

# Relationship between familial combined hyperlipidemia and insulin resistance

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**Summary:** *Background and aims:* Familial combined hyperlipidemia is the most frequent hereditary dyslipidemia, usually associated with insulin resistance. Recently, the diagnostic criteria of familial combined hyperlipidemia were redefined: There should be at least two 1st degree hyperlipidemic relatives with both triglycerides  $\geq 1.5 \text{ mmol.L}^{-1}$  and apolipoprotein B  $\geq 1.20 \text{ g.L}^{-1}$ . The aim of this study was to evaluate the relationship between this lipoprotein phenotype and the presence of insulin resistance and to assess the presence of metabolic syndrome. *Methods:* Lipid parameters and parameters associated with insulin resistance were determined in 90 subjects of families with familial combined hyperlipidemia and 38 controls. The members of affected families were further divided into the hyperlipidemic and normolipidemic group. *Results:* The hyperlipidemic group showed only significantly higher fasting proinsulin levels [HL  $17.4 \pm 1.5$  vs NL  $12.8 \pm 1.4$  ( $p = 0.030$ ); and vs CO  $11.1 \pm 1.4$  ( $p = 0.003$ )] in comparison with the normolipidemic and control groups. Differences in fasting insulin [HL  $9.40 \pm 0.78$  vs NL  $7.78 \pm 0.71$  ( $p = \text{NS}$ ); and vs CO  $7.30 \pm 0.76$  ( $p = \text{NS}$ )], C-peptide [HL  $2.56 \pm 0.19$  vs NL  $2.27 \pm 0.17$  ( $p = \text{NS}$ ); and vs CO  $2.07 \pm 0.18$  ( $p = \text{NS}$ )], and HOMA [HL  $2.16 \pm 0.21$  vs NL  $1.84 \pm 0.20$  ( $p = \text{NS}$ ); and vs CO  $1.69 \pm 0.21$  ( $p = \text{NS}$ )] did not reach statistical significance. On the contrary, the members of families with familial combined hyperlipidemia with the presence of metabolic syndrome (NCEP-ATP III) had significantly higher fasting insulin [FCH with MS  $12.74 \pm 1.42$  vs HL without MS  $9.21 \pm 0.92$  ( $p = 0.030$ ); and vs NL without MS  $6.75 \pm 0.80$  ( $p = 0.001$ )], and proinsulin levels [FCH with MS  $25.28$  vs HL without MS  $15.69 \pm 1.75$  ( $p = 0.002$ ); and vs NL without MS  $11.20 \pm 1.51$  ( $p = 0.0001$ )], and HOMA index [FCH with MS  $3.03 \pm 0.39$  vs HL without MS  $2.13 \pm 0.25$  ( $p = 0.042$ ); and vs. NL without MS  $1.56 \pm 0.22$  ( $p = 0.003$ )] in comparison with their relatives without metabolic syndrome and controls. *Conclusion:* The presence of the metabolic syndrome could detect the most insulin resistant subjects in families with familial combined hyperlipidemia who are at increased risk of cardiovascular disease.

**Key words:** familial combined hyperlipidemia – insulin resistance – metabolic syndrome

## Vztah mezi familiární kombinovanou hyperlipidemií a inzulinovou rezistencí

**Souhrn:** *Úvod a cíl:* Familiární kombinovaná hyperlipidemie je nejčastější dědičnou dyslipidemií, obvykle spjatou s inzulinovou rezistencí. Nedávno byla redefinována diagnostická kritéria familiární kombinované hyperlipidemie: v rodině by se měli vyskytovat alespoň 2 prvo-  
stupňoví hyperlipidemičtí příbuzní současně s triglyceridy  $\geq 1,5 \text{ mmol/l}$  a apolipoproteinem B  $\geq 1,20 \text{ g/l}$ . Cílem této studie bylo zhodnotit vztah mezi lipoproteinovým fenotypem a přítomností inzulinové rezistence a posoudit přítomnost metabolického syndromu. *Metodika:* Lipidové parametry a parametry asociované s inzulinovou rezistencí byly určeny u 90 jedinců z rodin s familiární kombinovanou hyperlipidemií a u 38 kontrol. Členové postižených rodin byli dále rozděleni na hyperlipidemickou a normolipidemickou skupinu. *Výsledky:* Ve srovnání s normolipidemickou a kontrolní skupinou vykazovala hyperlipidemická skupina pouze signifikantně vyšší hladiny proinzulinu nalačno [HL  $17,4 \pm 1,5$  vs NL  $12,8 \pm 1,4$  ( $p = 0,030$ ) a CO  $11,1 \pm 1,4$  ( $p = 0,003$ )]. Rozdíly v hladinách C-peptidu [HL  $2,56 \pm 0,19$  vs NL  $2,27 \pm 0,17$  ( $p = \text{NS}$ ) a CO  $2,07 \pm 0,18$  ( $p = \text{NS}$ )] a inzulinu [HL  $9,40 \pm 0,78$  vs NL  $7,78 \pm 0,71$  ( $p = \text{NS}$ ) a CO  $7,30 \pm 0,76$  ( $p = \text{NS}$ )] nalačno a HOMA indexu [HL  $2,16 \pm 0,21$  vs NL  $1,84 \pm 0,20$  ( $p = \text{NS}$ ) a CO  $1,69 \pm 0,21$  ( $p = \text{NS}$ )] nedosahovaly statistické významnosti. Naproti tomu členové rodin s familiární kombinovanou hyperlipidemií s přítomností metabolického syndromu (NCEP-ATP III) měli ve srovnání se svými příbuznými bez metabolického syndromu a s kontrolami signifikantně vyšší lačnou hladinu inzulinu [FCH s MS  $12,74 \pm 1,42$  vs HL bez MS  $9,21 \pm 0,92$  ( $p = 0,030$ ); a vs NL bez MS  $6,75 \pm 0,80$  ( $p = 0,001$ )], proinzulinu [FCH s MS  $25,28$  vs HL bez MS  $15,69 \pm 1,75$  ( $p = 0,002$ ); a vs NL bez MS  $11,20 \pm 1,51$  ( $p = 0,0001$ )] a HOMA index [FCH s MS  $3,03 \pm 0,39$  vs HL bez MS  $2,13 \pm 0,25$  ( $p = 0,042$ ) a NL bez MS  $1,56 \pm 0,22$  ( $p = 0,003$ )]. *Závěr:* Přítomnost metabolického syndromu by mohla detekovat nejvíce inzulin-rezistentní jedince v rodinách s familiární kombinovanou hyperlipidemií, kteří jsou v nejvyšším riziku kardiovaskulárních chorob.

**Klíčová slova:** familiární kombinovaná hyperlipidemie – inzulinová rezistence – metabolický syndrom

## Introduction

Familial combined hyperlipidemia (FCH) is the most frequent genetically conditioned dyslipidemia affecting 1–2% of the population, increasing the risk of premature cardiovascular

disease and predisposing to early coronary death [1–4]. FCH is found in 10–20% of patients surviving premature myocardial infarction [1,2,5]. FCH is supposed to be caused by hepatic apolipoprotein B (apoB) over-

production and relatively impaired clearance of triglyceride-rich lipoproteins (TGRLP). It is associated with an increased concentration of particles containing apoB – i.e. very low-density lipoproteins (VLDL), intermediate den-

sity lipoproteins (IDL) and low-density lipoproteins (LDL) [4,6–14]. A decreased concentration of protective high-density lipoproteins (HDL) is often found [11,15]. Simultaneously, the qualitative changes of lipoproteins include predominance of highly atherogenic small, dense LDL particles (LDL III, sdLDL) [4,6,13,16,17]. The affected family members show increased levels of total cholesterol (TC), triglycerides (TG) or both parameters. The lipid phenotype can vary substantially within any individual but also among family members (defined according to Fredrickson classification, types IIa, IIb, IV, rarely also type V) [2,4,7,8]. According to recent studies [8,18,19], the change in insulin resistance (IR) can modify lipid phenotype expression. Prevalence of IR is higher in FCH and more severe in subjects with hypertriglyceridemia (phenotypes IIb and IV) [20–24]. These patients display a typical lipid profile known as the atherogenic lipid trias (low levels of protective HDL, elevated TG, and predominance of sdLDL-particles) [6,7,25]. The predominance of sdLDL and concomitant elevation of other potentially atherogenic particles (VLDL, IDL) result in increased apoB concentration [13,26,27].

FCH is traditionally diagnosed by TC and/or TG levels above the 90th percentile adjusted for age and gender. Recently it was shown that the diagnosis of FCH on the basis of these diagnostic criteria was inconsistent in 26% of subjects over a 5-year period and thus a new definition of FCH was suggested based on concomitant hypertriglyceridemia  $\geq 1.5 \text{ mmol.L}^{-1}$  and apoB  $\geq 1.20 \text{ g.L}^{-1}$  [4,13,28,29].

The aim of our study was to evaluate the IR in FCH affected members diagnosed according to this new definition and to evaluate, if the presence of MS can represent a simple tool for detection of the most insulin resistant subjects of FCH families, who are at greatly increased risk of cardiovascular disease. Such evaluation of FCH families has not been previously done.

## Subjects and methods

To establish the diagnosis of FCH, following criteria were used: The proband and at least one of his hyperlipidemic relatives exhibit TG  $\geq 1.5 \text{ mmol.L}^{-1}$  and apoB  $\geq 1.20 \text{ g.L}^{-1}$  [4,13,28]. Simultaneously, one of them must be affected by early manifestation of atherosclerosis before his 60<sup>th</sup> birthday. In total, 128 subjects (men:  $n = 59$ , mean age  $40.2 \pm 13.9$  years; women:  $n = 69$ , mean age  $38.1 \pm 14.0$  years) were examined in the Lipid Center of the Department of Internal Medicine III, University Hospital Olomouc. The study population comprised 90 members of 29 FCH families, and 38 control subjects.

An exclusion criterion was hypolipidemic treatment during the last 6 weeks. Therefore, some probands could not be included in the study because hypolipidemic therapy cannot be discontinued due to the presence of clinical manifestations of atherosclerosis. In those cases, the family identification was derived from lipid values prior to the therapy and these subjects were not included. In the examined subjects, possible secondary causes of hyperlipidemia were excluded (diabetes mellitus, hypothyroidism, liver and kidney diseases). None of the examined subjects was homozygous for the apoE2 allele and none of them had tendon xanthomas. The design of the study was approved by the Ethics Committee of the University Hospital Olomouc and the Faculty of Medicine and Dentistry, Palacky University Olomouc; an informed consent was obtained from all participants. The population under study was divided into three groups: The hyperlipidemic (HL) group ( $n = 41$ , mean age  $46.8 \pm 12.1$  years, men/women = 23/18) comprised FCH probands and their hyperlipidemic first-degree relatives (i.e. relatives with TG  $\geq 1.5 \text{ mmol.L}^{-1}$  and apoB  $\geq 1.20 \text{ g.L}^{-1}$ ). The normolipidemic members of FCH families (NL) did not display any above-mentioned criteria for FCH hyperlipidemic subjects – they had either TG  $< 1.5 \text{ mmol.L}^{-1}$

or at least apoB  $< 1.2 \text{ g.L}^{-1}$  ( $n = 49$ , mean age  $31.7 \pm 10.7$  years, men/women = 20/29). The group of controls (CO) comprised spouses of the affected subjects and also healthy individuals with negative family history of hyperlipidemia and early atherosclerosis ( $n = 38$ , mean age  $40.2 \pm 14.8$  years, men/women = 16/22).

All participants were examined by a physician with emphasis on the following: gender, age, smoking habits, history of arterial hypertension (HN), premature clinical manifestation of atherosclerosis, and other clinically important data. Body mass index (BMI), waist circumference, systolic and diastolic blood pressure (SBP, DBP) were determined in all subjects. SBP and DBP were measured three times under resting conditions using a mercury tonometer; the final value was calculated as the mean of the last two BP values. Venous blood samples were drawn in the morning after 12-hour fasting. Plasma concentrations of total cholesterol, HDL-cholesterol and triglycerides were determined by the enzymatic method (Hitachi 917 analyzer, Roche, Basel, Switzerland). Concentrations of apoB and lipoprotein (a) [Lp(a)] were determined by the immunoturbidimetric method using specific antibodies [Tina-Quant apoB-kit – version 2; Lipoprotein (a) TQ SYS 917, Roche, Basel, Switzerland]. We measured and calculated markers of IR (fasting glycemia, insulin, HOMA), and associated parameters (C-peptide, proinsulin) which represent secretion of insulin and were interpreted to reflect a compensatory response to an underlying insulin-resistant state. To simplify this text, the term “markers of IR” is used for both, parameters of IR, and parameters of insulin secretion. Glucose concentrations (Glc) were measured enzymatically (Glucose GOD-PAP SYS 917 kit, Roche, Basel, Switzerland). Plasma concentrations of insulin (ins) and C-peptide (Cp) were determined by the IRMA method (Insulin and C-peptide kits, Immunotech, Marseille,

France). Concentrations of proinsulin (pins) were assessed by the RIA method (Proinsulin kit, DRG Instruments GmbH, Marburg, Germany). Levels of tissue activator plasminogen (tPA) and plasminogen activator inhibitor I (PAI-1) were determined by the ELISA method (Technoclone). The following values were calculated: LDLc concentrations for subjects with TG < 4.5 mmol.L<sup>-1</sup> (n = 119) according to the Friedewald formula, LDLc = TC - (HDLc + TG/2.2) [30]; nonHDL-cholesterol concentrations (nonHDLc), nonHDLc = TC - HDLc [31,32]; atherogenic index of plasma (AIP), AIP = log (TG/HDLc) [33,34]; homeostasis model assessment (HOMA), HOMA = fasting glucose × fasting insulin level/22.5 [35]; and body mass index (BMI), BMI = weight/height<sup>2</sup>. Metabolic syndrome (MS) presence was assessed using the NCEP-ATP III definition [36] as for this definition we have the data from the Czech population (Cifkova et al, unpublished data).

### Statistical evaluation

Comparison of individual groups was made by the ANOVA method after age and gender adjustment; and age, gender, BMI and waist circumference adjustment, using the SPSS software for Windows, version 12.0 (Chicago, Illinois USA). The parameters with shifted distribution were log-transformed before the statistical analysis (TG, insulin, proinsulin, C-peptide, HOMA). Multivariate regression analysis with HOMA as dependent variable was used to assess independent association of HOMA with other confounding factors. Relation between markers of IR and with further parameters was assessed using the simple linear regression. Probability values of p < 0.05 were considered as statistically significant.

### Results

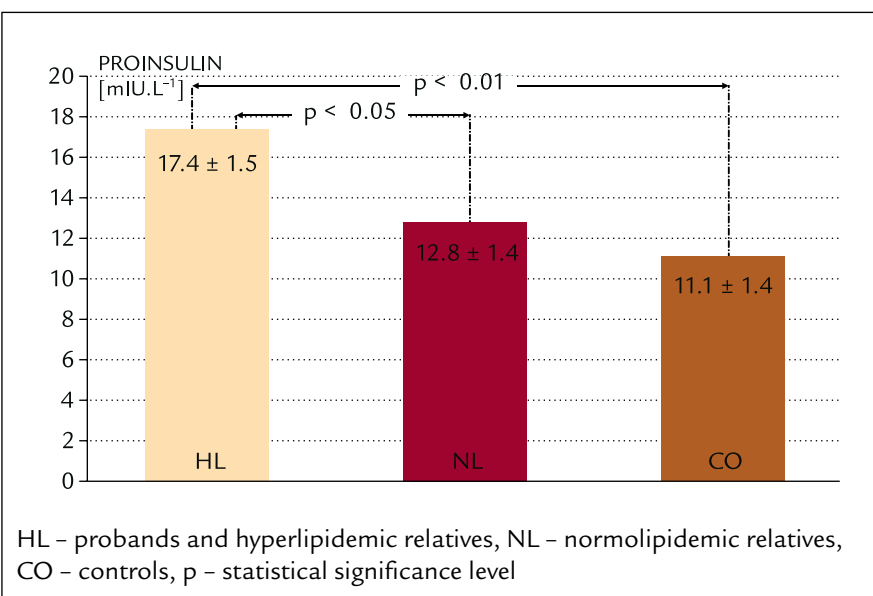
The mean values and standard deviations of the studied parameters after age and gender adjustment are given in tab. 1. By definition, the HL group

**Tab. 1. Lipid parameters and parameters related to insulin resistance and endothelial dysfunction – after adjustment for age and gender.**

Parameter	HL (n = 41)	NL (n = 49)	CO (n = 38)
total cholesterol [mmol.L <sup>-1</sup> ]	6.84 ± 0.18***	5.40 ± 0.16	5.07 ± 0.17
triglycerides [mmol.L <sup>-1</sup> ]	3.20 ± 0.29***	1.79 ± 0.26	1.18 ± 0.28
HDL cholesterol [mmol.L <sup>-1</sup> ]	1.36 ± 0.07*	1.48 ± 0.06	1.59 ± 0.07
LDL cholesterol [mmol.L <sup>-1</sup> ]	4.21 ± 0.16***	3.12 ± 0.14	2.93 ± 0.14
nonHDL cholesterol [mmol.L <sup>-1</sup> ]	5.48 ± 0.17***	3.92 ± 0.16	3.48 ± 0.17
apolipoprotein B [g.L <sup>-1</sup> ]	1.37 ± 0.04***	1.01 ± 0.04	0.93 ± 0.04
lipoprotein (a) [g.L <sup>-1</sup> ]	0.49 ± 0.07	0.37 ± 0.06	0.30 ± 0.07
atherogenic index of plasma	0.29 ± 0.05***	0.02 ± 0.04**	-0.18 ± 0.05
glycemia [mmol.L <sup>-1</sup> ]	4.94 ± 0.14	5.19 ± 0.13	5.06 ± 0.14
insulin [mIU.L <sup>-1</sup> ]	9.40 ± 0.78	7.78 ± 0.71	7.30 ± 0.76
proinsulin [mIU.L <sup>-1</sup> ]	17.4 ± 1.5**	12.8 ± 1.4	11.1 ± 1.4
C-peptide [mg.L <sup>-1</sup> ]	2.56 ± 0.19	2.27 ± 0.17	2.07 ± 0.18
HOMA [mIU × mmol.L <sup>-2</sup> ]	2.16 ± 0.21	1.84 ± 0.20	1.69 ± 0.21
waist circumference [cm]	90.0 ± 9.2***	78.0 ± 10.6	80.2 ± 11.5
BMI [kg.m <sup>-2</sup> ]	26.69 ± 2.87***	23.49 ± 3.66	23.80 ± 3.00
SBP [mm Hg]	126.7 ± 2.3	123.5 ± 2.1	122.2 ± 2.3
DBP [mm Hg]	81.7 ± 1.4***	79.1 ± 1.3**	73.7 ± 1.4
tPA [ng.mL <sup>-1</sup> ]	5.8 ± 0.8*	3.7 ± 0.7	3.2 ± 0.7
PAI-I [ng.mL <sup>-1</sup> ]	98.0 ± 6.5***	84.8 ± 5.9**	61.4 ± 6.3

HL – probands and hyperlipidemic, NL – normolipidemic relatives, CO – controls, HOMA – homeostasis model assessment, BMI – body mass index, SBP – systolic blood pressure, DBP – diastolic blood pressure, tPA – tissue plasminogen activator, PAI-I – plasminogen activator inhibitor I.

\*p < 0.05; \*\*p < 0.01; \*\*\*p < 0.001 – statistical significance level. Asterisks mark a statistically significant difference compared to the control group.



**Fig. 1. Comparison of the mean proinsulin levels in FCH subjects and controls [mIU.L<sup>-1</sup>].**

had significantly higher levels of lipid parameters defining FCH (TC, TG, apoB) as compared to the NL and CO

groups. Moreover, the HL group also exhibited more atherogenic values of other lipoproteins and derived param-

**Tab. 2. Lipid parameters and parameters related to insulin resistance and endothelial dysfunction – after adjustment for age, gender, BMI and waist circumference.**

Parameter	HL (n = 41)	NL (n = 49)	CO (n = 38)
total cholesterol [mmol. L <sup>-1</sup> ]	6.74 ± 0.18***	5.42 ± 0.16	5.14 ± 0.18
triglycerides [mmol.L <sup>-1</sup> ]	3.07 ± 0.30***	1.83 ± 0.26	1.26 ± 0.29
HDL cholesterol [mmol.L <sup>-1</sup> ]	1.40 ± 0.70	1.47 ± 0.06	1.56 ± 0.07
LDL cholesterol [mmol.L <sup>-1</sup> ]	4.16 ± 0.16***	3.13 ± 0.14	2.96 ± 0.15
nonHDL cholesterol [mmol.L <sup>-1</sup> ]	5.34 ± 0.17***	3.95 ± 0.16	3.58 ± 0.17
apolipoprotein B [g.L <sup>-1</sup> ]	1.33 ± 0.04***	1.01 ± 0.04	0.96 ± 0.04
lipoprotein (a) [g.L <sup>-1</sup> ]	0.51 ± 0.07*	0.35 ± 0.06	0.29 ± 0.07
atherogenic index of plasma glycemia [mmol.L <sup>-1</sup> ]	0.25 ± 0.05***	0.03 ± 0.04**	-0.15 ± 0.05
insulin [mIU.L <sup>-1</sup> ]	9.15 ± 0.80	7.80 ± 0.71	7.54 ± 0.77
proinsulin [mIU.L <sup>-1</sup> ]	17.12 ± 1.54**	12.90 ± 1.36	11.30 ± 1.48
C-peptide [mg.L <sup>-1</sup> ]	2.48 ± 0.19	2.28 ± 0.17	2.13 ± 0.19
HOMA [mIU × mmol.L <sup>-2</sup> ]	2.11 ± 0.22	1.84 ± 0.20	1.74 ± 0.21
SBP [mm Hg]	125.6 ± 2.4	123.6 ± 2.1	123.3 ± 2.3
DBP [mm Hg]	81.2 ± 1.5***	79.3 ± 1.3**	74.0 ± 1.4
tPA [ng.mL <sup>-1</sup> ]	5.7 ± 0.8*	3.7 ± 0.7	3.4 ± 0.7
PAI-I [ng.mL <sup>-1</sup> ]	90.6 ± 6.2**	86.6 ± 5.5*	67.1 ± 6.0

HL – probands and hyperlipidemic, NL – normolipidemic relatives, CO – controls, HOMA – homeostasis model assessment, SBP – systolic blood pressure, DBP – diastolic blood pressure, tPA – tissue plasminogen activator, PAI-I – plasminogen activator inhibitor I

\*p < 0.05; \*\*p < 0.01; \*\*\*p < 0.001 – statistical significance level. Asterisks mark a statistically significant difference compared to the control group.

**Tab. 3. Pearson correlation coefficients of markers of insulin resistance with other parameters for members of FCH families.**

Parameter	Insulin r	C-peptide r	HOMA r
gender	0.21	0.09	0.21*
age	0.10	0.31*	0.19
BMI	0.21*	0.36*	0.23*
waist circumference	0.23*	0.34*	0.26*
total cholesterol	0.13	0.27*	0.14
triglycerides	0.50*	0.55*	0.48*
LDL cholesterol	-0.06	0.11	-0.03
HDL cholesterol	-0.24*	-0.11	-0.19
apolipoprotein B	0.15	0.27*	0.17
atherogenic index of plasma	0.46*	0.43*	0.41*
insulin	1.00	0.81*	0.97*
HOMA	0.97*	0.81*	1.00
C-peptide	0.81*	1.00	0.81*
SBP	0.18	0.26*	0.23*
DBP	0.15	0.24*	0.17

Parameters with skewed distribution (triglycerides, insulin, C-peptide, HOMA) were log transformed to normalize their distribution before statistical analysis.

HOMA – homeostasis model assessment, BMI – body mass index, SBP – systolic blood pressure, DBP – diastolic blood pressure, \* p < 0.05 – statistical significance level; r – correlation coefficient.

eters [significantly higher concentrations of LDLc, nonHDLc, Lp(a), higher level of AIP, and lower concentrations of HDLc]. We anticipated finding of higher parameters linking to IR in the HL group compared to the CO group. Nevertheless, significant elevation was found only in proinsulin (fig. 1). There were some differences in concentration of fasting insulinemia, C-peptide and HOMA index among the three groups, but they did not reach statistical significance. The fasting glucose concentrations were similar for all three groups.

The tab. 1 shows significantly higher BMI and waist circumference in HL compared to NL and CO group. After age, gender, BMI, and waist circumference adjustment, we expected some change in significance levels. Nevertheless, the referred adjustment did not induce any important impact on the statistical significance (tab. 2). Association of IR markers with other followed up parameters for members of FCH families is summarized in tab. 3. Evaluation of independent association of HOMA index with other parameters under study for members of FCH families is presented in tab. 4.

The level of SBP was higher in the HL subgroup then in the CO and NL subjects although this was insignificant difference. But significant differences in DBP were recorded between the HL and CO subjects, and also between NL and CO subjects.

Impaired fibrinolysis, as determined by significantly increased levels of PAI-1 and tPA, was detected in HL when compared to CO. Interestingly, NL subjects from FCH families also differed from CO group in PAI-1 levels.

To estimate the impact of metabolic syndrome on markers of IR, we divided members subjects to these groups: The group A composed of FCH members with metabolic syndrome (11 HL and 3 NL subjects, n = 14), the group B comprised HL subjects without metabolic syndrome (n = 30), the group C formed by normolipidemic relatives without metabolic syndrome (n = 46),

Tab. 4. Multivariate regression analysis with HOMA as dependent variable for members of FCH families.

Coefficients	Unstandardized coefficients		Standardized coefficients	t	Sig.
	B	Std. error	Beta		
gender	0.437	0.340	0.157	1.283	0.203
BMI	0.062	0.081	0.169	0.763	0.447
waist circumference	-0.025	0.028	0.213	-0.886	0.378
SBP	0.015	0.010	0.158	1.364	0.176
triglycerides	0.294	0.110	0.469	2.680	0.009*
atherogenic index of plasma	-0.146	0.724	-0.037	-0.201	0.841

BMI – body mass index, SBP – systolic blood pressure, \*  $p < 0.05$  – statistical significance level

and the group D formed by controls ( $n = 38$ ) (tab. 5). Compared to group B, C and controls, group A showed the significantly higher levels of insulin, proinsulin and HOMA index, and C-peptide concentration was insignificantly higher in group A. Fasting glycaemia concentrations were similar in all four groups. We found no significant differences in IR parameters between FCH members without MS and controls. Further, group A had the highest concentration of triglycerides, the lowest concentration of HDL cholesterol, and the highest blood pressure compared to group B and C. It was in accordance with the definition of MS. Moreover, we have found that group B showed higher total cholesterol and LDL cholesterol level than group A.

## Discussion

FCH is the most important hereditary familial dyslipidemia resulting in premature atherosclerosis with negative impact on life quality and survival of the affected subject. Concentrations of lipids and lipoproteins in FCH usually do not reach extreme values as in familial hypercholesterolemia and are often just over 90<sup>th</sup> percentile of a given population [37]. Thus, it is probable that other factors beyond hyperlipidemia play a role in the premature development of atherosclerosis in affected FCH subjects.

Hyperlipidemia in FCH is fully expressed in adulthood [2], usually at about 30 years of age. As mentioned

above, the mean age of subjects included in the HL group ( $46.8 \pm 12.1$  years) was higher than those of the NL group ( $31.7 \pm 10.7$  years). Therefore, it is expected that with increasing age, the lipid phenotype may continue to develop in some NL individuals.

It is well known that FCH displays also intraindividual differences in lipid profile related to ageing and weight gain. Increased BMI and waist circumference, the well-established features of metabolic syndrome and IR, representing mass of visceral adipose tissue (VAT), result in elevation of triglycerides and in the typical conversion of lipid profile into the atherogenic lipid triad [13,20,21]. This was first described by Brunzell et al [7] and Vaverkova et al [38]. Similar to other authors, we also found significant interindividual differences in phenotype expression of lipid profile (defined according to Fredrickson) among FCH family members [2,4,6] – not shown in this paper.

HL subjects from FCH families showed decreased concentration of HDL cholesterol, higher triglycerides ( $TG \geq 1.5 \text{ mmol.L}^{-1}$ ), and high values of apoB, which indicates the presence of sdLDL subfraction. The AIP was higher in HL group compared to NL and CO group. AIP is an important marker of the LDL and HDL particles quality and it represents an important risk factor of atherosclerosis [33]. Elevated levels of AIP in HL group reflect predominance of small dense LDL, and less atheroprotective HDL. Signifi-

cantly higher AIP level in NL compared to CO group implies that the lipoprotein phenotype of some NL subjects is going to develop in future.

Increased IR in FCH families has been described several times using a spectrum of methods – more or less sophisticated [hyperinsulinemic euglycemic clamp with indirect calorimetry, glucose tolerance test, fasting and post-load insulin and glucose levels, free fatty acid (FFA) levels, HOMA] [8,9,19,21,22,39,40].

Pihlajamäki et al measured insulin sensitivity by the hyperinsulinemic euglycemic clamp with indirect calorimetry in nondiabetic FCH family members with various lipoprotein phenotypes. They found lower rates of insulin-stimulated glucose oxidation in members of FCH families with normolipidemic and hypertriglyceridemic phenotype, and in members with combined hyperlipidemic phenotype compared to subjects with hypercholesterolemic phenotype and controls. Also the rates of nonoxidative glucose disposal were lower in hypertriglyceridemic and in those with combined hyperlipidemic phenotype. FCH family members had higher free fatty acid levels compared to controls [19].

Karjalainen et al investigated insulin action by applying the hyperinsulinemic euglycemic clamp technique with indirect calorimetry in FCH families. They showed higher IR and impaired insulin's suppressive effect on FFA levels in patients with FCH – both

**Tab. 5. Lipid parameters and parameters related to insulin resistance and endothelial dysfunction; groups divided according to the presence of metabolic syndrome (NCEP, ATP III).**

Parameter	A HL + NL, MS+ (n = 14)	B HL, MS- (n = 30)	C NL, MS- (n = 46)	D CO (n = 38)
total cholesterol [mmol.L <sup>-1</sup> ]	5.82 ± 0.32*	6.77 ± 0.18#§	5.32 ± 0.15	5.07 ± 0.17
triglycerides [mmol.L <sup>-1</sup> ]	2.91 ± 0.24*#§	2.39 ± 0.14#§	1.28 ± 0.11	1.18 ± 0.28
LDL cholesterol [mmol.L <sup>-1</sup> ]	3.51 ± 0.30*	4.31 ± 0.17#§	3.14 ± 0.14	2.93 ± 0.14
HDL cholesterol [mmol.L <sup>-1</sup> ]	1.00 ± 0.13*#§	1.37 ± 0.08#§	1.60 ± 0.06	1.59 ± 0.07
nonHDL cholesterol [mmol.L <sup>-1</sup> ]	4.82 ± 0.30#§	5.40 ± 0.17#§	3.72 ± 0.14	3.48 ± 0.17
apolipoprotein B [g.L <sup>-1</sup> ]	1.26 ± 0.07#§	1.37 ± 0.04#§	0.97 ± 0.03	0.93 ± 0.04
lipoprotein (a) [g.L <sup>-1</sup> ]	0.30 ± 0.15	0.58 ± 0.09	0.38 ± 0.07	0.30 ± 0.07
atherogenic index of plasma glycemia [mmol.L <sup>-1</sup> ]	0.46 ± 0.08*#§	0.24 ± 0.04#§	-0.12 ± 0.04	-0.18 ± 0.05
insulin [mIU.L <sup>-1</sup> ]	5.40 ± 0.24	4.89 ± 0.14	5.06 ± 0.12	5.06 ± 0.14
HOMA [mIU × mmol.L <sup>-2</sup> ]	12.74 ± 1.42*#§	9.21 ± 0.92	6.75 ± 0.80	7.30 ± 0.76
proinsulin [mIU.L <sup>-1</sup> ]	3.03 ± 0.39*#§	2.13 ± 0.25	1.56 ± 0.22	1.69 ± 0.21
C-peptide [mg.L <sup>-1</sup> ]	25.28 ± 2.69*#§	15.69 ± 1.75	11.20 ± 1.51	11.10 ± 1.40
SBP [mm Hg]	2.94 ± 0.34	2.54 ± 0.22	2.12 ± 0.19	2.07 ± 0.18
DBP [mm Hg]	133.3 ± 3.9	123.8 ± 2.5	122.7 ± 2.2	122.2 ± 2.3
tPA [ng.mL <sup>-1</sup> ]	85.4 ± 2.2*#§	80.2 ± 1.4	78.7 ± 1.2	73.7 ± 1.4
PAI-I [ng.mL <sup>-1</sup> ]	8.8 ± 1.5#§	6.1 ± 1.0#§	2.6 ± 0.8	3.2 ± 0.7
number of MS features	126.5 ± 11.7*#§	99.3 ± 7.6#§	74.6 ± 6.6	61.4 ± 6.3
BMI [kg.m <sup>-2</sup> ]	3.2 ± 0.2*#§	1.4 ± 0.1#	0.5 ± 0.1	0.5 ± 0.1
waist circumference [cm]	29.2 ± 2.9	26.5 ± 2.5	23.1 ± 3.3	23.8 ± 3.0
	94.8 ± 7.6	89.3 ± 9.3	76.9 ± 9.8	80.2 ± 11.5

Parameters after adjustment for age and gender. HL – probands and hyperlipidemic relatives, NL – normolipidemic relatives, CO – controls, MS+ – presence of metabolic syndrome (NCEP ATP III), MS- – absence of metabolic syndrome, HOMA – homeostasis model assessment, BMI – body mass index, SBP – systolic blood pressure, DBP – diastolic blood pressure, tPA – tissue plasminogen activator, PAI-I – plasminogen activator inhibitor I, \*#§ p < 0.05 – statistical significance level, \*comparison to group B, #comparison to group C, §comparison to group D

in their hyperlipidemic and normolipidemic relatives [9].

Ascaso et al assessed IR in FCH measuring baseline and post glucose tolerance test concentrations of glucose and plasma insulin, the area under the curve (AUC) of insulin secretion [18], and the area under curve of glucose and free fatty acids [39,40]. They found the relationship of IR with the lipoprotein phenotype (IIa, IIb, IV) in FCH, and recorded significantly lower Si values (the peripheral sensitivity to insulin index) in the three FCH lipoprotein phenotypes, being more severe in subjects with hypertriglyceridemia [18]. In their previous study, they concluded that obesity (BMI ≥ 27 kg.m<sup>-2</sup>) exacerbates the hyperglycemia, hyperinsulinemia and blood pressure values in FCH patients [39]. But on the other hand, FCH subjects showed a higher

prevalence of hyperinsulinemia, even in the absence of obesity [41].

Cabezas et al divided FCH children into three tertiles on the basis of fasting plasma TG. Individuals in the highest tertile (TG > 2.5 mmol.L<sup>-1</sup>) had increased fasting plasma insulin concentrations and prolonged and exaggerated postprandial plasma concentrations of free fatty acids (FFA) compared to individuals in the lowest tertile and controls. Metabolism of FFA depends on insulin and therefore plasma levels of NEFA reflect IR. Moreover, the authors published that FCH children in the highest triglyceridemic tertile showed significantly higher BMI, systolic blood pressure, total cholesterol and apoB concentrations, and lower HDL-cholesterol levels [22].

Assessing HOMA index, Veerkamp found that FCH subjects were significantly

more insulin resistant compared to controls and also to normolipidemic relatives, even after correction for sex, age, and BMI. IR as a characteristic feature of FCH could not be fully explained by increased BMI and was associated with (change in) lipid phenotype expression [21].

Delawi et al found higher fasting insulin and HOMA index in FCH patients compared to healthy controls [8].

Van der Kallen et al found that increments of BMI, waist circumference, and waist-hip ratio (WHR) increased the frequency of hyperlipidemia in FCH relatives and their spouses. Predominant expression of hypertriglyceridemia was observed with higher categories of WHR in FCHL relatives but not in their spouses [20]. All these studies were done in FCH families diagnosed according to the old definition

(based on TC and TG 90<sup>th</sup> percentile values).

In the Spanish study, Martínez-Hervás et al found no differences between groups in systolic, but also diastolic blood pressure. They found significantly higher baseline and postload insulin levels in glucose tolerance test in FCH patients with acute myocardial infarction (AMI) compared to FCH patients without AMI and controls [42].

In the Greek study, the prevalence of metabolic syndrome was also higher in the subjects with FCH than in the control group [43].

Van der Vleutten et al studied adiponectin and other parameters in FCH families. Hyperlipidemic patients from FCH families were older and had significantly higher BMI, waist circumference, total and LDL-cholesterol concentrations, significantly lower HDL-cholesterol levels, and significantly higher insulin resistance that was reflected by higher HOMA index and K value [44].

In comparison with above mentioned studies, we found only significantly higher fasting proinsulin in HL members of FCH families. Other IR parameters did not differ significantly from control subjects. Elevated concentration of plasma proinsulin is the marker of compensatory escalated insulin secretion and therefore is indirect marker of presence of IR which could be probably confirmed by more sophisticated methods than HOMA index. Furthermore, exclusion of subjects with hypolipidemic therapy due to the clinical manifestation of atherosclerosis could also influence our results as these patients are usually the most insulin resistant.

In agreement with other authors, we recorded the highest BMI and waist circumference in HL subjects [4,11,12,20,21,45]. We presumed to confirm the impact of BMI and waist circumference on parameters of IR as well as already mentioned Karjalainen, Pihlajamäki and Ascaso [9,19,39]. In multivariate analysis, we did not find the

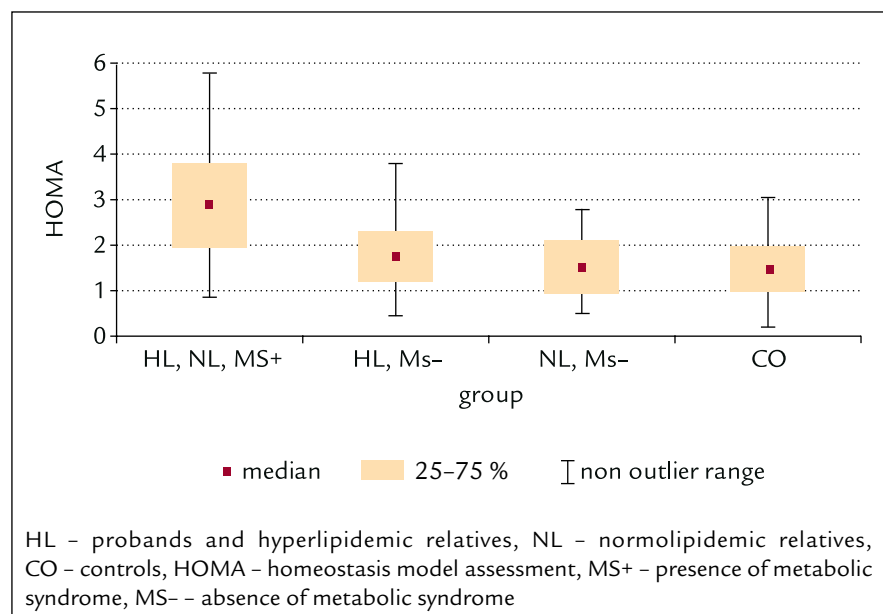


Fig. 2. Impact of metabolic syndrome on HOMA in FCH subjects and controls.

independent association of HOMA with BMI and waist circumference. This finding suggests that increased IR and proatherogenic potential in FCH could not be elucidated just by larger mass of visceral adipose tissue (VAT) which is a well-recognized factor associated with IR. In multiple regression analysis with HOMA as dependent variable, HOMA was independently associated only with TG (tab. 5).

Further, in accordance with previous studies [46–51], we found significantly elevated levels of PAI-1 and tPA in HL subjects. Impaired fibrinolysis, assessed by levels of tPA and PAI-1, is supposed to predict coronary artery disease (CAD) events and stroke [48,49,52] and is associated with IR [46,50,53]. This indicates presumed IR in HL subgroup although in our study, this hypothesis was not confirmed by measuring IR parameters except fasting proinsulin as already mentioned above.

We found higher TC and LDL cholesterol levels in hyperlipidemic subjects without metabolic syndrome (group B) compared to their hyperlipidemic relatives with metabolic syndrome (group A). This fact could indicate that in group B, atherosclerosis risk could be attributed to LDL cho-

lesterol meanwhile in group A, IR and probably sdLDL, IDL and VLDL particles could participate more in atherosclerosis.

The prevalence of metabolic syndrome in women of our FCH families was similar as in the Czech population [37] of this age, in FCH men was even less frequent. We confirmed that metabolic syndrome in FCH families aggravated IR (fig. 2) and could explain nearly completely the presence of IR in FCH family members. Thus the presence of metabolic syndrome appears to be a simple tool for detection of the most insulin resistant subjects of FCH families, who are at greatly increased risk of cardiovascular disease. This is important appreciating that current trends in occurrence in Czech Republic are alarming [54].

## Conclusions

Patients with familial combined hyperlipidemia display various dyslipidemic phenotypes that can vary substantially within any subject but also among relatives. Increased body weight and waist circumference, essential features of MS, aggravate hypertriglyceridemia and IR, and convert the lipid phenotype to classical atherogenic triad (increased TG, decreased HDLc, together

with elevated apoB concentration). Nevertheless, IR in FCH could not be explained only by increased BMI or visceral adipose tissue. In our study, FCH subjects with MS showed higher IR. Therefore, like in general population, the assessment of metabolic syndrome in FCH subjects could serve as a simple tool for detection of the most insulin resistant subjects with increased risk of premature manifestation of atherosclerosis.

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