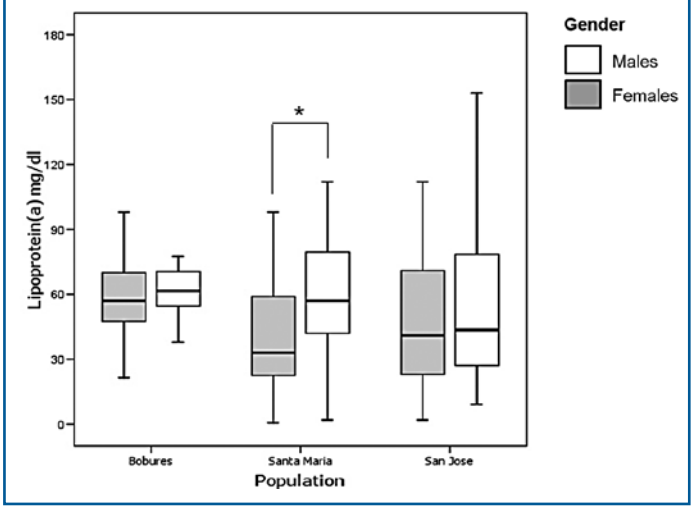


Table 1. Lipid Profile in the Studied Populations.

Population	Lipid Profile									
	CT (mg/dL)		LDL (mg/dL)		HDL (mg/dL)		VLDL (mg/dL)		TAG (mg/dL)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Bobures										
Men	157,90	34,20	100,10	33,08	41,89	13,95	17,80	9,95	81,40	44,62
Women	195,98	39,58	133,93	39,14	37,93	11,20	27,00	16,29	134,18	81,70
Both	189,05	41,11	127,78	40,05	38,59	11,64	25,29	15,65	124,58	78,69
San José										
Men	210,35	44,94	146,53	41,70	46,62	12,40	17,21	8,31	86,00	41,74
Women	200,22	37,53	134,30	33,15	45,93	11,87	19,18	10,70	95,99	53,58
Both	203,43	40,10	138,29	36,42	46,15	11,99	18,55	10,00	92,81	50,13
Santa María										
Men	200,69	45,62	134,32	44,12	47,14	12,39	20,15	12,27	103,10	62,08
Women	197,04	42,58	123,27	39,56	55,21	15,20	18,17	10,01	89,88	54,76
Both	198,81	43,95	128,70	42,05	51,38	14,46	19,13	11,16	96,30	58,59

Discussion

The physiological functions of Lp(a) remain unknown. Many investigations in the last twenty years have shown that high Lp(a) levels have pathogenic properties. Lp(a) is considered an independent risk factor for coronary artery disease[13]. Once the physiopathological role of Lp(a) as a pro-thrombotic and pro-atherogenic agent is elucidated, it becomes compulsory to determine its plasma concentration. Since its serum levels are determined genetically, in most cases it should not be necessary to determine Lp(a) levels more than once, which justifies the cost/benefit relationship.

The results previously exposed in this study in comparison with other researches, such as one carried out in 2007 by our research group, demonstrate significant differences among Lp(a) concentration according to ethnic origins. White Hispanic subjects from Maracaibo (a mixed urban population) showed a median of 11.50mg/dL[14] in contrast to unusually high values obtained from autochthonous Afro-American subjects from Sucre municipality, with statistically significant differences ($p < 0.001$).

Differences in Lp(a) levels according to ethnicity have already been described in the past. Even in 1987, Parra et al.[16] obtained evidence of this when comparing Lp(a) concentration in 81 individuals originary from Congo (median of 20.77mg/dL) with 81 white French individuals (median of 7.2mg/dL), observing statistically significant differences between these two groups ($p <0.0001$). Also, Sandholzer et al.[17] compared plasma Lp(a) concentration in 1150 individuals from different ethnic groups: Caucasian, (Iceland, Hungary and Tyrol), Asian (Malaysia, India and China) and African (Sudan), who were clustered according to phenotype characteristics, presenting the values that appear in Table 2.

It can be seen that the highest serum Lp(a) concentration in table 2 is expressed by the Sudanese group in comparison to other populations, agreeing with studies carried out in many other African-American-descending populations. However, their Lp(a) levels are lower than those found in our results (Bobures, 59.00mg/dl; Santa Maria, 47.00mg/dl). When these comparisons are made, it should be kept in mind that the results in Sandholzer's multiethnic study are expressed as arithmetic mean in all populations, even when an almost Gaussian distribution was only observed in the Sudanese group. This fact contrasts with our results, which are expressed as median due to the non-normal distribution of Lp(a) observed.

The ARIC study, with a total of 3,647 black and 10,574 white individuals, carried out by Tetsuya Ohira and cols.[6] found that black men have a median Lp(a) three times higher than white men (3.9 mg/dl vs. 11.9 mg/dl), similar situation revealed in females (4.8 mg/dl vs. 13.7 mg/dl), showing significant statistical differences if compared according to race ($p<0.001$) and gender ($p<0.001$), with males showing a higher Lp(a) concentration than females. These researches, along with the existent literature, show that phenotypical black race individuals exhibit a considerably higher Lp(a) concentration in comparison with other Caucasian and Asian populations, duplicating and even triplicating[6,7,8] in some cases their Lp(a) values.

Likewise, Howard and Cols.[7] in a sample of 4,125 individuals between the ages of 23 and 35, found Lipoprotein(a) levels three times higher in blacks (21.5 mg/dl in men and 23.9mg/dl in women), compared to whites (6.1 mg/dl in men and 6.4 mg/dl in women). Likewise, Okosun and Cols[18], related hyperlipoproteinemia(a) to a personal history of low birth weight in white and black children between the ages of 5 and 11, finding a mean (previous logarithmic conversion) of 13.7 ± 5.9mg/dl and 30.4 ± 9.9mg/dl for white and black children respectively, having these last ones an Lp(a) level twice as high as white children ($p<0.001$).

Table 2. Serum Lipoprotein(a) concentration (Mean) in several Multiethnic studies.

Population	n	Lp(a) (mg/dL)	SD
Tyrol[17]	279	14,1	19,4
Iceland[17]	184	13,5	17,7
Hungary[17]	202	8,3	11
Malaysia[17]	125	12,9	17,9
India[17]	143	20,1	15,9
China[17]	112	7,2	13,1
Sudan[17]	105	45,7	25,9
Venezuela[14]	500	11,45*	-
Brazil[13]	400	31,18	33,56
Nigeria[25]	252	12,7	7,2
EUA: Caucasian[28]	2158	6,9	7,1
EUA: Black[28]	2007	13,0	8,5
Cuba[29]	197	31,08	27,79

* = Value is showed as Median
P < 0.0001: for all populations, showing significant differences when comparing them, according to Kruskal Wallis test for the studied populations of the reference[17]

Thus, when comparing these results with ours, it is interesting to see that our populations from Sucre municipality not only exhibit a high serum Lp(a) concentration, but they also overcome, with values twice as higher, the mean observed on studies carried out by Howard[7] or Evans[19], where subjects with Nigerian origins, showed a mean of 24.0 mg/dl serum Lp(a) for the female group and 19.0 mg/dl for the male group. Furthermore, the arithmetic mean obtained by Okosun[18] reflects results which are almost half below ours. Therefore, our data exteriorize an unusual behavior of Lp(a) if compared with other afro-descending populations.

In most of the epidemiological literature reviewed, Lp(a) concentration in black people was not higher than 35.00mg/dl. This value contrasts significantly with the population of Bobures, which exhibits an Lp(a) median serum concentration of 59.00mg/dL, as well as the other two afroamerican populations (Santa María and San José) which show values over 40.00mg/dL.

For a full understanding of the unusual serum Lp(a) levels found in these African-American townships, it is necessary to deepen into the origins of these populations. Venezuela is a privileged territory with an extensive ethnic and cultural diversity, result of a historical, social, economic, geographical and political process. Thus, substantial genetic differences can be identified even inside the same state entity. Zulia State is not isolated from this reality, as it has been demonstrated in studies carried out by the Laboratory of Molecular Genetics of the Unit of Medical Genetics of Zulia University[21].

Zabala et al.[21] through an analysis of short tandem repeats loci (STR) demonstrated the genetic heterogeneity between ethnically diverse populations from Zulia State (Maracaibo, Toas Island and San José, as well as the indigenous ethnics, Yukpa and Bari). In an interesting way, Maracaibo's population exhibits a tri-racial origin with an important European contribution of 73.14 ± 1.11%, plus a 3.65 ± 0.92% due to African influences and a 23.22 ± 0.71% attributable to Amerindian origins contrary to San José's population (Sucre municipality) which possesses a 100% of African influences. To understand these discrepancies, it is inevitable to be remitted to the history of these townships. The prevalence of a Caucasian component in Maracaibo's population could be explained through the behavior of the migratory currents and the colonial process lived in this area, which resulted in a major European occupation, followed by an important race mixture and a mandatory reduction of the native population[22].

Contrary to Maracaibo's population, the autochthonous habitants of Sucre municipality (Bobures, Santa María, San José de Heras) remount their origins to sub-Saharan Africa in Cost of Gold and Cost of Slaves (Figure 2), as described in several Martínez J.D.'s[20,22] investigations, who was probably the most complete specialist in the afro-Caribbean culture and an active promoter and diffuser of unlimited data related to African traditions and their merger into local culture.

Figure 2. Migratory paths from subsaharian Africa to the south coast of Maracaibo's Lake

Kongo-Angolas (Congo-Angola)
Ewe Fon (Togo, Benín y Burkina Faso)
Fanti-Ashanti (Ghana, Sierra Leona y Guinea)

According to García's[23] observations, black communities of south Lake Maracaibo clearly exhibit a common afro-sub-Saharan origin, reaffirmed by cultural connections such as the presence of the long drum, the saya (a type of dance) and the chimbangle (instrument used to worship Saint Benito de Palermo),

name that descends from the term Imbangala, Kingdom of Angola, from where several captive groups proceeded[23,24].

These anthropologic and historical links have a special epidemiologic interest. Due to the genetic relationship between Sub-Saharan African people with Afro-American population established in the south coast of Lake Maracaibo, it is possible to find key similarities when comparing our results with others studies. In a Nigerian sample studied by Rotimi et al.[25] the median Lp(a) plasmatic concentration was compared with a US afro-American population, showing a marked difference between the 20.5 ± 12.0mg/dl found in the North American sample and the 12.7 ± 7.2mg/dl (p=0.0001) from the African population. Likely, other Nigerian groups studied by Osinubi.[26] had a mean serum Lp(a) of 22.1mg/dl. These results in comparison with our studies show apparent differences that might bring to the field the importance of environmental effects over Lp(a) serum concentration in the studied samples, hypothesis that needs to be proved.

Mortality reports of Sucre Municipality[15] might reflect these unusually high Lp(a) levels. Heart diseases are the main cause of death with a rate of 83.63 deaths for each 100,000 habitants in this municipality. Deaths due to stroke also play an important role in mortality indexes being the sixth cause of death among the first ten with a rate of 12.20 deaths for each 100,000 habitants. By finding these unusually high Lp(a) concentrations in our populations, it is expected to see a significant effect on mortality reports and hypothesize connecting relationships between elevated Lp(a) levels and high mortality rates due to coronary artery disease. Nonetheless, in spite of this high Lp(a) level, the mortality rates due to cardiovascular diseases and stroke do not show a disproportionate increase, when compared to those of other municipalities like Maracaibo (Heart Disease and Stroke rates in Maracaibo: 115.58 and 28.01 vs. Sucre: 83.63 and 12.20, respectively)[15] , showing even a lower mortality rate. However, it is important to emphasize that the Lp(a) isoform size also plays a key role in determining cardiovascular risk (considering the smaller particles as the most atherothrombogenic ones), variable that was not explored in the current research, which would represent our main limitation and also explain the lack of impact of the unusually high Lp(a) levels found on the mortality rate reports in these Afro-American populations from Zulia State.

This fact makes it indispensable to begin deep researches in these populations; studies involved with other topics like isoform size to ascertain its etiologic relationship with cardiovascular morbidity-mortality rate. After analyzing studies like Lugalawa[27] (1999), it can be established that the potential role of Lp(a) in the early stages and evolution of cardiovascular disease is not simple nor easily predictable by only determining the plasmatic Lp(a) concentration as a starting point.

Although genetics plays an important role in Lp(a) serum concentration, there are also other cited facts as isoform size, African origin of black Zulian and Venezuelan populations due to migration currents or environmental factors (nutrition, ethnic fusions) that explain the reason behind this phenomena. Moreover, for a precise elucidation of possible influences of serum Lp(a) concentration on the developing of cardiovascular disease in ethnically different people, further investigations must be made to deepen on the related variables, including Lp(a) isoforms identification, and its link to the phenotype of the studied individuals, establishing therefore predictable associations for ethnic origins, isoform size and cardiovascular risks.

High Lp(a) concentrations on black populations from the south coast of Lake Maracaibo, compared with other Afro American groups, which actually pose higher concentrations than any other ethnic group, impel the importance and the wake up call for further studies on the behavior of this variable in Venezuela. That being done, adequate preventive measures can be applied on all bendable risk factors, shortening the morbidity-mortality rate due to cardiovascular disease.

"If the UNESCO recognizes my work it must be for some reason. It does not matter if here they kick me when my work is internationally recognized... "

Juan de Dios Martínez Suárez

Dedicatory:
This article is dedicated to Juan de Dios Martínez Suárez (1945-2005), an exceptional Venezuelan researcher dedicated to the rescue, maintenance, and teaching of most of the African-Venezuelan culture and history. Investigator and friend who made possible that this and other works became a reality today.

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