Lipid Club Letter

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Editorial

L'ANNEE 2005 COMMENCE SOUS DE BONS AUGURES

Nous avons bon espoir que la mesure du risque cardiovasculaire global, ajusté à la population belge, entre dorénavant en ligne de compte pour le remboursement des médicaments hypolipidémiants. Ceci constituerait une satisfaction supplémentaire aux revendications du BLC pour un accès plus juste au traitement efficace des dyslipidémies.

Comme promis, le BLC a désormais son site Internet : **www.lipid-club.be**. Je vous engage à le consulter : vous aurez accès au nouveau guide de poche à et vous pourrez le télécharger, vous pourrez prendre connaissance des réunions scientifiques auxquelles le BLC apporte son appui ainsi qu'aux prix décernés par notre association. D'autres données seront disponibles prochainement. Faites-nous part de vos suggestions et commentaires.

Le présent numéro de la Lipid Club Letter vous permettra de prendre connaissance des travaux réalisés par des lauréats du Prix de Lipidologie MSD-BLC et du Prix Orbita. Nous vous rappelons, par la même occasion, l'ouverture des candidatures pour le prix 2005 Research Fellowship in Lipidology, destiné à subsidier la recherche belge en lipidologie. Le dossier des candidatures doit être déposé avant le 30 juin 2005. Les formulaires de participation sont disponibles sur le site web (Prix du BLC).

Dans ce numéro également, appel est fait à tous pour participer aux travaux sur le projet de consensus belge concernant la prise en charge des hypercholestérolémies familiales, en particulier chez les enfants.

Prof. F.R. HELLER,
Président BLC

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ORBITA (Pfizer) PRIX

Weight-loss associated induction of PPARalpha and PPARgamma correlate with reduced atherosclerosis and improved cardiovascular function in obese insulin-resistant mice

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Background

The metabolic syndrome is characterized by a group of metabolic risk factors that include obesity, raised blood pressure, dyslipidemia, insulin resistance or glucose intolerance, and a prothrombotic state, and its incidence in the Western world is rising to epidemic proportions. Obesity, particularly visceral adiposity, contributes to the clustering of the other metabolic syndrome components, such as insulin resistance/type-2 diabetes, dyslipidemia and hypertension. The molecular mechanisms underlying the metabolic abnormalities induced by visceral adiposity have yet to be fully elucidated.

Fat distributed in the abdominal region is associated closely with insulin resistance and is a risk factor for type 2 diabetes and cardiovascular disease (CVD) [1, 2]. Weight-loss in insulin-resistant obese persons reduces their CVD risk [3]. It is however not known to what extent changes in the intra-abdominal adipose gene expression profile are important for the reduction of the risk [4].

We, therefore, have investigated the cardioprotective mechanisms of weight-loss in mice with combined leptin and LDL-receptor deficiency (DKO). We have selected those mice because they have several metabolic syndrome components - obesity, hypertension, dyslipidemia, and diabetes – that are associated with increased oxidative stress and inflammation, resulting in accelerated atherosclerosis and loss of cardiovascular function [5]. Because weight-loss in DKO mice was associated with a reduction in markers of cardiovascular risk, our second objective was to identify the underlying mechanisms. Therefore we studied the effect of weight-loss on changes in the gene expression profiles in the visceral adipose tissue that correlate with changes in lipoprotein and lipid profile, oxidative stress, insulin sensitivity, glucose tolerance, blood pressure and heart rate regulation, and atherosclerosis. The following is an overview of results previously published in Circulation [6].

Experimental Protocol

In order to obtain the weight loss, food intake of DKO mice was restricted. Food intake of free-fed DKO mice was ~ 5.7g/day from weaning for 12, 24 or 36 weeks. Food intake of diet-restricted mice was restricted to 2.5g/day for 12 weeks between 12 and 24 weeks of age (24-week diet-restricted mice) or between 24 and 36 weeks of age (36-week diet-restricted mice). At 12 weeks, DKO have no detectable atherosclerosis, and their LV function is not different from that of lean mice. Starting the diet-restriction at 12 weeks is thus a proxy for a primary intervention study. At 24 weeks, DKO have already developed atherosclerosis, and their LV function is lower compared to that of lean mice, so starting the diet-restriction at 24 weeks is a proxy for a secondary intervention study.
As a result of the diet-restriction, diet-restricted mice showed a 45% weight loss compared to free-fed mice of the same age. By measuring body composition with PIXImus Mouse Densitometry (Lunar Corporation, Brussels) [7] we showed that the weight-loss was due to a 33% loss of fat mass.

PPAR Gene Expression

Several adipokines, and more specifically peroxisome proliferator activated receptors (PPAR), regulate a number of the processes that contribute to the development of atherosclerosis, including dyslipidemia, arterial hypertension, endothelial dysfunction, insulin resistance, and vascular remodeling. It has been demonstrated that PPAR deactivation (mainly obesity-related) is a key phase of metabolic syndrome initiation [8-10]. Approaches to reduce adipose tissue depots, including diet-restriction, could stimulate adipocyte differentiation and as a result positively alter PPAR levels.
PPARgamma and PPARalpha gene expression in white visceral adipose tissue was measured with quantitative RT-PCR. PPARgamma and PPARalpha gene

expression decreased in time in DKO mice (Fig. 1A), and was down-regulated compared to lean mice. Diet-restriction resulted in an upregulation of PPARalpha and PPARgamma expression in the adipose tissue of diet-restricted DKO mice compared to age-matched free-fed DKO mice (Fig. 1B). Because we observed up-regulation of PPARalpha and PPARgamma in the adipose tissue from diet-restricted compared to free-fed DKO mice, we also compared PPAR expression in extracts from the heart and aortic arch of those mice. PPARalpha and PPARgamma expression was higher in the heart and aortic arch of diet-restricted mice compared to free-fed DKO mice.

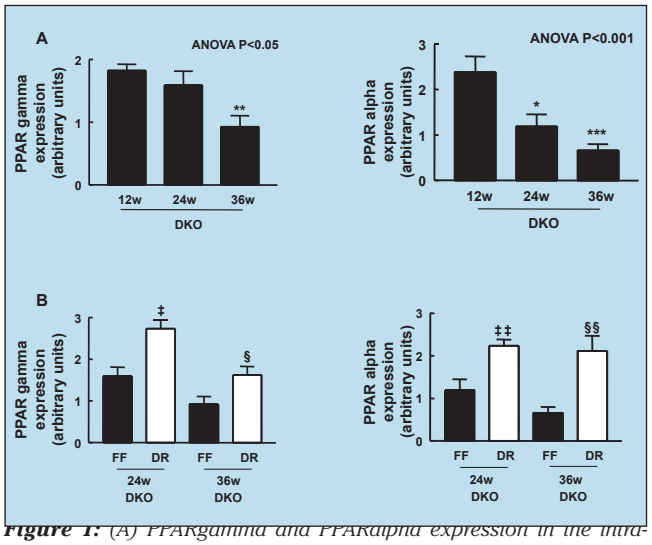

Figure 1: *(A) PPARgamma and PPARalpha expression in the intra-abdominal adipose tissue from 12-week (n=8), 24-week (n=5) and 36-week (n=8) free-fed DKO mice. (B) Effect of diet-restriction on PPARgamma and PPARalpha expression at 24 (free-fed n=5; diet-restricted n=7) and 36 weeks (n=8 per group). FF= free-fed, DR= diet-restricted; *P<0.05, **P<0.01 and ***P<0.001 compared to 12-week DKO mice; ‡P<0.05 and ‡‡P<0.01 compared to 24-week free-fed DKO mice; §P<0.05 and §§P<0.01 compared to 36-week free-fed DKO mice.*

Micro-array analysis of gene expression in adipose tissue

To identify genes that change according to the differences in PPAR expression we performed 3 independent experiments with Agilent Mouse cDNA micro-arrays (product number: G4104A). We compared the abundance of transcripts in two mRNA samples, one from the visceral adipose tissue from a free-fed mouse, the other from a diet-restricted mouse, both at 24 weeks. The upregulation of PPAR expression was associated with a change in the expression of genes regulating glucose transport and insulin sensitivity, lipid metabolism, oxidative stress and inflammation, resulting in a reduction of markers for cardiovascular risk.

Effect of weight loss on markers of cardiovascular risk

Weight-loss resulted in a decrease of triglyceride levels without changing total, non-HDL and HDL-cholesterol levels. Compared to free-fed DKO mice, insulin levels were lower in the diet-restricted groups but glucose levels did not change. Insulin resistance was calculated by a homeostasis model assesment (HOMA). HOMA for diet-restricted mice was 77% lower than that for free-fed mice. Diet restriction also resulted in normalization of the glucose tolerance. Weight-loss was also associated with a decrease of the titer of Ig autoantibodies against oxidized LDL indicating a decrease in oxidative stress in diet-restricted DKO mice. This decrease in oxidative stress could be attributed to an increase in the activity of two anti-oxidative enzymes, namely Paraoxonase (PON) and lecithin:cholesterol acyltransferase (LCAT).

Effect of weight loss on atherosclerosis, blood pressure, heart rate and LV function

Because weight-loss in DKO mice was associated with a reduction in markers of cardiovascular risk we then looked at the effect of weight loss on atherosclerosis, blood pressure, heart rate and LV function.

Atherosclerosis

The extent of atherosclerosis was measured by analysis of stained cross-sections from the aortic root. Lesions in 12-week free-fed DKO mice were very small fatty streaks. Plaque volumes increased from 12 to 36 weeks (Fig. 2A). Plaque volumes in 24-week diet-restricted mice were 12-times smaller than in 24-week free-fed mice. Plaque volumes in 36-week diet-restricted mice were similar to those in 24-week free-fed mice and 2.1–times smaller than in 36-week free-fed mice (Fig. 2A). Macrophage content was 52% lower (P<0.01) and Ox-LDL content was 16% lower (P<0.05) whereas smooth muscle content was 95% higher (P<0.05) in 36-week diet-restricted mice compared to 36-week free-fed mice. This indicates that the plaques in diet-restricted DKO mice are more stable compared to that of free-fed DKO mice.

There was a negative correlation between both PPARgamma and PPARalpha expression and plaque volume (Fig. 3A) and % of the plaque surface that was stained for Ox-LDL (Fig. 3B) in free-fed and diet-restricted DKO mice. This indicates that changes in PPAR gene expression in the adipose tissue could result in changes in the development of atherosclerosis.

Blood Pressure, Heart Rate and Ejection Fraction

BP signals, and HR, derived from pressure waves from the aortic arch, were measured in conscious, unrestrained animals with surgically implanted miniaturized telemetry devices (DSI model TA11-PA-C20, Datascience Corp, St Paul, MN, USA). In control (C57BL6) mice, continuous (24 hours) BP and HR recordings revealed a typical variation during the light-dark cycle, i.e. light (corresponding to a resting period for mice) values of systolic (S) BP, diastolic (D) BP and HR were significantly lower than dark (activity period for mice) values. By contrast, circadian variations of HR and BP were

totally abolished in free-fed DKO mice. These mice also had higher mean 24-hour SBP and DBP values and higher mean HR compared with controls. Diet restriction reduced all parameters in DKO mice to control values. Similar changes were observed during light and dark cycles.

To determine LV function, transthoracic echocardiography of C57BL6, 24-week free-fed and 24-week diet-restricted mice was performed using a Philips SONOS 5500 with a 5-12 MHz S12 neonatal ultraband cardiac phased probe. At 24 weeks, ejection fraction of DKO mice was significantly lower (38±7.1 % vs. 51±6.2 %; P<0.01) compared to control C57BL6 mice. Diet restriction restored ejection fraction to 50±5.5 (P<0.001) (Fig. 2B).

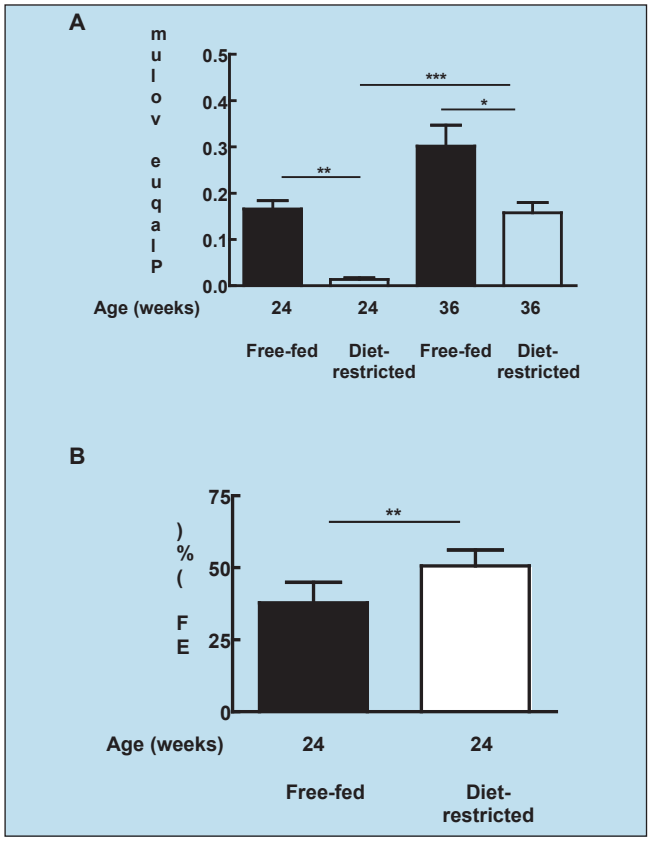

Figure 2: *(A) Plaque volumes in the aortic arch from 24- and 36-week free-fed (n=10 and n=8 respectively) and diet-restricted (n=10 for both) DKO mice. (B) Ejection fraction (EF) in free-fed and diet-restricted DKO mice at 24 weeks. *P<0.05; **P<0.01; ***P<0.001.*

Conclusions

Inhibition of atherosclerosis and improvement of cardiovascular function following weight-loss in leptin-deficient, obese and insulin-resistant mice can be explained by expressional changes in the adipose tissue of key genes regulating insulin sensitivity, oxidative stress, lipid metabolism, inflammation and endothelial function, most of which are under the transcriptional control of PPARs. Our observation of restored/increased expression of PPARs in the same condition and the correlation between PPAR expression and plaque volume in DKO mice, and the accumulation of Ox-LDL in particular, points to the critical role of these transcription factors both in the pathogenesis and the potential treatment of these features of the metabolic syndrome. Because PPARalpha and PPARgamma are down-regulated in double knockout mice and because they feature most of the metabolic syndrome components, they could prove to be a useful model to test the effects of PPAR agonists and statins.

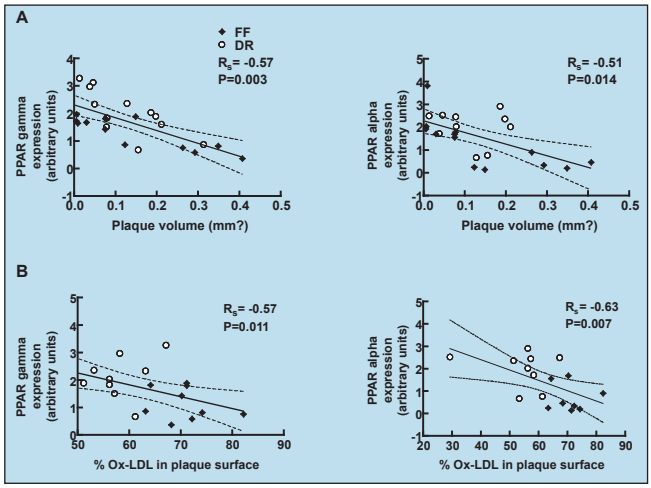

Figure 3: *(A) Correlation of PPARgamma (n=25), respectively PPARalpha (n=23), expression with aortic plaque volume in free-fed (FF) and diet-restricted (DR) DKO mice. (B) Correlation between both PPARgamma (n=19) and PPARalpha (n=17) expression and Ox-LDL in aortic plaques in free-fed and diet-restricted DKO mice. Rs= Spearman correlation coefficient.*

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GENETIC TEST MAY HAVE ADDITIONAL PREDICTIVE POWER OVER AND ABOVE THE ACCEPTED RISK FACTORS IN PATIENTS WITH SEVERE HYPERCHOLESTEROLEMIA.[1]

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The present article summarizes two works recently published in European Journal of Clinical Investigation [1 & 2].

Acknowledgements

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Abstract

Among 273 patients with severe hypercholesterolemia and a family history of early cardiovascular disease, we demonstrated that, those carrying LDL-R or ApoB genes mutations causing familial hypercholesterolemia (63 men and 59 women) had significantly greater carotid (delta = +0.27 mm in men and 0.10 mm in women) and femoral (delta = +0.22 mm in men and +0.20 mm in women) intima media thickness and were more likely to have positive exercise test (OR=6.15 in men OR=4.76 in women) and coronary calcification on CT scan (OR=3.90 in men OR=2.34 in women) than those without familial hypercholesterolemia (87 men and 64 women). Given the fact that such findings are associated with greater occurrence of CHD events, we suggest that molecular-genetic identification of familial hypercholesterolemia may better the awareness of the high cardiovascular risk of these patients and should motivate more intensive preventive hygieno- et chemo-therapy.

INTRODUCTION

Currently, patients with severe hypercholesterolemia and family history of early cardiovascular disease (CVD) are considered at high risk of CVD, whatever the underlying cause of this hypercholesterolemia and the familial aggregation of early CVD. With the emerging capability to perform genetic analysis, a critical issue is whether precise identification of the underlying molecular defect by genetic analysis may be of any help to improve assessment of CVD risk and prevention management.

Some hereditary defects of lipid metabolism such as familial hypercholesterolemia (FH), have been well characterized at the molecular level. FH is a autosomal dominant disorder caused by the presence at the heterozygous state of one mutant allele of the LDL-receptor (LDL-R) gene [3] or of the apolipoprotein B (APOB) gene [4]. Its prevalence is approximately 1 in 500. There is no doubt that cardiovascular events and atherosclerosis [3] develop more frequently and earlier in patients with FH in comparison to normolipemic patients. But in clinical practice, the question is rather whether FH individuals are at greater CHD risk compared to non-FH individuals who are clinically undistinguishable from FH because they have the same phenotype (that is : severe hypercholesterolemia and the same familial history of early CVD).

In our work [1, 2], we assessed this question by evaluating non invasively carotid [1], femoral [1] and coronary [2] atherosclerosis in series of patients free of any CVD symptoms (primary prevention) but displaying the same CVD risk phenotype with severe hypercholesterolemia and familial history of early CVD).

MATERIALS AND METHODS

In our lipid clinics, we recruited 273 patients (25-65 years) with severe hypercholesterolemia (cholesterol level above the 95th percentile for age and sex [5]) and a family history of early cardiovascular disease (at least one first-degree relative with early cardiovascular disease before the age of 55 years in men or 65 years in women). Persons with any known history of CVD or abnormal resting electrocardiogram were excluded from this study. The local ethical committee approved the study and the patients gave informed consent to participate to the study.

[1] The present work has been awarded by the jury of the Belgian Lipid Club with the "Belgian Lipid Club / Merck Sharp Dohme prize of lipidology" in 2004.

The patients were classified as having FH or not FH on the basis of the molecular screening for LDLR and APOB mutations performed in our laboratory as previously described [1, 2, 6]. Carotid and femoral atherosclerosis [2] was evaluated by the ultrasonographic measurement of intima-media thickness (IMT) in the carotid and femoral arteries [7]. Atherosclerosis in coronary arteries [2] was estimated non invasively by exercise stress testing (EST) [8] that allows for the determination of physiological variables in relation to blood flow limitation and by helical computed tomography [9] that provides anatomic information by detecting calcific deposits in the coronary arteries (see paper [1,2] for more detailed methodology). Although intima-media thickness was assessed in all 273 patients, exercise stress testing and helical computed tomography were performed in a large subset of the selected patients (N=235, 95 FH and 140 non FH). For ethical reason, helical computed tomography was only performed in women above 35 years. Amongst our patients, exercise stress testing (EST) was interpretable in 42 FH men, 66 non-FH men, 32 FH women and 36 non-FH women. The EST was equivocal in the other patients due to inadequate level (heart rate<85% of predicted maximum) of exercise (mostly, prematurely stopped due to limb cramps).

RESULTS

According to the genetic test, we classified 122 patients (63 men and 59 women) as FH-patients and the 151 others (87 men and 64 women) as non-FH patients. In these FH patients, we found 24 different mutations in the LDL-receptor gene (108 patients) and one mutation (14 patients) in the apolipoprotein B gene. All FH patients were heterozygous. As seen in *table 1*, FH and non-FH patients had a different distribution of classical risk factors. The concentrations of LDL-C and Lp(a) were higher in FH patients whereas the prevalence of hypertension, diabetes and current smoking as well as the mean values of body-mass index and waist-to-hip ratio were greater in non-FH patients.

	Non-FH	FH
N	151	122
Age, ans	51 ± 9	44 ± 10 *
LDL-C, mg/dl	314 ± 81	221 ± 32 *
Lp(a), mg/dl	49 ± 41	27 ± 42 **
BMI, kg/m^2	28,6 ± 3,9	27,2 ± 4,0 *
AGR	0,94 ± 0,07	0,90 ± 0,07 *
Tabagisme	33%	19% *
Hypertension	34%	16% *
Diabètes	15%	3% *

* p<0,05 FH versus non-FH * *p<0,05 FH versus non-FH by log transformation

Compared to non-FH-men, FH-men had significantly greater **carotid intima-media thickness** (1.27 ± 0.47 mm versus 1.00 ± 0.40 mm) and significantly greater **femoral intima-media thickness** (1.30 ± 0.53 mm versus 1.08 ± 0.46 mm). Similarly, FH-women had significantly greater femoral intima-media thickness compared to non-FH-women (1.05 ± 0.49 mm versus 0.84 ± 0.32 mm) *(figure 1)*. After adjustment for the classical risk factors *(figure 2)*, the difference of the carotid and femoral intima-media thickness between FH and non-FH patients remained statistically significant.

Fig. 1. FH patients had greater carotid & femoral intima media thickness

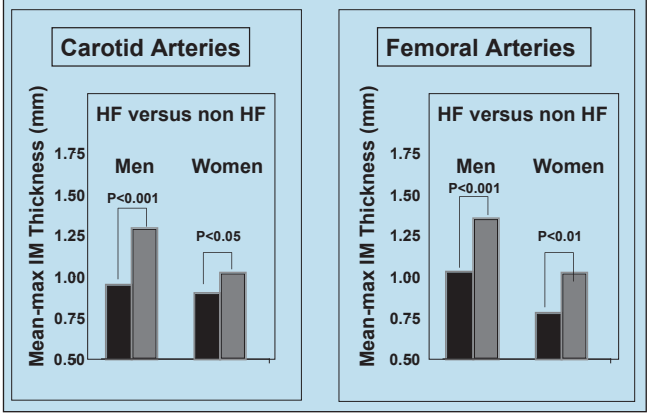
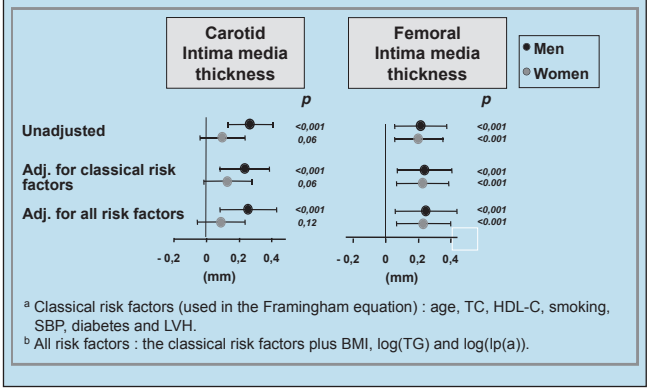


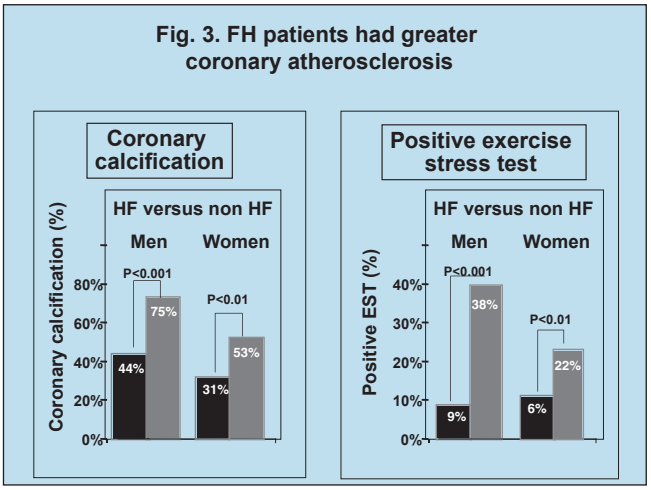
Fig. 2. Mean differences of IMT between FH and non FH- individuals after adjustment for others risk factors.



[a] Classical risk factors (used in the Framingham equation) : age, TC, HDL-C, smoking, SBP, diabetes and LVH.
[b] All risk factors : the classical risk factors plus BMI, log(TG) and log(lp(a)).

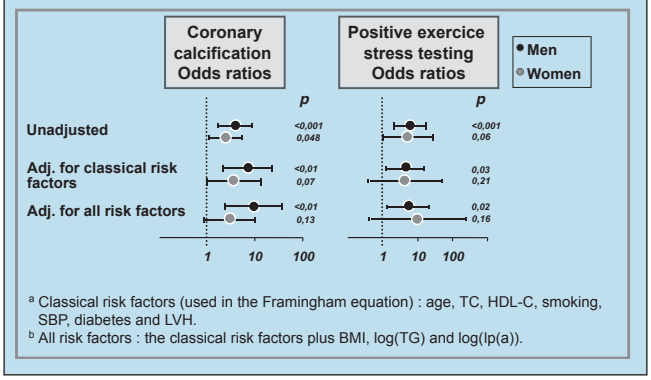
Coronary calcification (CC) were present in 75% of the FH-men compared with 44% of the non-FH men (odds ratio = 3.90; p<0.001) and in 53% of the FH women compared with 31% in the non-FH women (odds ratio = 2.65; p<0.01) *(figure 3)*.

Fig. 3. FH patients had greater coronary atherosclerosis



Positive exercise stress testing (EST) was present in 38% of FH men compared to 9% of non-FH men (odds ratio = 6.15; p<0.01) and in 22% of FH-women compared to 6% of non-FH women (odds ratio = 4.76 ; p=0.06). The EST was positive only on the basis of electrocardiographic criteria and none of the patient had complained of angina-like chest pain during the test. After adjustment of the odds ratios for the classical risk factors *(figure 4)*, these odds ratios for CC and for positive EST remained statistically significant.

Fig. 4. Odds ratios for coronary calcification and positive exercise stress testing in FH versus non-FH patients after adjustment for others risk factors.



[a] Classical risk factors (used in the Framingham equation) : age, TC, HDL-C, smoking, SBP, diabetes and LVH.
[b] All risk factors : the classical risk factors plus BMI, log(TG) and log(lp(a)).

DISCUSSION

The present work indicates that patients with genetically-ascertained FH have a higher degree of atherosclerosis than non-FH patients in the carotid, femoral and coronary arteries when compared with a cohort of non-FH patients with severe hypercholesterolemia and a family history of early cardiovascular diseases. Remarkably, the group of non-FH patients that we selected, accumulated more risk factors than the group of FH patients (higher prevalence of smoking, hypertension, diabetes and obesity) and yet, FH patients had a higher degree of atherosclerosis than non-FH patients.

As the carotid and femoral intima-media thickening [(7)], the presence of coronary calcification [(9)] and positiveness of exercise stress test are associated to greater occurrence of CHD events [(8)], this suggests that FH patents are at greater risk of CVD than non-FH patients even if these last shared similar findings of severe hypercholesterolemia and a family history of early cardiovascular diseases.

Some previous studies have shown greater intima-media thickness [(10)], greater prevalence of coronary calcification [(11-12)] and greater prevalence of positive exercise stress testing [(13)] in FH patients compared with normolipidemic controls studies. The present study is however the first to compare FH patients with hypercholesterolemic patients likely to be confounded in routine practice.

The greatest degree of atherosclerosis in FH patients may be explained by their longer exposure to higher LDL-cholesterol concentrations [(14)]. It has been also suggested [(15)] that the higher concentrations of lp(a) found in FH patients may play a role in the higher risk of CVD of FH patients. In our study, FH patients had higher concentrations of lp(a) than non FH patients and the concentration of lp(a) was associated with greater frequencies of CC and of positive EST.

From a practical point of view, the presented situation where the group of non-FH patients accumulated even more risk factors (in term of number) than FH patients, illustrates an interesting paradox. For most physicians, it would have made no doubt that the non-FH patients had greater CVD risk on the basis of such cluster of risk factors, specially as the genetic nature of the lipid disorder is usually not known precisely in routine practice. Such impression may be misleading as the present work shows that markers of atherosclerosis appeared more frequently in FH than in non-FH patients. This reinforces the idea that the precise identification of FH, preferably by molecular DNA diagnosis, may be useful for proper CHD risk assessment, especially in primary prevention.

POST-STUDY

Although coronary angiography was not intended to be performed systematically when EST was abnormal, we decided with 7 FH-men and 2 non-FH men of the present cohort to investigate their coronary arteries. These patients cumulated severe and multiple risk factors (some had diabetes, all were current smokers, some had brothers recently died of sudden death, 2 developed typical symptoms in the following years). All of these 7 FH-men and 2 non-FH men had multiple CC, strongly positive EST as well as severe thickenings of carotid and femoral IMT. Coronary angiography demonstrated the presence of severe coronary stenosis (>75% stenosis) and, finally, PTCA was proposed in 3 patients and CABG in the 2 patients with triple vessels disease… .

This high prevalence of severe CVD was further confirmed after the present work ended (December 2000), by a survey (16) that we performed in 2001 and 2002 by recruiting all young FH-men (25-55 years old) admitted in our hospital to estimate the incidence of coronary heart diseases. In this cohort of 66 young FH men, 32% (N=21 with 8 below age 45) had earlier history of symptomatic ischaemic disease and 20% (N=13 with 7 below age 45) had significant ST/T changes during exercise stress test. Amongst the 8 patients who were further investigated by coronary angiography, 6 (with 2 below age 45) underwent coronary angiography or surgical bypass.

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BELGIAN LIPID CLUB
2005 Research Fellowship in Lipidology
25.000 €

1. Le Belgian Lipid Club a décidé d'accorder pour la troisième fois des subsides de recherche pour une somme globale de 25.000 €.
2. Des projets centrés sur la lipidologie pourront être financés, soit dans le domaine de la recherche clinique, soit dans le domaine de la recherche fondamentale. Les fonds pourront couvrir le financement du chercheur, l'achat d'équipement et/ou des frais de fonctionnement.
3. Les candidats devront être membres du Belgian Lipid Club ou être parrainés par un membre du Belgian Lipid Club qui supervisera le travail effectué dans son service ou dans son laboratoire.
4. Les candidatures, rédigées en anglais, devront être déposées le **30 juin 2005** au plus tard, à l'aide de formulaires spécifiques disponibles auprès du Président du Belgian Lipid Club, le Professeur F.R. HELLER*.
5. Les projets seront analysés par des experts internationaux de renom. Ceux-ci feront rapport au Bureau du Belgian Lipid Club qui prendra la décision finale. La proclamation des lauréats aura lieu en octobre 2005.
6. Les récipiendaires s'engagent à présenter les résultats de leurs travaux lors d'une réunion du Belgian Lipid Club et d'en publier un résumé détaillé dans la Lipid Club Letter dans les deux ans suivant l'attribution des prix.
7. Tout renseignement complémentaire peut être obtenu en s'adressant au Professeur F.R. HELLER, Président du Belgian Lipid Club.

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REMAINING QUESTIONS ON FAMILIAL HYPERCHOLESTEROLEMIA (FH)

O.S. Descamps
Centre Hospitalier
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Le Docteur Olivier DESCAMPS propose aux lecteurs de la "Lipid Club Letter" une réflexion sur l'hypercholestérolémie familiale hétérozygote et en particulier sur le diagnostic et traitement chez les enfants.
Toutes les suggestions, remarques et critiques sont les bienvenues et devront lui être envoyées à :
descaoli@skynet.be

As presented at the last meeting of the BLC, we would like to launch a new project of discussion in the Belgian Lipid Club aiming to establish guidelines on some specific questions remained unanswered on heterozygous familial hypercholesterolemia (HFH).

One of the major question that remained opened in HFH is «When should we start a treatment in HFH patients?». This implies the question «Should we treat young adults or even children ?» and, if yes, this brings the new question «how could we identify the young adults and children that need our attention ?». All these questions are not easy to answer, because there is no clear «evidence-based medicine» to support any action or abstention. There is a need however to agree on a common attitude between pediatricians, general practitioners, and internists as patients will move from one hand to the other along their life. Consistency between our attitudes may be an important determinant for long-life compliance of the patient to treatment

Historically, till the early 90ís, intervention for CVD prevention in children was not advised (except in homozygous FH) [1-3]. This attitude was based on the belief that [1)] HFH children are completely asymptomatic and are not expecting to get any CVD complication before 20 years or more (why to worry so early of such relapsed problem ?), [2)] that drug treatment appeared unconceivable given the unproved benefit on future CVD (at this time, it was the same debate in adults), possible hormonal disequilibrium, questionable increase of non-cardiovascular mortality and potentially associated with hormonal disequilibrium (lack of long experience with statins except with bile acid-binding resin (expected 15% reduction of LDL-C, but a very poor compliance), [3)] that diet was poorly effective in children (Restriction Saturated Fat/cholesterol : -5% LDL-C), poorly complied and potentially associated with nutrition disequilibrium. Finally, some studies have also raised the issue of psychological problems (may create unnecessary and unproductive anxiety in parents and children, could lead to labeling and family conflicts) so that, it was questioned whether the psychosocial costs of labeling would outweigh the expected benefits of diets and early treatment,

We should worry about the fact that most of this «wait and see» attitude do not rely on scientific facts but mostly, on belief, lack of clear scientific evidence, lack of experience and perhaps also on the discouraging observation that implementation of CVD prevention (and cholesterol reduction to target) in adult population at risk represents already a difficult step in practice (why then, to attempt the more difficult step of children treatment ?)

Since then, some studies have brought some new scientific evidences that restimulate the debate on whether or not to care about children in the perspective of CV prevention. [4]

First, it appears that elevated cholesterol in childhood results to substantial subclinical impact in child [5] and may be a good predictor for future cardiovascular events later in life [6-8]. Early atherosclerotic lesions or fatty streaks, begin in childhood [5] and are related to cholesterol levels and other CHD risk factors that exist in adults [5]. In FH children, flow mediated dilation is impaired [9] and intima-media thickness is greater than in non FH children.[10-11]

Second, plant sterol / stanols (that allow a 10 to 15% LDL-C reduction) has entered the market [12] and trials on statins in children have shown their efficacy (with a 30 to 40% LDL-C reduction, maximum study duration: 2 years) and their good tolerance (no side effect, no growth problem, no particular hepatic of muscular toxicity) (13). FDA has approved the treatment by simvastatin in 1995, atorvastatin 10-20mg (in 2000), and pravastatin (in 2002).

Finally, treatment with statins have been showed to improve atherosclerosis in children with changes of flow-mediated diameters over 28 weeks of statins treatment [14] and of intima-media thickness over two years of statins treatment [15-16].

At the present time, some guidelines exist [17-19] in the US. Although there was no clear discussion in the last version of the European guidelines [20], some European experts have recently met and published some interesting conclusions [21].

We thus need to enter in the debate and establish an consensual attitude for the medical practice in Belgium. After collect of relevant publications on the following questions (keeping in mind the need to be in accordance with the existing consensus on these questions if they exist)

1. Do we have to screen children for cholesterol levels ? (We cannot avoid this debate if we want to develop a logical attitude)

Collect arguments in favor of cholesterol screening

1. "Tracking" of cholesterol over time.
2. The presence of atherosclerotic lesions in adults (intima-media thickness , clinical events) is related to risk factors during childhood.
3. "Tracking" of atherosclerosis over time.
4. Early atherosclerotic lesions in blood vessels of youth is correlated with childhood levels of low-density lipoprotein cholesterol and other risk factors

Collect arguments against cholesterol screening

1. Frequency of elevated cholesterol in the general population of children
2. Psychological problems specific to the knowledge of a high cholesterol in children for the child and his family.
3. Potential means for the physician to deal with these psychological problems

2. Diagnosis of FH in children.

Which criteria to suspect HFH in children : 2 situations to explore :

1. Children in a family which is known to carry FH.
2. Children where a high cholesterol level is discovered in a blood sample (see 1).

Psychological problems with identifying HFH in children.

The questions that we should address include reported concerns or worries subsequent to the notification of a diagnosis of an inherited disease in the child (Child, parents, brothers and sisters, physicians)

3. Treatment of FH in children or in young adults (that is the main question)

Who ?
Debate the absence of evidence based medicine
Target ? LDL-C
Treatment ?

1. Diet (harm ? type ? Follow-up)
2. Stanols / Plant sterols (dosage?, side effect?Ö)
3. Statins (which ?, dosage)
4. Ezetimibe (not registered, ! Do we have to introduce a demand ?)
5. Fibrates (not indicated ?)

4. Do we have specific problems with FH in Belgium ?

1. Age-specific normal values of cholesterol and LDL (HDL-C & TG) (required to set biological criteria of suspicion of FH)
2. Reimbursement of statins and ezetimibe. At the present time, only one drug is registered for children in Belgium (atorvastatin) and the current condition of reimbursement could cause a problem for many children (very few children at age 10-17 have one parent* with CHD, specially if CHD prevention has been applied in their parents).
3. Psychological aspects for diagnosis and therapy. which could be specific to our culture and education (poor education on what is inherited cholesterol in our country). Finally, there is only one drug registered for children in Belgium and the current condition of reimbursement could cause a problem for many children (very few children at age 10-17 have one parent* with CHD, specially if CHD prevention has been applied in their parents).

We hope you will join us in this new useful and exciting mission

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CHU TIVOLI

Symposium

LIPIDES ET ATHEROSCLEROSE

«Etat de la question en 2005»

Le samedi 24 septembre 2005 au CHU Tivoli
Salle de conférence, Aile H, 1er étage
avenue Max Buset 34
7100 La Louvière

Avec la collaboration de

Belgian Lipid Club
Fonds pour la Recherche Médicale dans le Hainaut (FRMH)

PROGRAMME

8.30h. ***Café d'accueil***

9.00h. Introduction
J. DUCOBU, CHU Tivoli, La Louvière.

PREMIERE SESSION
Nouvelles données sur l'athérosclérose

9.10h. «Le NO et la paroi artérielle»
J-L. BALLIGAND, UCL.

9.35h. «Rôle de la myéloperoxidase dans l'oxidation des lipides»
K. ZOUAOUI, CHU de Charleroi.

DEUXIEME SESSION
Progrès dans la physiologie des lipoprotéines

10.00h. «Récepteurs nucléaires et modulation des lipides»
B. STAELS, Institut Pasteur, Lille.

10.30h. «De la physiologie à la thérapeutique de l'avenir»
M. FARNIER, Dijon.

11.00h. Discussion

11.10h. ***Pause-café***

TROISIEME SESSION
Aspect cliniques

11.30h. «Hypercholestérolémie familiale : du diagnostic au traitement»
O. DESCAMPS, Centre Hospitalier de Jolimont.

11.50h. «Nouvelles cibles dans le syndrome métabolique»
A. SCHEEN, Université de Liège.

12.10h. «Les recommandations de la pratique clinique – Qu'est-ce qui importe réellement ?»
G. DE BACKER, Universiteit Gent.

12.30h. Discussion générale avec tous les orateurs

12.50h. Remarques et conclusions
M. FARNIER et J. DUCOBU.

13.00h. ***Lunch***

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