Atherogenic Dyslipidemia in Latin America: Prevalence, causes and treatment


ABSTRACT

This is an executive summary made by a group of experts named Latin American Academy for the study of Lipids (ALALIP). In the current clinical guidelines, atherogenic dyslipidemia (AD) is a poorly recognized entity. Due to the frequent lipid alterations associated with AD in Latin America (LA), we organized a group of experts named (ALALIP) to generate a document in order to analyze their prevalence and to offer practical recommendations. Methodology: using the Delphi methodology, we conducted a comprehensive literature review with emphasis on those publications related to LA. Subsequently, we developed key questions for discussion. As a convention, those recommendations that had a 100% of acceptance were considered unanimous, those with ≥80% were consensual, and those with <80% were in disagreement. Results: a systematic analysis of national health surveys and regional cohort studies showed a consistently high prevalence of the lipid abnormalities that define AD: low levels of high-density lipoprotein cholesterol (HDL-C) range from 34.1% to 53.3% and elevated triglycerides (TG) range from 25.5% to 31.2%. These abnormalities could be related to high consumption of food with a high caloric density, cholesterol and trans fats, a sedentary lifestyle and perhaps epigenetic changes. Conclusions: lipid abnormalities that define AD have a high prevalence in LA. The interaction between an unfavorable lifestyle, inheritance and epigenetic changes is probably their cause. It is important to design a global study of risk factors in LA to know its true prevalence in the region, its consequences and to derive from its treatment strategies.

1. Foreword

AD is a clinical entity frequently underdiagnosed and not extensively treated. Current literature shows that AD is only briefly and superficially considered on preventive cardiology and lipid clinical guidelines [1].

AD is characterized by an increase in triglyceride-rich lipoproteins (TGLP), small and dense low-density lipoprotein particles (sdLDL-C), and a decrease in HDL-C. Scientific interest in TGLP across the years has fluctuated from being an important cause of atherosclerotic cardiovascular disease (ASCVD) to discarding them as a significant cardiovascular risk factor (CVRF). However, nowadays there is general agreement on their optimal diagnosis and treatment as a way to reduce the cardiovascular residual risk (CVRR).

LA has its own ethnic, socioeconomic and cultural characteristics and it is in the middle of an epidemiological transition that exposes its population to adverse variables such as a substantial increase in consumption of ultra-processed food (UPF) with a high caloric density (as fried flour and beverages with a high amount of sugar added), and a sedentary lifestyle related to the process of urbanization. These variables are causing a significant increase in obesity/overweight and cardiometabolic diseases (CMD) higher than in other regions of the world [2].

ALALIP performed a bibliographic research to analyze the prevalence of AD in LA in order to make specific recommendations to optimize...
its prevention, diagnosis and treatment with the aim to reduce CV morbidity and mortality in the region.

2. Methodology

A modification of the Delphi Method [3] was used to achieve a systematic and structured communication and to draw consensual conclusions derived from comprehensive discussions of the available evidences of AD in LA.

A panel of academic experts from different LA countries was selected and organized in small task force groups to answer specific questions later discussed and endorsed by the whole group. As a convention, those recommendations that had a 100% of acceptance were considered unanimous, those with >80% were consensual, and those with <80% in disagreement.

A systematic literature review using the bibliographic bases MEDLINE, ScIELO, Revencyt, BIREME, ScIENTI, LIVECS and PERIÓDICA was made to publications with data derived from epidemiological and clinical research in LA and/or with conclusions applicable to this region, using as key words: atherogenic dyslipidemia, triglycerides, triglyceride-rich lipoproteins, high-density lipoprotein cholesterol, CV risk, obesity, cardiometabolic disease and LA. Non-indexed medical literature, official publications and publications from international organizations were also selected if the methodology used for their elaboration was considered appropriate for the steering committee.

3. Definition of atherogenic dyslipidemia

AD is defined by [4]:

1. An increase of TGRLP.
2. Normal or slight increase in low-density lipoprotein cholesterol (LDL-C) mass on serum but with a predominance of sdLDL-C.
3. Elevated Non-HDL-cholesterol (total cholesterol minus HDL-C) as a surrogate for all atherogenic lipoproteins.
4. Low levels of HDL-C.

This altered lipid profile could favor the initiation and development of atherosclerosis [4], but it is poorly reflected in the traditional scales of risk [5,6].

4. Epidemiology of AD in LA

ASCVD is the first cause of death in LA, being both myocardial infarction (MI) and stroke responsible for 70% of these deaths. In both conditions atherosclerosis plays a major role influenced by the demographic, socio-economic and cultural changes seen in LA during the last few decades: increase in life expectancy, tobacco use, obesity and modification of feeding patterns, urbanization and sedentary lifestyle that, combined with a limited access to proper health care, have favored the growing incidence of ASCVD in LA [7,8].

5. What is the prevalence of AD in LA and how can it be compared with the rest of the world?

The results of all studies performed in LA that used representative samples of the general or regional population and that included a lipid profile are presented on the electronic appendix.

The 1992–1993 Health Survey from Mexico that included 2256 adults aged between 20 and 69 with blood samples taken after 9–12 h of fasting reported a prevalence of HDL-C < 35 mg/dL in 46.2% of men and 28.7% of women. A level of TG ≥ 150 mg/dL was found in 49.7% of men and in 30.8% of women showing an increase proportional to age. A combination of low HDL-C and elevated TG (≥ 200 mg/dL) was observed in 12.9%, being more prevalent in men than in women (20.9% vs 7.2%) [9]. This figures increased 41.8%, reaching a prevalence of 18.3% in a new survey, also made in Mexico in 2006 [10].

In the Chilean Survey, with a randomized sample of 4965 subjects (age 18 to 74), with blood test measured after 9 or more hours of fasting, the prevalence of TG ≥ 150 mg/dL was 31.2% (more frequent in men than in women: 35.6% vs 27.1%, respectively) and HDL-C < 40 mg/dL in men and < 50 mg/dL in women was 45.4% (more frequent in women than in men: 52.8% vs. 37.6%, respectively) [11].

A Dominican Republic [12], study made in 4976 adults (aged 18 to 75) reported a 30.7% prevalence of HDL-C < 40 mg/dL, being this significantly higher in men than in women (40% vs 26.4% respectively; p < 0.0001), and a 21% prevalence in TG > 150 mg/dL of 21% (26.3% males vs 18.3% females; p < 0.004,) [12].

The Latin American Consortium of Studies in Obesity (LASO) [13] analyzed the results from 11 cross-sectional independent population studies including a total of 31,019 participants. This study showed a 53.2% prevalence of low HDL-C ( < 40 mg/dL in men and < 50 mg/dL in women), and a 25% prevalence of high TG levels (≥ 150 mg/dL). It has been suggested a possible bias in this study since there was no central laboratory for sample processing.

In Venezuela, a study made in 3108 subjects with 20 or more years of age [14] showed that age-adjusted AD prevalence was 24.1%, with a low HDL-C frequency of 65%. Similar numbers (24.7%) were obtained in a several more recent studies [15].

All this scattered data has made us conclude that there is an urgent need to design a global epidemiological study in order to find out the real prevalence of AD in LA.

When comparing HDL-C and TG LA data with reports coming from other countries, a higher prevalence of these alterations was found in LA. The National Survey on Nutrition and Health (NHANES 2009–2010) showed a low HDL-C prevalence of 30.1% (95%CI: 29.9–33.2%), lower than the one found in LA [16]. Similarly, a study from Murcia (Spain) found a prevalence of low HDL-C of 27.3% (95%CI: 25.1–29.4%) [17]. These results suggest that the prevalence of low HDL-C in LA is higher than in other countries.

If we define a high TG level as ≥ 150 mg/dL, the prevalence of hypertriglyceridemia showed in the LA studies (with the only exception of the LASO study [15]) is, in general, higher than the one found in the NHANES study (24.3%; 95%CI:21.6–26.9%) [16] and in the Spanish study (22.8%; 95%CI: 25.1–29.4%) [17].

There are no studies in LA that have quantified the levels of sdLDL-C.

6. Which could be the cause for the prevalence of these lipid abnormalities in LA?

6.1. Socio-economic and cultural

LA has a series of ethnic, economic and cultural characteristics that are unique and that could possibly determine the high prevalence of AD lipid abnormalities in the region [18], besides, the psychosocial stress has been recognized as an additional and very important risk factor for ASCVD in LA [19].

6.2. Feeding patterns

6.2.1. Fats

Saturated fats are consumed in a similar way as in other underdeveloped regions of the world, but unsaturated FA are less consumed, especially omega-3 FA obtained from fish. There are countries like Argentina, Bolivia, Mexico and Paraguay where its consumption is < 50 g/day [20].

The most important sources of fats in LA are lard and fried foods, especially fried carbohydrate preparations.

6.2.2. Sugars and UPF

Refined sugars, soft beverages with sugar added and UPF are extensively consumed in LA since they are practical, ubiquitous, very

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well publicized, with an intense flavor and not less important, could be addictive [21,22].

The Pan-American Health Organization (PAHO) used national surveys from 12 countries from 1999 to 2013 and found a positive association between changes in per capita sales of UPF (in Kg) and average standardized changes in adult Body Mass Index (BMI) [21].

This study also showed that the LA market is third in the world after Asia and Canada with an increase by 50% between 2000 and 2013.

Educating the population and establishing public policies to modify these feeding patterns could be an unfulfilled opportunity to reduce obesity and AD in LA.

6.2.3. Genetics/Epigenetics

Epidemiological studies have shown that the most frequent lipid abnormality in LA is a low HDL-C. A recent publication has suggested that there is a genetic factor associated with hyper-α-lipoproteinemia in populations of native origin in LA [23].

Environmental factors like food can induce epigenetics changes: methylation and acetylation on the chromatin that alters the expression of the genetic code modifying the phenotype. These changes generate modifications in the genetic information, transcription on the quality and quantity of proteins and in the metabolic pathways regulated by these peptides [24] (Fig. 1).

The increase in CMD in LA could be the result of epigenetic changes due to the discrepancy between the nutritional milieu during the fetal period and early life, the so-called “first one thousand days” and the adult environment [25]. Perhaps the findings of the INTERHEART study [7], where obesity was the highest population attributable risk, could be a proof of this.

7. Pathophysiology of AD and its relationship with ASCVD

7.1. What mechanisms can cause AD?

Insulin resistance (IR) seems to be the main mechanism for AD production. Under normal conditions TG lipolysis on adipocytes is suppressed by insulin, but in the states of IR associated with abdominal obesity and overweight this phenomenon does not occur, resulting in an augmented production of free FA (FFA) on the portal circulation. These FFA reach the liver producing an augmented synthesis of TG and its consequence is an overproduction of particles of VLDL-C with apoprotein CII rich on TG that have a longer time of residence in plasma. Lipolysis of this excess of TG from VLDL produces remnants of VLDL, IDL and, finally, sdLDL.

VLDL rich in TG favors an exaggerated exchange of TG for cholesterol from HDL-C thanks to the action of the enzyme cholesterol-esters transfer protein (CETP) producing HDL-C particles abnormally charged with TG. These particles are later depleted of its TG content by the lipoprotein lipase hormone sensible and hepatic lipase producing HDL-C particles less efficient for the reverse cholesterol transport and eliminated more rapidly from circulation reducing its blood concentration [26–28].

7.2. Can excess of TG be considered the father of AD?

In IR states, the half-life of TRLP is prolonged in the post-prandial period due to their higher size and content of TG (post-prandial hypertriglyceridemia [29]). These cause that TRLP transports cholesterol in a higher proportion and consequently hypertriglyceridemia must be considered as a marker of an increase in numbers of atherogenic

Figure 1. Origin of atherogenic dyslipidemia.
particles [29]. In consequence in patients, with high levels of TG, LDL-C measurement sub-estimates the total burden of atherogenic particles in plasma; therefore, in these patients, Non-HDL-cholesterol gives us a better estimation of CV risk.

7.3. Are there any epidemiological evidences that prove AD is a cause of CV disease?

It is well-known that reductions in LDL-C produce substantial drops in CV morbidity and mortality; however, an important level of CVR [30] persists in these cases due to coexistence of other risk factors, individual basal risk, familial and genetic factors, and the presence of AD.

In a recent Mendelian randomization study [31] made in 73,513 individuals from the Copenhagen Heart Study, a genotype analysis for gen variants that could affect levels of cholesterol, LDL-C, non-fasting cholesterol remnants and HDL-C was performed in order to look for a causal association between lipoproteins and ischemic heart disease (IHD). This study showed that an increase in 39 mg/dL in non-fasting cholesterol remnants was proportionally associated with a 2.8 times increased risk of IHD, independently of low levels of HDL-C. This finding implies that the cholesterol content transported in TGLRP is related to IHD.

Based on the disparities found between fasting and non-fasting TG, it has been suggested that TGLRP levels [TGLRP = total cholesterol minus (LDL-C + HDL-C)] could be a better marker of risk instead of TG.

7.4. Can TGLRP generate atherosclerosis?

The TGLRP have a positive atherogenic potential due to [32]:

1. Small size: VLDL type 2 and its remnants cross the vascular endothelium easily without need of transport.
2. Remnants have approximately 40 times more cholesterol than LDL-C.

Table 1
Keeping a healthy weight
- Normal weight = BMI 20–25
- Weight reduction by 5–10%, if patient is overweight.
Recommended total daily calorie intake (TDCI)
- TDCI = 25–30 Kcal × Kg ideal weight
- Distribution = Carbohydrates 50%, Fats 25–35%, Proteins 15–20%
- Reduction of carbohydrate consumption
  - <50–60% of TDCI
  - Of fast absorption sugars or with a high glucose index
Modification of FFA and cholesterol consumption pattern
- Saturated FFA <7% of the TDCI
- Trans fats <1% of TDCI
- Mono-unsaturated FFA >20% of TDCI
- Poly-unsaturated FFA >10% of TDCI
- Consumption of olive oil
- Cholesterol <200 mg/day
Protein consumption
- <15% of the TDCI
Alcohol consumption
- Men ≤3 alcoholic beverages per day and/or <170 g per week
- Women ≤2 alcoholic beverages per day and/or <100 g per week
Salt consumption control
- Na+: <3 to 5 g per day (7.5–12.5 g of salt/day)
Physical exercise
- Walking (moderate physical activity) >150 min per week or 75 min of more vigorous physical activity per week. They must be combined with resistance exercises to prevent sarcopenia
Other elements
- >8 glasses of water per day
- Soluble fiber >20 g per day
- >5 daily rations of the following: fruits, vegetables, and integral cereals
- Control of psycho-social stress

BMI: Body Mass Index; TDCI: Total Calories Daily Intake; FFA: Free fatty acids.

3. Once in the sub-endothelium, the remnants could be phagocited by macrophages without oxidation to produce foam cells.

7.5. Why are sLDL-C particles more atherogenic?

They are more atherogenic because they have a few particular characteristics [33]:
1. Less affinity for the LDL receptor and a longer residence time in plasma.
2. Can penetrate 1.5–1.9 times more the endothelial barrier.
3. Higher affinity for sub-endothelial matrix proteoglycans.

7.6. Is atherosclerosis development stimulated by low levels of HDL-C?

There are multiple anti-atherosclerotic actions related to the HDL-C particles [34,35]. All these properties have contributed to the elaboration of a functional athero-thrombotic protection hypothesis that could explain a beneficial effect of HDL-C increase.

On the contrary, low HDL-C has been associated with the increased production of CV events [36]. In AD the high levels of TGLRP result in a smaller and dysfunctional HDL-C 3 rich in TG that in vitro does not have anti-atherogenic properties.

8. Population and individual measures to prevent and treat AD

8.1. How can AD be prevented on an individual and population scale?

Improvements in eating habits and lifestyle, an appropriate caloric content adapted to daily energy consumption and an increase in physical exercise help to prevent and minimize complications associated with dyslipidemia. A detailed review of useful non-pharmacological measures is out of the scope of this document, but some unanimous recommendations are shown in Table 1.

Despite the lack of LA studies, but keeping in mind the medical literature on this issue, some public policies could be recommended in our region:
1. To reduce availability and accessibility of UPF
2. To reduce the availability to trans fats
3. To increase availability to healthy food
4. To educate the population and to change the perception towards UPF and different sources of fats
5. To increase the education since childhood in the necessity of exercise and healthy life style

9. How can the diagnosis and treatment of AD be performed?

9.1. Should the lipid profile be done during fast?

This question continues to be controversial. Some recent publications [31,37] state that, comparatively, performing the lipid profile without fasting is more useful and more informative to the prediction of CV risk. Recently, two European scientific societies issued a joint consensus statement [37] saying that fasting is not routinely required to perform the lipid profile. We in a unanimous way do not recommend measuring TG during fast.

9.2. Which are the therapeutics goals in patients with AD?

Unanimously for our group is imperative to define and reach goals based on individual risk (Table 2) because are useful in the orientation of therapy, optimize and individualize risk reduction and monitoring adherence to therapy. Reduction of LDL-C is the primary objective in the treatment of dyslipidemia [30,38–40] LDL-C goals depend on the level of individual risk (low risk ≤130 mg/dL, intermediate risk ≤100 mg, and high and very high risk ≤70 mg/dL). Nevertheless, in patients with AD the sole evaluation and treatment of LDL-C...
underestimates CVR. For this reason, once the LDL-C goal is reached according to risk, we recommend considering the Non-HDL-C levels as a second therapeutic target (low risk ≤160 mg/dL, intermediate risk ≤130 mg, and high and very high risk ≤100 mg/dL). Also, considering that there is a close relationship between plasmatic concentration of apoB100 and Non-HDL-C, it is most reasonable and cost-effective to evaluate and treat the latter (see Table 2). We in a unanimous way consider that this approach gives a better reduction of the atherogenic potential of plasma in these patients [41,42].

10. Which drugs have been effective in the treatment of AD?

Patients that continue to show high levels of TG and Non-HDL-C after optimal treatment of LDL-C must receive drugs to reduce CVR associated to TGRLP. The following drugs have shown a beneficial effect on TG levels: fibrates, Omega 3 FA, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and niacin. Although their strength varies, these drugs have metabolic effects on the TGRLP, reducing effectively the TG and Non-HDL-C and increasing HDL-C.

A more detail description of these drugs is out of the scope of this article.

10.1. Pharmacologic treatment of AD

The ultimate goal of lipid-reducing therapy must be LDL-C, but those patients that continue to show high levels of TG and Non-HDL-C after optimal treatment must undergo pharmacological treatment in order to reduce CVR associated to TGRLP. The therapeutic recommendations made on this document are exclusively for patients with a TG level >200 mg/dL and <500 mg/dL as a way to reduce the risk of ASCVD.

We unanimously suggest that the treatment of AD must be based in correction of all metabolic alterations: reduction of TG and sLDL-C levels, increase of HDL-C, and acceleration of the clearance of all TGrLP. Combinations of drugs (statins plus Omega 3 FA and/or fibrates) are suggested, especially on secondary prevention and in patients with high CVR and AD that persist with HTG despite optimal treatment with statins.

A consensus was reached in our group to suggest a treatment paradigm on patients with AD in LA: after an optimal treatment with statins, the Non-HDL-C used as a surrogate of TGRLP must be treated to reduce CVR [43].

10.2. Is there a treatment algorithm for the patient with AD?

Based on our analysis of the current literature, as a consensus the following algorithm is suggested [44–46]:

<table>
<thead>
<tr>
<th>Basal TG levels (mg/dL)</th>
<th>Classification according to TG levels</th>
<th>Primary treatment objective</th>
<th>Secondary treatment objective</th>
<th>Pharmacological treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>150–199</td>
<td>Mild</td>
<td>LDL-C for reducing CVR</td>
<td>Non HDL-C for reducing CVR</td>
<td>Statins</td>
</tr>
<tr>
<td>200–499</td>
<td>Moderate</td>
<td>LDL-C for reducing CVR</td>
<td>Non HDL-C for reducing CVR</td>
<td>Ezetimibe</td>
</tr>
<tr>
<td>≥500</td>
<td>Severe</td>
<td>TG for reducing risk of pancreatitis</td>
<td>Non HDL-C for reducing CVR</td>
<td>Omega 3 FA</td>
</tr>
</tbody>
</table>

TG: Triglycerides; LDL-C: Low-Density Lipoprotein Cholesterol; CVR: Global Cardiovascular Risk; Non-HDL-C: Non High-Density Lipoprotein Cholesterol; FA: Fatty Acids.
1. Evaluate the global cardiovascular risk (GCVR). This is mandatory in order to estimate the chances of a CV event in the following 5 to 10 years. Although there are multiples scales (Framingham score [5], Systematic Coronary Risk Evaluation, SCORE) [6], it was not possible to recommend as a consensus one of them to LA patients since they have not been evaluated in the region. Therefore, we unanimously recommend that whichever scale the clinician uses in a patient, the same scale must be used on the follow-up. Also, we strongly suggest the urgent need to develop and validate a risk scale for LA.

Besides the risk calculation, a systematic search for subclinical atherosclerosis must be done. Finally, psychosocial stress in LA is a very important factor that should be taken into account.

2. Apply therapeutic changes to lifestyle (TCL) as an initial and vital step. (Table 1)

3. Identify the therapeutic objectives (LDL-C and Non-HDL-C) according to risk and TG levels (Table 2 and Fig. 2). On every successive visit, the patient must be inquired on the adherence to treatment. Additionally, we recommend building a team of nutritionists, psychologists and physical therapy technicians. Use of electronic applications is suggested.

4. Calculate the LDL-C and Non-HDL-C percentage of reduction to reach the goal.

5. Statins are the first choice. Choose the average statin that can reach the desired LDL-C goal. If the goal is not achieved, intensify treatment, add ezetimibe or chose a more powerful statin (Table 2).

6. If Non-HDL-C goal is not achieved, use a combination therapy with Omega 3 FA and/or fibrates (Table 2).

10.3. Therapy to achieve non-HDL-C goal

As it is well-known statins reduce levels of TG in 15–50% and increase HDL-C up to 15%. These last effects are proportional to the basal level of TG. Briefly:

- Statins are the first option to treat dyslipidemia.
- If Non-HDL-C levels remain high after having reached LDL-C level goals, a combined therapy must be chosen (Table 2), specifically, Omega 3 FA or new fibrates (fenofibrate and ciprofibrate [47, 48–50]) because the chance of interaction and adverse drug reaction of this combination is quite low.

11. Conclusions

In LA the lipid abnormalities related to AD have a high prevalence, probably higher than in other regions of the world. The causes are multiple: genetic load and epigenetic modifications combined with a sedentary lifestyle and an inadequate nutrition (high intake of UPF, trans fats and cholesterol, and sweetened beverages).

The primary goal in the treatment of AD is the reduction of the global cardiovascular risk according to the individual risk. Once it is achieved, it is necessary to reach the Non-HDL-C target adding Omega 3 FA and/or fibrates.

LA is a region with great economic and social inequities that imposes variable difficulties to the population to the access to proper diagnosis and treatment. For that reason, the prevention of ASCVD, based on a better understanding of our risk factors and our social and cultural characteristics, should be a priority with the additional advantage of its high cost-effectiveness. Cardiovascular prevention should not be an option, but an obligation.

It is important to clarify that our main objective with this work has been to help generate a hypothesis that could motivate to perform a big regional prospective study to provide us with a better understanding of the causes of this presumed high prevalence of AD in LA and its impact on CVD, and to encourage the design and implementation of public policies and medical actions to reduce the role of AD on CVD.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jcird.2017.05.059.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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