The lipid triad, or how to reduce residual cardiovascular risk?

La triade lipidique ou comment réduire le risque vasculaire résiduel ?

S. Girard-Mauduit

Service d’endocrinologie-diabétologie, hôpital Ambroise-Paré, 9, avenue Charles-de-Gaulle, 92100 Boulogne-Billancourt, France

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Résumé

Depuis les premières études d’intervention sur le cholestérol, de nombreux et larges essais prospectifs ont montré que les statines permettaient de réduire le risque d’évènement cardiovasculaire majeur de 25 à 35 %. Cependant, malgré la baisse globale du niveau de LDL-cholestérol dans la population générale depuis 20 ans et les traitements par statines, on constate la persistance d’un risque vasculaire résiduel important chez certains patients. Ce risque résiduel est constaté essentiellement chez les patients porteurs d’une dyslipidémie athérogène, associant HDL-cholestérol bas, hypertriglycéridémie et une prépondérance de particules de LDL-cholestérol petites et denses, profil fréquemment retrouvé en cas de diabète non insulinodépendant, d’obésité ou de syndrome métabolique et que l’on nomme la « triade lipidique ». La nette augmentation de la prévalence de ces anomalies métaboliques dans la population mondiale remet en cause les bénéfices acquis ces dernières années dans la prévention cardiovasculaire. Non seulement il paraît indispensable d’améliorer le traitement de tous les facteurs de risque (HTA, tabac, etc), mais il semble désormais nécessaire de prendre en charge l’ensemble des paramètres lipidiques, en diminuant le LDL, mais aussi les triglycérides et en augmentant le HDL. Le développement de nouvelles voies de recherche et la mise à disposition de nouvelles molécules ayant apporté la preuve de leur efficacité clinique notamment concernant le HDL sont particulièrement attendus.

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Mots clés : Dyslipidémie ; Syndrome métabolique ; Statines ; Fibrates ; Acide nicotinique ; Laropiprant

Abstract

Since the first interventional studies on cholesterol, many large prospective trials have demonstrated that the statins can reduce the risk of a major cardiovascular event by 25 to 35%. But, in spite of the overall decrease in LDL-cholesterol in the general population over the last 20 years and treatments with statins, the persistence of a high residual vascular risk is observed in some patients. This residual risk is observed mainly in patients with atherogenic dyslipidaemia with low HDL-cholesterol, elevated triglycerides and a preponderance of small and dense LDL-cholesterol particles, a profile frequently found in patients with non-insulin dependent diabetes mellitus (NIDDM), obesity or metabolic syndrome and which has been called the « lipid triad ». The frank increase in the prevalence of these metabolic abnormalities in populations worldwide casts doubt on the benefits acquired over the last few years in cardiovascular prevention. Not only does it appear essential to improve the treatment of all risk factors (hypertension, smoking, etc.), but it now seems necessary to manage all lipid parameters by decreasing LDL and also triglycerides and by increasing HDL. The development of new pathways of research and the introduction of novel compounds, which have demonstrated their clinical effectiveness, with regard to HDL in particular, are awaited.

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Keywords: Dyslipidaemia; Metabolic syndrome; Statins; Fibrates; Nicotinic acid; Laropiprant

Since generalisation of treatment with statins, cardiovascular (CV) morbidity and mortality has decreased by 25 to 35% in western countries. But, in spite of the decrease in LDL-cholesterol (LDL), a high residual vascular risk (RVR) persists in some patients, partly as a result of the current worldwide epidemic of obesity, metabolic syndrome and type 2 diabetes (NIDDM).

1. Why the interest in metabolic syndrome today?

Although no real consensus exists on the exact definition of metabolic syndrome and despite the fact that it is a subject
of controversy [1,2,3], nevertheless, currently the majority of experts agree in recognising that metabolic syndrome is based on the existence of insulin-resistance and hyperinsulinism, and that it is a combination of some or all of the following abnormalities [4]: carbohydrate intolerance or type 2 diabetes (NIDDM), arterial hypertension, dyslipidaemia, android obesity (defined as the ratio of waist circumference over hip circumference greater than 0.85 in women and 1 in men). Today, it is of increasing importance due to its increased prevalence and as a result of the fact that it is associated with increased CV risk, all the more so when many abnormalities which so define it exist.

The “lipid triad” consisting of dyslipidaemia usually observed in the metabolic syndrome, is characterised by the combination of preponderant small and dense LDL-cholesterol (LDL) particles, decreased HDL-cholesterol (HDL) and increased triglycerides (TG) [5]. Total cholesterol and LDL-cholesterol can sometimes be high, and in such cases the CV risk is higher. In particular, dyslipidaemia is atherogenic because the formation of these small, dense oxidised LDL particles, known to aggressively alter the artery wall, is promoted. This lipid profile is largely underestimated in the general population and is insufficiently managed overall.

Prevalence of the metabolic syndrome in adults is about 10 to 30% in the industrialised countries and is constantly increasing, in particular in women, which justifies generalised measures of screening and management to prevent the resultant CV risk [1,4].

2. What is residual vascular risk?

RVR is the risk of macrovascular events and microvascular complications, which persists in the vast majority of patients in spite of appropriate therapeutic intervention including the achievement of low LDL and intensive management of blood pressure and blood glucose.

Progressive intensification of treatment with statins over the past 20 years has made it possible to achieve an overall decrease in mean LDL in the general population [6]. On the contrary, during the same period, it was observed that little change was obtained in levels of HDL and that TG tended to increase. Thus, it is estimated that in the US about 2/3 of patients in secondary prevention treated with statins have low HDL (less than 0.40 g/l in men and 0.50 g/l in women), while about half of adults in secondary prevention have TG greater than 1.50 g/l [7]. This probably partly explains the persistence of high CV risk, even when goals defined by the recommendations for LDL, blood pressure and blood glucose are reached.

3. What cardiovascular risk is associated with HDL and triglycerides?

The combination of high TG and low HDL is closely correlated with CV risk.

The PROCAM observational study [8] in particular demonstrated that CV morbidity and mortality is inversely proportional to levels of HDL, independently of LDL (Fig. 1).

Concerning TG, a meta-analysis of 29 prospective trials which included 262,525 patients, compared based on level of TG, showed that the atherogenic characteristic of TG is independent of HDL: the odds ratio for coronary risk was 1.72 (95% confidence interval [CI95], 1.56–1.90) between the group with TG greater than 1.78 g/l and the one with TG less than 1.15 g/l [10].

Observational studies have shown that postprandial TG are a more significant CV risk factor than fasting TG (measured after 12 to 14 hours fasting), as shown in a cohort study conducted on almost 15,000 patients from 1976 to 2004 in Denmark [11].

Another prospective study, which included 26,509 women of whom 20,118 were fasting and 6391 not fasting, confirmed that a correlation existed between CV disease and TG with postprandial TG and not with fasting TG measured, even after adjustment for total cholesterol, HDL and insulin-resistance parameters [12]. It was TG measured 2 to 4 hours after a meal which were the most strongly correlated with CV events (hazard ratio between highest and lowest tertile: 4.48; [CI95]: 1.98–10.15; p < 0.001).

Therefore, the true impact of hypertriglyceridaemia may have been underestimated beforehand, since only fasting TG was measured, and all the more so since outside of the early hours of the day, the subjects were in postprandial status most of the time.

4. What cardiovascular risk is associated with the lipid triad?

The PREV-ICTUS study [13] investigated CV risk when several associated lipid abnormalities exist and showed that it is the lipid triad which results in a higher CV risk than an isolated increase in LDL. In fact, when groups of patients presenting

![Fig. 1. PROCAM study: Low HDL is a predictive marker of cardiovascular risk independently of LDL even when LDL is low [9]. y-axis: 10-year risk of MI (%). Étude PROCAM : le HDL bas est un marqueur prédictif du risque cardiovasculaire indépendant du LDL y compris lorsque celui-ci est bas [9].](image-url)
with one or more lipid abnormalities were compared, the odds ratios for CV risk were: 1.30 (CI95: 1.11–1.53) for the group with combined high LDL and TG; 1.57 (1.30–1.97) for group with high LDL and low HDL ($p < 0.001$); and 1.86 (1.52–2.28) for the group with high LDL, low HDL and high TG, respectively, compared to the group with isolated elevation of LDL. The studied population was comprised of 6010 subjects, mean age 71.7 years, 53.5% of whom were women, and 73.2% of whom had hypertension, 29.2% diabetes and 24.3% were in secondary prevention. LDL was elevated in 78.1% of cases, HDL was low in 23.3% of cases, TG were increased in 35.7% of cases and mixed dyslipidaemia existed in 40.3% of cases.

5. What about drug treatment trials?

Statins provide imperfect control of vascular risk attributable to elevated TG and low HDL as shown by a post hoc analysis of the 4S study (Scandinavian Simvastatin Survival Study), a study of secondary prevention, where it was observed in the placebo group that patients who had both low HDL, elevated TG and elevated LDL had a risk increased by 52%, while such risk was only increased by 14% in subjects in whom only LDL was elevated [14].

Three other studies confirmed these results.

5.1. The TNT study

In the TNT study [15], in spite of achievement of very low LDL (less than 0.70 g/l), by treatment with a high dose statin, low HDL (less than 0.37 g/l) was associated with a 39% increase in risk of a major CV event within five years, when these patients were compared to those with high HDL (greater than or equal to 0.55 g/l) (Fig. 2).

5.2. The PROVE IT-TIMI 22 study

In the PROVE IT-TIMI 22 study (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction) [16], a post hoc analysis [2] showed that:

- TG less than 1.50 g/l in patients with an acute coronary syndrome was correlated with a 27% decrease in coronary events;
- TG greater than 1.50 g/l was associated with a higher coronary risk, of almost 50%, even when LDL was less than 0.70 g/l during treatment with a statin;
- TG greater than 2 g/l was associated with a 56% increase in risk of CV morbidity and mortality, even when LDL was less than 0.70 g/l with statin therapy (Fig. 3).

5.3. A study of 491 diabetics in secondary prevention

In a study of 491 diabetic patients in secondary prevention, followed for 5.6 years on average, low HDL and apolipoprotein A1, elevated TG and small dense particles of LDL-cholesterol were identified as factors predictive of CV risk in statin-treated patients, while total cholesterol, LDL-cholesterol and apolipoprotein B were not (adjusted hazard ratio: $1.30 \ [1.11–1.53], p = 0.001$) [17].

Moreover, a recent study showed that 54.6% of patients hospitalised for coronary artery disease had low serum HDL (HDL < 0.40 g/l in men and 0.50 g/l in women), confirming that management of this factor is important although difficult to achieve [18].

6. The lipid triad: pathophysiologic mechanisms

In the lipid triad, alterations in lipoprotein metabolism are characterised mainly by an increase in particles high in TG, remnants, such as chylomicrons, VLDL and IDL (intermediate density lipoproteins) present in the plasma. Like LDL, these remnant particles penetrate the intima and preferably are trapped in the artery wall [11]. The presence of TG contributes to formation of small and dense LDL-cholesterol particles (replacement of LDL-cholesterol esters by TG), increasing their capacity to penetrate the vascular endothelial wall. They are more readily oxidised, and thus more likely to bind to proteoglycans in the blood vessel wall [19].
Dyslipidaemia is also associated with a pro-inflammatory condition, which promotes vascular risk, in particular in patients with type 2 diabetes. Remnants have direct and indirect effects on the vascular endothelium by potentiating the inflammatory response. Apolipoprotein C-III, present on particles with high amounts of TG, produces a direct unfavourable effect on the vascular wall. The activation of pro-inflammatory genes leads to oxidative stress and endothelial dysfunction; secretion of inflammatory and atherogenic cytokines (TNFα, interleukines) is stimulated, and produces inflammation as well as defective vasodilation with micro and macroangiopathy.

HDL protects against atherosclerosis partly as a result of its capacity to promote the reverse transport of cholesterol from cells in the vascular wall to the liver to be eliminated. It also fights oxidative stress by preventing the oxidation of LDL and by reducing inflammation [20]. In the metabolic syndrome, the elevation of markers of inflammation (such as CRP) may be involved in qualitative changes in HDL, which would attenuate its protection against atheroma, as well as inflammatory cytokines that decrease its capacity to prevent oxidation of LDL [7].

Moreover, apolipoprotein B (apoB) seems to be a more sensitive marker of lipid abnormalities in the metabolic syndrome than the level of LDL itself. In fact, although LDL is often normal or moderately elevated in such patients, apoB is increased.

ApoB reflects VLDL and LDL concentrations since each of these particles carries a molecule of apoB. Several studies tend to demonstrate that apoB is more closely correlated with CV risk than LDL, in particular in metabolic syndrome, as a result of elevation of VLDL. Thus, apoB could be a better marker of risk than LDL, since measurement of it does not by itself take into account the atherogenic potential of VLDL particles. But, it is not currently used in routine practice and in recommendations due to a lack of standardisation in assay measurements and the absence of an international consensus on goals of management [7].

7. Which treatments to offer?

7.1. Measures involving diet and lifestyle modification

A change in life style is an important first step in management of the lipid triad, all the more so when a metabolic syndrome exists. Initiation of a lipid-lowering diet, increased intake of omega-3 and omega-6 unsaturated fatty acids, restriction of salt intake in patients with hypertension, weight reduction, and cessation of smoking are essential measures. Regular physical activity improves insulin sensitivity and can reduce CV risk and diabetes by 50% [7]. In addition, smoking cessation makes possible an increase of 0.04 g/l in HDL, while regular physical activity increases it by 3 to 9%.

But these measures often are inadequate and difficult to maintain over the long-term, and most often must be combined with pharmacological therapy.

7.2. Pharmacological therapy and results in interventional studies

The purpose of such therapy is to treat all lipid abnormalities and HDL in particular, which up until then was of secondary importance, behind LDL.

Fibrates, which decrease triglyceride levels by 30 to 50% and increase HDL by 5 to 15%, reduce LDL by 17 to 22% [7]. In terms of CV prevention, the VA-HIT trial [21], the Bezafibrate Infarction Prevention study (BIP study) [22] and the HHS study [23], in primary and secondary prevention, demonstrated clinical benefit in patients with metabolic syndrome. Lastly, the FIELD study [24] did not find a decrease in overall mortality, but a decrease of 27% versus 13.5% with placebo (p = 0.005) in the subgroup treated with fenofibrate which had low HDL and TG greater than 2 g/l. A pooled analysis of results of these studies is lacking to clearly determine the effectiveness of fibrates in atherogenic dyslipidaemia [7].

Statins can increase HDL by 3 to 12% depending on compound and dose used [25]. Their efficacy on LDL no longer needs to be demonstrated. On the contrary, their effect on TG is moderate (a decrease of 10 to 15%) and is inconsistently significant. This produces an even greater impact when baseline hypertriglyceridemia is pronounced and with use of high dosages. These agents are not indicated in pure hypertriglyceridemia.

In some cases, the use of a statin in combination with a fibrate (preferably fenofibrate to limit adverse events) is possible, but should be reserved for specific groups of high risk patients: when HDL is less than 0.35 g/l in men and 0.40 in women and with TG greater than 4 g/l and good compliance with diet, or greater than 2.5 g/l in a population with high vascular risk (for example, diabetic patients), and provided that the patient is strictly monitored [7].

A few studies have evaluated ezetimibe, an inhibitor of intestinal absorption of cholesterol, in combination with a statin [26] or a fibrate [fenofibrate] [27], with satisfactory results on lipid profile in the metabolic syndrome and a good safety profile. Studies on CV risk prevention need to be conducted. Nevertheless, a very recent study demonstrated that niacin produced a decrease in thickness of the intima-media layer, contrary to ezetimibe, when one of these two treatments was added to a statin, even though LDL-cholesterol was lower in the ezetimibe group [28].

Niacin has long been known and is one of the most effective treatments on HDL. It increases HDL by 20 to 25%, and decreases TG by 15 to 25% and LDL by 10 to 15%. In prevention, since 1975, it has been shown that it allows obtaining a decrease of 15% in CV mortality (p < 0.05), 24% in cerebrovascular events, 26% in non-fatal myocardial infarction, and 47% in revascularisation procedures, with mean follow-up of 6.2 years [29,30,31]. After 15 years follow-up, niacin produced an 11% reduction in overall mortality (p = 0.0004) and a 12% decrease in CV mortality (p = 0.005) [7].

Considering their complementary profile of action, the use of niacin in combination with a statin seems especially beneficial. In this regard, a recent study showed that such a treatment
combination partly normalised changes observed in the composition of HDL particles in patients with coronary artery disease [32]. In fact, after a year of treatment, apolipoprotein E in HDL decreased while macrophage proteins involved in the reverse transport of cholesterol increased, leading to an HDL profile more similar to that of healthy control subjects.

In the Atherosclerosis Treatment Study (HDL HATS Study), treatment of 160 patients (mean LDL and HDL of 1.25 g/l and 0.31 g/l respectively) with niacin (mean dose of 2.4 g/d) and simvastatin (13.6 mg/d on average) produced a 0.4% decrease in coronary atheroma seen with angiography (versus a mean progression of 3.9% in patients treated with placebo; p < 0.001), as well as a 90% decrease in CV events (CV mortality, myocardial infarction, cerebrovascular events and revascularisation procedures) (p = 0.03), after about three years follow-up [33].

ARBITER-2 studies on plaque regression [34] which followed and involved a small number of patients (n = 167), in secondary prevention, who received 1 g of niacin a day in addition to a statin did not find an improvement in the intima-media thickness at one year, but the decrease was significant at two years after open-label extension of the study (ARBITER-3) [2,35].

A meta-analysis of six randomised studies in which niacin was given in combination with a statin or a bile acid chelator showed regression or slowing of progression of atherosclerosis in patients with high vascular risk. Among these trials, which included a relatively low number of patients, three demonstrated a significant improvement in clinical prognosis: HATS, Familial Atherosclerosis Treatment (FATS Study), and Armed Forces Regression Study (the AFREGS Study) [36].

These results show that it is essential to set up large prospective trials to clearly evaluate the benefit of niacin in combination with a statin in terms of clinical events.

Nevertheless, to date the widespread use of niacin has been limited due to frequent occurrence of hot flush side effects (vasomotor flush). The probable imminent marketing of tredaptive, a combination of nicotinic acid and laropiprant, should allow its better use. In fact, laropiprant is a selective prostaglandin D2 receptor antagonist, primarily involved in the mechanism of flush. Studies on patients treated with tredaptive (with a dose of 1 g and then 2 g nicotinic acid combined with 20 mg and then 40 mg laropiprant), demonstrated the same efficacy on lipid parameters as niacin alone while tolerability was significantly improved with a decrease in the incidence of vasomotor flush (22% versus 49%, p < 0.001) at time of treatment initiation and in the short-term [37]. The frequency of treatment discontinuations due to an adverse event was decreased. On the contrary, efficacy and safety of the product in the long-term have not yet been established.

8. Future perspectives

Currently, several studies are ongoing to confirm the clinical usefulness of add-on therapy with niacin to a statin, two of which in particular:

- Atherothrombosis Intervention in Metabolic syndrome with low HDL – High TG and Impact on Global Health outcomes (AIM-HIGH) is comparing niacin in combination with simvastatin versus simvastatin alone in 3300 patients with known vascular disease and atherogenic dyslipidaemia. Results are expected in 2011;
- Heart Protection Study 2 – Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) has the aim of comparing the efficacy of tredaptive versus placebo in about 20,000 patients in secondary prevention in which LDL is treated efficaciously with statins. Results are expected in 2012 [7].

Other treatments designed to increase HDL have not lived up to expectations due to the occurrence of serious adverse events, such as torcetrapid, a cholesterol ester transfer protein (CETP) inhibitor, whose study had to be terminated because of the occurrence of unexplained excess mortality in the treated group [38].

New compounds, which more specifically target the qualitative aspect of HDL or its metabolism are still under development. Their aim is to modify the composition of HDL particles in favour of a protective profile: niacin variants, PPAR alpha and gamma agonists, ApoA-I mimetics or recombinant ApoA-I Milano (a genetic variant which causes familial hypoHDLemia in association with increased longevity) whose administration by infusion during five weeks resulted in a moderate regression of coronary atheroma [39]. These are possible future avenues of research.

A consensus on the goals to achieve remains to be defined, keeping in mind that the quantitative evaluation of HDL requires standardisation of assay techniques used, and qualitatively remains very complex due to the heterogeneity of these particles.

This specific risk profile associated with metabolic syndrome, obesity, diabetes and atherogenic dyslipidaemia currently is a fundamental challenge to public health, as well as management of CV risk in patients treated with statins. The latter of course are an integral part of the treatment and prevention of CV disease. Patient education and information are essential to optimise management at an early stage of disease.

Today, in this regard challenges are arising: first, improving the management of LDL by improved compliance with statin therapy and better adherence to recommendations, and second, in patients with persistent risk in spite of well-controlled LDL, the option of offering appropriate, well-tolerated treatment in case of low HDL and/or hypertriglyceridaemia. Improved understanding of lipoprotein metabolism now should allow us to achieve this goal, while making the conduct of large interventional studies essential, the only ones which can clearly demonstrate the clinical benefit of management of the lipid triad, and, in particular, of HDL.

Conflict of interest

None.

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