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REVIEW

New cardiovascular risk factors and physical activity

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Abstract

Recent research has suggested that a number of new cardiovascular risk factors should be added to the 'traditional' risk factors of hypercholesterolemia, hypertension, hyperglycaemia, nicotine poisoning, etc. Some of these non-conventional, 'emergent' conditions are related to plasma lipids whilst others, for example, markers of inflammation, homocysteinaemia, impaired fasting glycaemia and asymmetric dimethylarginine, are not. The emergent factors have obvious implications for preventative and therapeutic decisions. Physical exercise can have a modifying effect, though this is not, as yet, generally well known (especially with regard to homocysteinaemia and asymmetric dimethylarginine).

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PALABRAS CLAVE

Factores de riesgo cardiovascular;
Actividad física;
Homocisteinemia;
Dimetilarginina asimétrica

Los nuevos factores de riesgo cardiovascular y la actividad física

Resumen

Desde hace años se conocen varios factores de riesgo cardiovascular, llamados tradicionales, como son la hipercolesterolemia, la hipertensión, la hiperglucemia, el tabaquismo etc. Por otra parte, a lo largo de los últimos años han surgido con fuerza, estudios que proponen la introducción de nuevos factores de riesgo cardiovascular, no convencionales o «emergentes», varios de ellos relacionados con los lípidos plasmáticos, pero otros no, como son; los marcadores de inflamación, la homocisteinemia, la glucemia en ayunas alterada, y la dimetilarginina asimétrica. Con sus consiguientes implicaciones en las decisiones preventivas y terapéuticas. Estos factores de riesgo emergentes, también

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pueden ser modificados por el ejercicio físico, pero este efecto es poco conocido todavía, sobre todo en lo que respecta a la homocisteína y a la dimetilarginina asimétrica.

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Introduction

A cardiovascular risk factor (CRF) is a biological characteristic or behaviour that increases the possibility of cardiovascular disease (CVD).¹ The concept of risk factors first appeared some fifty years ago with the publication of the Framingham Study.² Since that time, advances in the field of epidemiology have made large scale clinical studies possible and have led to the identification of a series of cardiovascular disease risk factors that induce the formation of atheromatous plaques. The establishment of a specific biological characteristic, environmental factor or habit as a CRF requires a standardised methodology; concordant prospective studies; an added effect when various risk factors concur in an individual; and that the modification of the factor (in the case that the factor is modifiable) results in a diminution of the risk (Table 1).³

Historically, there has been clear evidence of a series of 'traditional' CRFs, such as hypercholesterolemia, hypertension, hyperglycaemia, nicotine poisoning, sedentarism, etc., which have been used in the stratification of individual risk.⁴ In the recent past, a number of important studies have proposed the inclusion of new or 'emergent' CRFs in the evaluation and stratification of cardiovascular risk and this has implications for preventative and therapeutic strategies.

Numerous documents and reports that include recommendations for the prevention of CVD and control of the

main cardiovascular risk factors have been published by national and international scientific institutions and organisations (from the USA, Europe,⁵ etc.). Following the latest recommendations of the world renowned National Cholesterol Education Program (NCEP),⁴ Table 1 lists the most significant 'traditional' CRFs whilst Table 2 shows the 'emergent' factors. Some of the 'new' factors have been recognised for decades though they have been subject to debate and controversy and consensus has not been reached on their inclusion in cardiovascular risk evaluation.

The NCEP Panel III identifies three classes of CRFs that influence the possibilities of suffering CVD, although only the first two are relevant to the modification of treatment objectives: major CRFs, factors linked to lifestyles and emergent risk factors.

Panel III recognises that, in addition to the main CRFs, CVD is influenced by the presence of other factors whose modification can have a positive effect on some of the major CRFs and reduce risk; these therefore represent direct treatment objectives. These factors act through other intermediate elements or worsen independent risk factors such as, obesity, sedentarism, a family history of premature CVD, psychosocial conditions or being male. Although they do not figure in algorithm calculations on the stratification of risk,⁶ two of them, obesity and sedentarism, are considered as causal CRFs by the American Heart Association.

Traditional cardiovascular risk factors

Lipid risk factors

Hypercholesterolemia is one of the main cardiovascular risk factors that is modifiable. The *Multiple Risk Factor Intervention Trial* demonstrated the existence of a continuous and

Table 1 Major ('traditional') cardiovascular risk factors.⁴

Age and sex (men ≥ 45 years old, women ≥ 55 years old)
Nicotine poisoning
Arterial hypertension (AP $\geq 140/90$ mmHg or undergoing antihypertensive treatment)
Increased LDL cholesterol
Fall in HDL cholesterol (< 40 mg/dl) ^a
Family history of premature coronary heart disease
Male first degree relatives < 55 years
Female first degree relatives < 65 years
Diabetes mellitus ^b
Lifestyle (overweight/obesity, sedentarism, atherogenic diet) ^c

AP: arterial pressure; HDL: high density lipoproteins; LDL: low density lipoproteins.

^aAdapted from the National Cholesterol Education Program (NCEP)⁴.

^bIf HDL cholesterol is ≥ 60 mg/dl, it is considered as a 'negative' risk factor".

^cDiabetes mellitus carries a risk equivalent to a secondary prevention situation.

^dThese factors are not computed in the algorithms for stratification of risk.

Table 2 Emergent cardiovascular risk factors.

Lipid risk factors
Total cholesterol quotient/HDL cholesterol
Apolipoproteins
HDL subclasses
Triglycerides
"Small and dense" LDL particles
Residual or remnant lipoproteins
Non-lipid risk factors
Markers of inflammation
Homocysteinaemia
Impaired fasting glycaemia
Thrombogenic/hemostatic factors

HDL: high-density lipoproteins; LDL: low-density lipoproteins.

graded relationship between cholesterolemia and total mortality and mortality due to ischemic heart disease.⁷

The three main classes of lipoproteins are: low-density lipoproteins (LDLs); high-density lipoproteins (HDLs); and very low-density lipoproteins (VLDLs). There is another class of lipoproteins known as intermediate-density lipoproteins (IDLs) that is between VLDL and LDL, though in clinical practice, it is included in the LDL category.

With the exception of HDLs, which play a role in reverse cholesterol transport and therefore exercise a vasoprotector action, lipid particles are more atherogenic due to the more cholesterol that they transport. Chylomicrons carry such a small quantity of cholesterol that their increase in hyperchylomicronemia (type I dyslipidemia) is not associated with arteriosclerosis lesions. In contrast, with the accumulation of VLDLs, a fifth of which are made up of cholesterol, an increase in atherogenesis is observed. Given that LDLs are particles with a higher level of cholesterol, they are the main cause of atherogenesis when they are in excess.

Levels of HDL cholesterol are inversely related with the risk of CVD; they seem to play a protective role against the onset of atherosclerosis as they capture free cholesterol from the peripheric tissues such as the cells of the vascular wall. This cholesterol is transformed into cholesterol esters, a part of which is transferred to the VLDLs by the cholesterol esters transfer proteins (CETPs) and returned to the liver by IDLs and LDLs and another part is transferred directly to the liver by the HDL particles. The liver reuses the cholesterol for the synthesis of VLDLs, for the synthesis of bile salts or excretes it directly into the bile. Therefore, HDLs tend to reduce cholesterol levels.

Although LDLs receive most attention in clinical management, there is a growing body of evidence that indicates that VLDLs play an important role in atherogenesis.

Non-lipid risk factors

Hypertension

Hypertension is a principal and independent CRF, but its damaging effect is increased when associated with other coronary risk factors such as smoking, diabetes and dyslipidemia. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure defines hypertension as a systolic arterial pressure of ≥ 140 mmHg or diastolic ≥ 90 mmHg or the need for antihypertensive treatment.⁸ A number of studies, for example the Framingham study, have demonstrated an increase in total mortality and cardiovascular risk in cases of increased levels of arterial pressure (diastolic and systolic), with a continuous and gradual relationship.⁹⁻¹¹ The association applies to men and women, young and old alike.

Smoking

Smoking contributes to CVD. The relationship between smoking and the risk of CVD is dose dependent and affects men and women equally. Observational studies suggest that stopping smoking leads to a substantial reduction of the risk of a cardiovascular event.

Diabetes

Diabetes is defined as the presence of a level of glucose, on an empty stomach, more than, or equal to, 126 mg/dL.¹² The risk of cardiovascular disease is significantly increased for sufferers of diabetes mellitus type 1 and type 2.¹³ The increase of risk attributed to hyperglycaemia is independent of other risk factors such as obesity, overweight or dyslipidemia that are often observed in diabetics.

Mortality in 80% of diabetes mellitus patients is caused by complications associated with atherosclerosis with ischemic heart disease being responsible in 75% of cases.¹⁴ In addition, the risk of acute myocardial infarction in diabetes mellitus type 2 patients with no previous history of myocardial infarction is similar to non-diabetics who have previously suffered a heart attack.¹⁵

Although it is probable that strict control of diabetes reduces micro-vascular disorders and other complications such as renal disease and retinopathies, statistics relative to the effects of glycemic control on coronary episodes are uncertain. Diabetics often present dyslipidemia, characterised by moderate hypercholesterolemia and hypertriglyceridemia with low concentrations of HDL cholesterol that involve increased cardiovascular risk. This is frequently associated with central obesity, hyperinsulinism and AHT. Therefore, the association of numerous CRFs explains why many individuals already exhibit disorders when they are diagnosed with diabetes mellitus.

Emergent cardiovascular risk factors

Apolipoproteins

Apolipoprotein A

Apolipoproteins are a group of proteins that are variably distributed among different lipoproteins. Apo A-I is the most abundant apolipoprotein in plasma and is nearly 90% of the HDL and 60–70% of the protein fraction of the sub-fractions HDL2 and HDL3, respectively. Apo A-I is initially synthesised in the liver and intestine as a protein precursor, which is degraded to its mature form in plasma; it is a simple polypeptide chain that contains 243 amino acids. It is the highest concentration protein component of HDL and participates in the reverse transport of cholesterol. The apolipoprotein apo A-II is the second highest concentration protein component of HDL, although it is absent in the HDL2 sub-fraction and plasma levels do not correlate with HDL-cholesterol levels.

The measurement of concentration of apo A-1 in serum perfectly reproduces the predictive value of coronary disease of concentration of HDL in serum. Nevertheless, this correlation is not valid in subjects with hypertriglyceridemia, in which the fraction of HDL is enriched with triglycerides and cholesterol is almost absent.

Results of some studies have shown that the relationship between apo B/apo A-1 is better for evaluating cardiovascular risk than the total cholesterol/HDL cholesterol relationship or LDL cholesterol/HDL.^{16,17} The number of particles and, in particular, the balance between them, that is to say, the apo B/apo A-1 relationship, may be more important than the lipid quantity carried by each particle.

Apolipoprotein B

B apolipoprotein is a protein of large molecular weight, present in chylomicrons and VLDL and LDL lipoproteins. There are two molecular forms in plasma, apo B-100 (apo B) and apo B-48. Apo B is a unique polypeptide chain of 4536 amino acids (one of the biggest plasma proteins), synthesised in the liver and secreted in VLDLs. It is quantitatively maintained during the conversion of VLDL to IDL until LDL, of which it is the only protein component, and for this reason, levels of apo B are correlated with levels of these lipoproteins. Studies have established the relationship between B concentrations in serum and cardiovascular risk.^{18–20}

Given that each particle of VLDL, IDL and LDL contains only one apo B molecule, its concentration in serum reflects the risk associated with all these atherogenic particles. Although considered as a risk factor by the NCEP, its determination is not recommended in clinical practice, due to the unavailability of clinical guides or risk stratification algorithms based on its concentration.

Nevertheless, from an experimental point of view, it can offer important additional information. Concentration of apo B in serum provides data on the number of particles, especially LDL particles, as they contain approximately 90% of total circulating apo B. It has been suggested that a LDL/decreased apo B relationship is an indicator of the predominance of small and dense LDL particles.²¹

The estimation of LDL cholesterol using the Friedewald formula is inexact when triglycerides levels are higher than 300 mg/dl and, if no validated direct method or ultracentrifugation is available, the concentration of apo B can be used as an alternative for the stratification of risk and the setting of therapeutic objectives.²² A modification of the Friedewald formula has been described for the calculation of LDL cholesterol that includes apo B. The LDL cholesterol obtained in this way has been shown to be more independent of hypertriglyceridemia than calculations made with the Friedewald formula.²³

Triglycerides

In spite of the evidence put forward by some epidemiological studies on the relationship between hypertriglyceridemia and incidence of CVD,^{24,25} results of other, more recent, multivariate works do not allow the definitive classification of triglycerides as an independent CRF.⁴ This is due to the close relationship between increased levels of triglycerides and other lipid CRFs (the presence of residual lipoproteins or remnants of VLDLs and chylomicrons in plasma, the predominance of 'small and dense' particles of LDL in plasma or decreased plasma concentration of HDL cholesterol), non-lipid CRFs (hypertension) and emergent CRFs (glucose intolerance, prothrombotic state). The NCEP Panel III believes that increases in levels of triglycerides (>200 mg/dL) are associated with a higher risk of CVD. It is also commonly associated with other lipid and non-lipid risk factors and indicates that therapeutic objectives should be based on lifestyle changes (loss of weight, physical exercise, stopping smoking). Aerobic exercise reduces levels of triglycerides and total cholesterol and may increase levels of HDLs, especially if accompanied by weight loss.

Lipoprotein (a)

In recent years, lipoprotein (a) has attracted enormous interest as a cardiovascular risk factor.^{26,27} Lp(a) is a spherical lipoprotein, rich in cholesterol esters and phospholipids. It has a composition that is similar to LDL and contains a specific glycoprotein, apolipoprotein (a), linked by a disulphide bridge to the apolipoprotein B-100. In addition, it has great structural homology to the plasminogen fibrinolytic proenzyme (Figure 1).²⁸

A variety of mechanisms that may explain the relationship between Lp(a) and cardiovascular disease have been described in published works. Firstly, it is argued that as Lp(a) is an LDL particle it plays a role in the initiation, progression and possible rupture of the atheromatous plaque. Secondly, it is suggested that this particle competes with the plasminogen particle and inhibits thrombolytic activity.²⁹ Finally, cell line studies with rats have shown that lipoprotein (a) inhibits NO synthesis.³⁰

Although an increase in the plasma concentration of Lp(a) implies a higher risk of CVD, mainly in individuals at greater global risk,³¹ the principal consensus documents, such as the NCEP Panel III and the latest European STORE project proposal³², do not include it among cardiovascular risk factors that are computable for the evaluation of overall risk. This is due to the fact that some studies do not corroborate independent prediction, based on Lp(a) levels, of suffering CVD^{33,34} and there is no evidence that elimination benefits the patient.³⁵

Ultra-sensitive CRP

The inflammatory process characterises all phases of atherothrombotic development. There are many studies that relate a variety of elements that intervene in the inflammatory process with the risk of CVD. These elements include the intercellular-1 adhesion molecule (ICAM-1); the vascular-1 adhesion molecule (VCAM-1); E-selectin; P-selectin; and proinflammatory cytokines, such as interleukine-6 (IL-6), and the tumor necrosis factor-alpha (TNF- α). All of the aforementioned have been shown to be predictors of CRFs.³⁶ In clinical practice, difficulties in determining these markers and the short half-life of these molecules in circulatory blood mean that it is not possible to include them in the daily clinical routine. Of the other

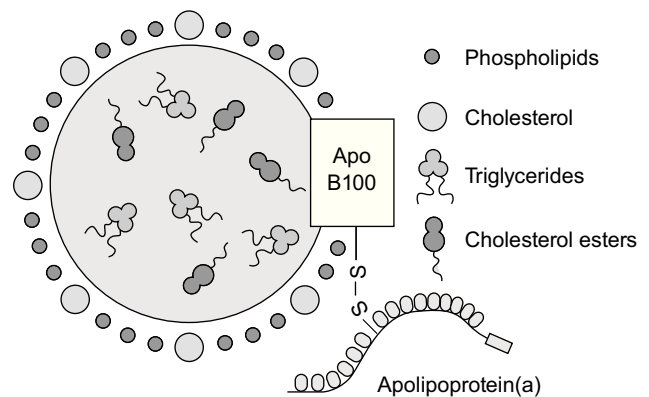


Figure 1 Structure of lipoprotein (a).

markers of inflammation that have been suggested, such as serum amyloid A, the leukocyte count, fibrinogen, nitrotyrosine, myeloperoxidase and c-reactive protein (CRP), only the latter has been consolidated as a candidate due to its stability, analysis precision and accessibility.³⁷ The AHA and CDC (Centers for Disease Control) say that of all the markers of inflammation, only ultra-sensitive CRP (US-CRP) has the characteristics necessary for use in clinical practice.³⁸

Ultra-sensitive CRP (US-CRP) is currently the best characterised inflammation biomarker and has been established as a potential marker of cardiovascular risk. US-CRP in plasma is a firm candidate for use in clinical practice as it is considered as an independent predictor of coronary illness for the general population, for both sexes and for patients who have already presented clinical manifestations of CVD.^{36,37}

CRP is a member of the pentraxin family of proteins, which are characterised by having a pentameric structure and radial symmetry, formed by five protomers of 24 kD and 206 amino acids that are linked among themselves by non-covalent bonds and have the capacity to bond to a great variety of substances, such as phosphocholine, fibronectin, chromatin, histones and ribonucleoproteins.³⁹

The differentiation of monocytes and macrophages that takes place during atherosclerotic process frees proinflammatory molecules, which include interleukin-6 (IL-6), which activates, in the liver, the liberation of inflammation markers like CRP. High levels (> 10 mg/dl) are registered in bacterial infections though ultra-sensitive analysis can detect very low levels (0–3 mg/dl) that are associated with the atherosclerotic process. Their half-life is more than 24 h and their blood levels are not altered by diet.

Homocysteine

In the last decade, numerous studies have been published that relate homocysteinaemia (Hcy) increases to CVD.^{40–44} Nevertheless, the mechanism that controls this relationship is not completely understood. Homocysteine has a direct cytotoxic effect on endothelial cells in cultivation. An alteration in endothelial function has been observed, evaluated by echo-Doppler, in individuals with moderate hyperhomocysteinaemia and improvements have been noted on reducing the concentration of homocysteine by means of folic acid treatment. It should be remembered that levels of plasma homocysteine are related to levels of vitamin B12 and folic acid.⁴⁵

Homocysteine can promote LDL oxidation through the production of reactive oxygen species such as hydrogen peroxide and studies have described the promotion of the multiplication of smooth muscle cells and a reduction in DNA synthesis in endothelial cells. A large number of prospective and retrospective studies support the hypothesis that an excess of plasma homocysteine is associated with a higher risk of coronary illness, peripheral and cerebrovascular disease.^{43,46–48}

Asymmetric dimethylarginine

The relationship established between a high concentration of asymmetric dimethylarginine (ADMA) and endothelial

dysfunction and the possible relationship between high ADMA values and the incidence of cardiovascular accidents has led a number of research groups to study the association between high ADMA and death by any cause.

Some studies indicate that ADMA plasma levels may predict the risk of cardiovascular events. In 2001, Valkonen et al.⁴⁹ showed that subjects with ADMA levels of more than 0.62 $\mu\text{mol/L}$ (percentile 75) had almost four times more risk of suffering an acute cardiovascular event. Similar results have been described by other authors in cases of patients with unstable angina; it was noted that those patients with higher ADMA levels (> 0.62 $\mu\text{mol/L}$, percentile 75) had five times more risk of suffering a cardiovascular event.⁵⁰

Zoccali et al.⁵¹ showed that in haemodialysis patients, ADMA plasma levels are an independent predictor of mortality and cardiovascular risk. In their multivariate study, only ADMA and age were significantly predictive, independent of the incidence of cardiovascular episodes (such as chest angina and heart attack) and death by any cause. Patients whose concentration of plasma ADMA was above the percentile 75 had three times more risk of suffering a cardiovascular episode than patients whose initial ADMA levels were lower than the average.

There are currently a number of case studies, controls and prospective clinical trials taking place with a variety of patient populations that are aimed at gaining greater understanding of the role of ADMA as an independent risk factor for CVD and mortality. The data generated by these studies will help determine the significance of ADMA as a risk factor and explore its diagnostic importance in different illnesses and diseases.

Cardiovascular risk factors and physical activity

There is much research on the effect of physical activity on the alteration of risk factors associated with heart disease. The most beneficial effect of exercise is on the level of oxidative metabolism, which influences levels of lipids in the blood. Although reductions in total cholesterol and LDL cholesterol generated by physical exercise seem to be relatively small (in general, they are less than 10%), there are important increases in HDL cholesterol and significant reductions in triglycerides. Transversal studies with sportspersons and non-sportspersons unequivocally demonstrate that individuals with higher levels of aerobic activity have higher HDL levels and lower levels of triglycerides. Nevertheless, results from longitudinal studies, over relatively long periods of time, are much less clear. Many studies on physical exercise have described the increase in HDL and the reduction in triglycerides but others have described very small changes or no changes at all. However, almost all studies have shown that proportions of LDL/HDL and total cholesterol/HDL fall after resistance training and this means less cardiovascular risk.

It must not be forgotten that one of the significant factors, both in terms of lipids and the other biochemical parameters expressed as a concentration, in the evaluation of changes engendered by physical exercise, is the change in the volume of blood that affects plasma concentrations, independently of changes in lipid totals. The failure to correctly take this factor into account could explain some of

the controversies concerning studies on CRFs and physical exercise.

There are reliable data that demonstrate the effectiveness of physical exercise on the reduction in blood pressure in patients with mild or moderate hypertension. Resistance training can reduce SAT and DAT by approximately 10 mmHg, in individuals with moderate essential hypertension.

With regard to the other traditional cardiovascular risk factors, physical exercise can play a role in the reduction and control of weight and in the control of diabetes. Exercise has also been shown to be effective in the control and reduction of stress and anxiety.⁵²

Whilst the effect of exercise on 'traditional' CRFs is well documented, the effect of exercise on 'emergent' CRFs has not been studied in depth and results are not well known.

The beneficial effects of exercise, leading to the reduction of levels of apolipoprotein B, have been widely reported, but this has not been the case with the relationship between exercise and levels of apolipoprotein A-1.^{53,54} Some authors have found that long-term, regular physical exercise does not seem to modify levels of apolipoproteins in comparison with sedentary groups.⁵⁵ There is relatively little information available on levels of lipoprotein (a) in young people although some studies have confirmed a favourable relationship between regular physical exercise and levels of lipoprotein (a).^{53,55}

The previously mentioned studies have been undertaken by different authors with different population groups and there are no published works that, at the same time, analyse the influence of intense physical exercise and the influence of continuous physical exercise (training) on levels of apolipoproteins A-1, B and lipoproteins (a), in the same population group.

The beneficial effects of physical exercise also seem to be related to the effect on the inflammatory process. In the short term, intense physical exercise produces a transitory inflammatory response, which is reflected in an increase in acute phase reactants and cytokines that is proportional to the amount of exercise and muscle damage. Nevertheless, regular physical activity (training) is associated with a chronic anti-inflammatory response that influences levels of acute phase reactants such as ultra-sensitive CRP and also affects lipids and lipoproteins.^{56–58}

Some factors (BMI, sex of the subject, moment when the post-exercise sample is taken, diet, etc.) can have an influence on the response of ultra-sensitive CRP to physical exercise.⁵⁷ Another issue that must be taken into account is that many studies that have examined the effects of intense physical exercise on levels of ultra-sensitive CRP have not made a concentration correction in accordance with the changes in plasma volume after exercise.⁵⁷ Results should be individually corrected according to the post-exercise levels of hemoconcentration or hemodilution.⁵⁹

With regard to homocysteine, studies with large population groups have shown that regular physical exercise can reduce homocysteine plasma levels.^{46,60,61} However, other studies have concluded that intense physical exercise increases levels of Hcy.^{62,63} More recent studies, undertaken by our work group,⁶⁴ demonstrate increased plasma homocysteine levels, both in total and reduced, after intense exercise. This increase is independent of the type of exercise and the vitamin level but could be related to

changes in renal function.⁶⁴ The mechanism of this effect is not clearly understood though a study on alterations in the redox state of the homocysteine might lead to the comprehension of the underlying process. Furthermore, a study on its relationship with plasma concentrations of NO, ADMA and their proximate metabolites might lead to an understanding of how intense physical exercise produces an increase in levels of homocysteine, as long as regular, moderate physical exercise (training) seems to be a beneficial modulator of homocysteine. Also related to homocysteine is the proven fact that that regular physical exercise produces a series of beneficial effects on oxidative metabolism, which result in less oxidative stress and a greater defensive capacity against oxidative damage; this is caused by the increase in activity of endogenous antioxidant systems and the greater resistance of the LDL particles to oxidation.^{64,65} All this signifies a reduction in oxidised LDL levels and systematic markers of inflammation, as explained by Arquer et al.⁶⁵ in 2010.

In spite of the fact that the role of ADMA as a cardiovascular risk marker is reflected in an increasing number of clinical studies and scientific publications, no studies have looked at the effect of intense or sustained (training) physical exercise on ADMA plasma levels.

It is therefore recommended that studies should be undertaken on the effect of intense and sustained (training) physical exercise on emergent cardiovascular risk factors, especially on homocysteine and ADMA.

Conflict of interests

The authors have no conflicts of interest.

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