

# Gender differences in lipoprotein metabolism

Giuseppina T Russo<sup>1</sup>, Annalisa Giandalia<sup>1</sup>, Elisabetta L Romeo<sup>1</sup>, Domenico Cucinotta<sup>1</sup>

1. Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy.

Received 28 September 2015; accepted 10 December 2015.

**Summary.** Gender-differences have been reported in lipid metabolism. Physiologically, lipid profile is similar in the two genders until childhood, but starting from puberty lipoprotein levels tend to diverge. Lipid profile changes more dramatically in women than in men, due to complex hormonal modifications throughout their lifetime, especially those related to pregnancy and menopause. Menopause is therefore associated with a more atherogenic lipid pattern, which is thought to influence increased cardiovascular (CVD) risk in postmenopausal women. The drop in oestrogens during this period is responsible, both directly or indirectly through the modulation of adiposity, for most of these lipid modifications. Genetic background may influence lipid and lipoprotein plasma concentrations and significant gene-gender interactions in several genetic loci involved in lipid metabolism, such as apolipoprotein E (APOE), APOC3 and cholesteryl ester transfer protein (CETP), have been reported to modulate plasma lipids and their response to diet or drugs. Also metabolic derangement associated with diabetes differentially affects lipid levels in men and women, having particularly adverse effects in women, with serious consequences in terms of CVD risk. Another important issue to consider is whether the relative CVD risk associated with lipoprotein abnormalities may vary according to gender, as data in the literature seem to indicate. All these findings point to the urgent need of diagnosing and treating lipid disorders differentially in men and women, in order to reduce the impact of CVD, which is still the first cause of mortality in women as well.

**Key words.** Gender, lipoproteins, metabolism.

## Lipoproteine e loro metabolismo: differenze di genere

**Riassunto.** Esistono differenze legate al genere nel metabolismo lipidico. Fisiologicamente, durante l'infanzia il profilo lipidico è simile nei due sessi, ma già a partire dall'adolescenza i livelli di lipoproteine iniziano a discostarsi. Nell'arco della vita, il profilo lipidico mostra cambiamenti più radicali nelle donne rispetto agli uomini, a causa delle complesse modifiche ormonali che si verificano nelle donne, soprattutto legate alla gravidanza e alla menopausa. Infatti, la menopausa si associa a un pattern lipidico più aterogeno e questo si pensa abbia una importante influenza sull'aumentato rischio cardiovascolare (CV) che caratterizza le donne nel periodo post-menopausale. La caduta del tasso estrogenico in questo periodo è responsabile di larga parte delle modifiche nel profilo lipidico, sia direttamente che indirettamente, attraverso la modulazione del grado di adiposità. Il background genetico può influenzare le concentrazioni di lipidi e di lipoproteine e sono state identifi-

cate interazioni significative tra il sesso e diversi loci genici coinvolti nel metabolismo lipidico, come quelli dell'apolipoproteina E (APOE), dell'APOC3 e della proteina di trasferimento del colesterolo esterificato (CETP), in grado di modulare i livelli lipidici e la loro risposta a dieta o farmaci.

Anche le alterazioni metaboliche associate al diabete sembrano avere effetti diversi negli uomini e soprattutto nelle donne, con gravi conseguenze in termini di rischio CV. Un altro importante aspetto da considerare è se il rischio relativo CV associato alle singole frazioni lipidiche sia diverso nei due sessi, così come sembrano suggerire i dati disponibili in letteratura. Tutte queste evidenze indicano come sia ormai necessario diagnosticare e trattare le dislipidemie in modo diverso negli uomini e nelle donne, al fine di ridurre l'impatto delle malattie cardiovascolari, che sono ancora la prima causa di morte anche nel sesso femminile.

**Parole chiave.** Genere, lipoproteine, metabolismo.

## Lipid profile according to gender and age

Cardiovascular disease (CVD) is one of the most important causes of morbidity and mortality in the industrialized world and it is the primary cause of death in women as well.

As compared to men, women tend to develop coronary heart disease (CHD) 10 to 20 years later, and the risk of developing a major CVD event rises up to 25% after the age of 40 years<sup>1,2</sup>.

CVD has a multifactorial aetiology, and cigarette smoking, hypertension, diabetes mellitus, low high-density lipoprotein cholesterol (HDL-C) and elevated low-density lipoprotein cholesterol (LDL-C) levels have all been recognized as independent risk factors<sup>3</sup>.

Although dyslipidaemia is a common CVD risk factor in both sexes, gender-differences have been reported in the pathophysiology, diagnosis and treatment of lipid disorders<sup>4,5</sup>. Lipid profile is similar in the two genders until childhood, but starting from puberty lipoprotein levels tend to diverge physiologically. LDL-C levels usually rise from young adulthood to the age of 60 years in men and 70 years in women, and then the curves decrease, probably for the selective survival of subjects with lower LDL-C levels<sup>6</sup>.

Overall, through middle age, women have lower LDL-C, non-HDL-C and total cholesterol (T-C) levels than men, whereas by the time of menopause, LDL-C

levels rise more in women than in men, inverting the curves of LDL-C<sup>6,7</sup>. Consequently in older age groups, women show higher LDL-C levels than men.

This age-dependent increase of LDL-C levels has been related to reduced catabolism due to the reduction of the activity of the LDL receptors in the liver, as indicated by kinetic studies of LDL-apoB in a group of subjects with a broad age range<sup>8</sup>.

In addition to age and sex-related quantitative modification in LDL-plasma levels, qualitative variances in lipoproteins have also been noted between sexes. In the Bogalusa Heart Study that evaluated lipid profile in a large cohort of teenagers, boys had a smaller mean LDL and larger very low-density lipoprotein (VLDL) particle size as compared with girls<sup>9</sup>. This smaller LDL particle size has been persistently shown in men, irrespective of age<sup>10,11</sup>.

Sex-related differences in lipid profile have been clearly reported in the Framingham Offspring Study that evaluated lipid profile in over 3,000 middle-aged subjects, taking into account menopausal status. Mean plasma levels of LDL-C and apoB were higher in men than in women, but the age-related increment in LDL-C was more evident in women than in men. LDL-C and apoB levels were significantly higher in postmenopausal than in premenopausal women, even after age- and BMI-adjustment, indicating a hormonal effect on LDL metabolism<sup>6</sup>.

Differences are reported also in lipoprotein(a) (Lp[a]) concentration, which tends to remain constant in men and increases with age in women<sup>5</sup>.

Also triglycerides are usually higher in men than in women at every age<sup>6</sup>, whereas HDL-C concentrations tend to decrease with ageing in men, but not in women<sup>6,12</sup>, leading to a ~10 mg/dl difference in HDL-C levels<sup>3,6,12</sup>. Gender-related differences in HDL subclasses have also been reported between male and female adolescents. In the Bogalusa Heart Study, young males showed smaller mean HDL particle size as compared with females and this difference was evident even after correction for HDL-C<sup>13</sup>.

### **Lipid profile in pregnancy and menopause: role of oestrogen**

Lipid profile changes more dramatically in women than in men, due to complex hormonal modifications throughout their lifetime, especially those related to pregnancy and menopause.

During pregnancy, T-C, triglycerides and LDL-C levels increase due to the effects of a number of hormones, including human chorionic gonadotropin hormone, beta-estradiol, insulin, and progesterone<sup>5,14-16</sup>. Total HDL-C, HDL2-C and apolipoprotein A1 concentra-

tions increase in pregnancy<sup>15</sup>, then going back to baseline values in the post-partum<sup>17,18</sup>. Due to the effects of androgens or insulin-resistance, HDL-C levels remain lower after post-partum so that parous women tend to have lower HDL-C levels than nulliparous ones<sup>17,18</sup>.

Lipid modifications typically occur after menopause. Epidemiological studies have consistently shown higher T-C and LDL-C, and lower HDL-C levels in postmenopausal compared to premenopausal women. A decrease in LDL-particle size has also been documented after menopause<sup>19</sup>, though with controversial reports<sup>10,20</sup>.

Adverse lipoprotein patterns found in postmenopausal women are thought to be partly responsible for their high CVD risk.

The fall of oestrogen levels after menopause is certainly responsible for most of these modifications, either through direct effects on lipid metabolism or through the regulation of body composition and energy balance<sup>21,22</sup>. After menopause, women begin to show a redistribution of body visceral fat and a typical abdominal localization.

Oestrogen may also directly influence lipid metabolism through the suppression of gene expression and activity of lipoprotein lipase (LPL), the rate limiting enzyme in triglycerides metabolism<sup>23,24</sup>, or through the modulation of lipolysis by the up-regulation of  $\alpha 2$ -adrenergic receptors<sup>25</sup>.

Moreover, it has been shown that oestrogen replacement therapy in postmenopausal women decreases the expression of several lipogenesis genes, such as sterol regulatory element binding protein 1c, fatty acid synthase, acetyl-CoA carboxylate, LPL and peroxisome proliferator-activated receptor- $\gamma$ <sup>24,26</sup>. This treatment may also impact cholesterol metabolism through the increase in hepatic cell surface LDL receptors and faster clearance of LDL particles<sup>27</sup>. Furthermore, it has been shown to increase cholesterol excretion in humans and to decrease the conversion of VLDL into LDL in rabbits<sup>28,29</sup>.

The effects of oestrogens on lipid metabolism may also be mediated by their action on adipose tissue. Oestrogens are potent regulators of adipogenesis and adipose metabolism and oestrogen receptors (ERs), ER- $\alpha$  and ER- $\beta$  are expressed both in human and rodent adipocytes, with a pattern that varies according to the stage of adipocyte differentiation and adipose tissue localization<sup>30,31</sup>.

The key role played by oestrogen in lipid metabolism is corroborated by the common observation that many of the menopause-related modifications in lipid profile are reversible with hormonal replacement therapy (HRT). However, the effects of HRT on lipid metabolism depend on the type of oestrogen and progestin combination, the route of administration and dosage<sup>32</sup>. Many of the beneficial effects on lipid fractions seem

to be mediated by the oestrogenic component, whereas they are usually counterbalanced by the progestin component. Exogenous oestrogen has been shown to markedly decrease both LDL-C and ApoB levels in dyslipidaemic postmenopausal women<sup>33,34</sup>, and to increase HDL-C, HDL2-C, and triglyceride levels<sup>35</sup>. Data are also available in pre-menopausal women from the Bogalusa study<sup>36</sup>, where oral contraceptive use was associated with significant modifications in T-C, triglycerides, VLDL-C, and LDL-C, but no changes were reported in HDL-C levels.

### Gene-gender interaction affecting lipid profile

Both environmental and genetic factors play a role in determining lipid and lipoprotein plasma concentrations. The heritability of the most common forms of dyslipidemias is polygenic, and specific mutations at several candidate genes have been associated with altered lipid levels, although these mutations usually account for a small proportion of the variability observed in the general population<sup>37,38</sup>.

Although men and women share most genetic information, significant gene-gender interactions affecting plasma lipids have been reported.

Apolipoprotein E (*APOE*) offers a significant example of the possible interactions between genes, gender and environmental factors that ultimately modulate circulating plasma lipids.

*APOE* serves as a ligand for the LDL receptor (LDLR) and the LDL receptor-related protein (LDLRP). The most commonly studied genetic variation at the *APOE* locus results from 3 common alleles: *E4*, *E3* (the most frequent form in Caucasian populations) and *E2*<sup>37, 38</sup>. Population studies have shown that *APOE* alleles affect T-C, LDL-C, ApoB and triglycerides plasma levels, accounting for up to 7% of the variation in T-C and LDL-C concentrations in the general population, with a greater effect in women than in men<sup>37,38</sup>. Significant *APOE*-gender interactions have been reported in several studies testing the genetic susceptibility to CHD and the response to diet, and to hypolipidemic drugs<sup>37,38</sup>. Interactions of *APOE* gene with diet and alcohol consumption has been observed in men but not in women, and population studies showed significant *APOE* gene-gender association with CVD risk<sup>37-39</sup>.

An *APOE*-gender interaction modulating the lipid response to statins has also been observed<sup>40</sup>. Furthermore, Tsuda et al. showed that the *APOE* genotype may modulate total and LDL-C response to HRT, with a reduction in T-C and LDL-C levels that was the greatest in women *E2* carriers, intermediate in *E3/E3* carriers and the lowest in carriers of *APOE4* allele<sup>41</sup>.

Another example of the modulating effect of sex on

the relationship between genetic background and plasma lipids is related to the apolipoprotein C3 (*APOC3*) gene, which is clustered with the *APOA1*, *APOA4*, and *APOA5* genes on the long arm of human chromosome 11, a highly polymorphic region that has been extensively studied. The common *SstI* polymorphism on *APOC3* gene has been associated with increased triglycerides and ApoCIII plasma levels<sup>42</sup>. In the Framingham Offspring Study the minor S2 allele was found to be associated with lower concentrations of HDL-C and HDL2-C and higher *APOC3* non-HDL and triglyceride levels in men; conversely, in women, the S2 allele was associated with increased T-C, LDL-C and ApoB levels. Lipoprotein subfractions were also examined using nuclear magnetic resonance (NMR) spectroscopy. S2 male carriers had significantly lower concentrations of large LDL and a significant reduction in LDL particle size, while in female participants there was a significant increase in intermediate LDL particles with no significant effect on lipoprotein diameters<sup>43</sup> (Table 1).

The importance of the genetic effect on different lipid fractions is extremely variable, with more than 50% of circulating HDL-C that is genetically determined<sup>44</sup>. Besides *APOA1* genetic variants<sup>38</sup>, a common *TaqIB* variant in gene coding for cholesteryl ester transfer protein (CETP), a key enzyme in reverse cholesterol transport (RCT), has been associated with lower CETP activity, higher HDL-C levels and a greater atheroprotective HDL subpopulations profile<sup>45-47</sup>.

Significant gene-gender interactions have been reported also for this genetic variant: in male participants of the Framingham Offspring Study, B2 uncommon allele was associated with increased particle size for HDL and LDL, but a similar effect was demonstrated only for HDL particle size in females. Furthermore, the protective association of this genetic variant on CHD risk was reported in men but not in women<sup>47</sup>.

The effect of CETP *TaqIB* polymorphism on lipid and lipoprotein profile, as well as on the distribution of the HDL LpA-I and LpA-I:A-II subclasses, as determined by two-dimensional gel electrophoresis, was also explored in a group of women with and without type 2 diabetes<sup>48</sup>. The effect of CETP polymorphism was limited to diabetic women among whom it showed significant interactions with HOMA(IR), BMI and triglycerides concentrations (Table 2).

### Diabetes, gender and lipid profile

CVD is the primary cause of morbidity and mortality in diabetic patients. Relative CHD risk is higher in both type 2 and type 1 diabetic women than in diabetic men<sup>49,50</sup>.

Among the various and not fully elucidated reasons

for this excessive CVD risk associated with diabetes in the female gender<sup>51-53</sup>, several lines of evidence indicate that lipoprotein profile plays an important role.

Diabetic women usually have substantially higher triglyceride concentrations and significantly lower HDL-C levels than non-diabetic ones, even after adjustment by age and body weight<sup>48,54</sup>. Low levels of HDL-C seem to have a peculiar role on CVD risk in this population. Low HDL-C levels are a well-recognized CVD risk factor: data from a 6-year follow-up of the PROCAM study showed that the incidence of CHD decreased with higher levels of HDL-C<sup>55</sup>. The Framingham study showed that high levels of HDL-C reduce the risk of CHD at all levels

of LDL-C<sup>56</sup>. Based on these and other epidemiological studies, current Adult Treatment Panel III- ATP III Guidelines<sup>3</sup> identify HDL-C  $\geq 60$  mg/dL as a “negative” risk factor since it removes 1 risk factor from the total count.

However, recent findings suggest that the atheroprotective role of HDL-C is not limited solely to its circulating concentration, but depends on qualitative properties of HDL particles, which may be dysfunctional despite normal levels. Therefore, HDL is a heterogeneous class of lipoproteins differing in size, density, charge, and composition. HDL particles can be divided into sub-fractions by different methods, and some authors have demonstrated that HDL qualitative properties may strongly modulate CHD risk<sup>57</sup>.

The metabolic derangement associated with diabetes may strongly impact HDL composition and function. In a selected group of women with and without type 2 diabetes (T2DM), not taking hypolipidemic medications, we compared apoA-I-containing HDL subclass distribution, as determined by two-dimensional gel electrophoresis, taking also menopause into account. Diabetic women showed lower levels of the large  $\alpha$ -1,  $\alpha$ -2, and pre- $\alpha$ -1 HDL particles, and a higher concentration of the small  $\alpha$ -3 HDL particles when compared to non-diabetic subjects, and this less atheroprotective HDL pattern was evident also in pre-menopausal groups, independently from HDL-C and triglyceride concentrations<sup>48</sup>. Notably, these modifications in HDL subclass profile in diabetic women without CHD were comparable both quantitatively and qualitatively with those found in men with CHD<sup>58</sup>.

**Table 1.** Plasma lipids and lipoprotein according to gender:

	Men (1,219)	Women (1,266)	P
Age (yrs)	52.0 $\pm$ 10.1	51.4 $\pm$ 9.8	NS
T-C (mg/dl)	203 $\pm$ 37	204 $\pm$ 39	NS
LDL-C (mg/dl)	133 $\pm$ 34	127 $\pm$ 35	0.0001
HDL-C (mg/dl)	43.7 $\pm$ 11.7	55.8 $\pm$ 15.0	0.0001
HDL2-C (mg/dl)	5.4 $\pm$ 3.9	9.7 $\pm$ 5.7	0.0001
HDL3-C (mg/dl)	38.4 $\pm$ 9.0	46.1 $\pm$ 11.1	0.0001
Triglycerides (mg/dl)	135 $\pm$ 100	108 $\pm$ 82	0.0001
Apo A1 (mg/dl)	135 $\pm$ 24	154 $\pm$ 32	0.0001
Apo B (mg/dl)	102 $\pm$ 25	95 $\pm$ 26	0.0001

Modified from Russo GT et al.<sup>43</sup> Values are n, mean  $\pm$  SD. T-C, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; NS, not significant.

**Table 2.** Plasma lipids, lipoprotein and apo-A-I-containing HDL subpopulations in CHD-free pre- and postmenopausal women with and without type 2 diabetes:

	Type 2 diabetic women		Control women		P1	P2
	Pre-menopause	Post-menopause	Pre-menopause	Post-menopause		
T-C (mg/dl)	189.0 $\pm$ 32.4	192.5 $\pm$ 26.9	179.8 $\pm$ 29.3	203.9 $\pm$ 24.7	NS	0.04
HDL-C (mg/dl)	45.9 $\pm$ 13.8	48.6 $\pm$ 13.4	56.9 $\pm$ 11.8	55.6 $\pm$ 11.7	0.0004	0.01
LDL-C (mg/dl)	127.1 $\pm$ 30.3	122.3 $\pm$ 24.6	116.3 $\pm$ 27.4	134.2 $\pm$ 27.3	NS	0.04
VLDL-C (mg/dl)	28.0 $\pm$ 20.3	20.8 $\pm$ 9.1	15.6 $\pm$ 5.3	19.4 $\pm$ 8.7	<0.001	<0.001
Triglycerides (mg/dl)	140.1 $\pm$ 101.5	104.1 $\pm$ 45.5	78.2 $\pm$ 26.5	96.8 $\pm$ 43.7	<0.001	<0.001
<i>Apo-A-I- containing HDL subpopulations</i>						
$\alpha$ -1 HDL (mg/dl)	18.2 $\pm$ 8.2	20.2 $\pm$ 9.6	22.8 $\pm$ 8.1	23.8 $\pm$ 10.8	0.02	0.01
$\alpha$ -2 HDL (mg/dl)	42.5 $\pm$ 11.0	40.3 $\pm$ 8.2	45.9 $\pm$ 8.6	45.1 $\pm$ 9.4	NS	0.01
$\alpha$ -3 HDL (mg/dl)	17.8 $\pm$ 6.7	18.5 $\pm$ 4.3	16.4 $\pm$ 3.6	16.3 $\pm$ 3.9	NS	NS
Prea-1 HDL (mg/dl)	5.7 $\pm$ 3.4	5.3 $\pm$ 3.4	6.9 $\pm$ 2.5	6.6 $\pm$ 4.1	NS	NS

Modified from Russo GT et al.<sup>48</sup> Values are n, mean  $\pm$  SD. T-C, total cholesterol; -C, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; VLDL, very low-density lipoprotein; NS, not significant. P1, pre-menopause diabetic vs controls; P2, post-menopause diabetic vs controls.



Besides their role in RCT, several lines of evidence indicate that HDL particles may affect the atherosclerotic process also through the modulation of subclinical inflammation<sup>59</sup> and the differences in HDL size and composition reported in diabetic women may also affect their anti-inflammatory properties. This hypothesis was explored in a group of CHD-free women with and without diabetes by measuring inflammatory markers and HDL subpopulations<sup>60</sup>. Compared to controls, diabetic women showed greater subclinical inflammation with higher hsCRP and IL-6 serum levels (age- and BMI-adjusted  $P < 0.001$ ). Notably, HDL subclasses significantly correlated with inflammatory markers: hsCRP inversely correlated with  $\alpha$ -1 and pre- $\alpha$ -1 HDL, while IL-6 inversely correlated with  $\alpha$ -1,  $\alpha$ -2, and pre- $\alpha$ -1 HDL particles and positively with  $\alpha$ -3 HDL, indicating that more atheroprotective HDL subclasses are associated with lower levels of inflammatory markers, especially in diabetic women. These data suggest that different HDL subclasses may influence CHD risk also through the modulation of inflammation<sup>60</sup>.

Differences in lipid profile affecting CVD risk in diabetic women are not limited to HDL particles, and LDL-C levels remain the major goal of CHD prevention also in subjects with T2DM<sup>61</sup>. In a representative sample of Italian T2DM patients, it has been reported that women were 42% more likely to have LDL-C above the recommended target of 130 mg/dL, as compared to men, in spite of lipid-lowering treatment and in the context of an overall lower quality of care<sup>62</sup>, and this finding has been consistently reported also in other cohorts<sup>63,64</sup>. In order to better clarify this issue, we explored age- and gender-related differences in LDL-C management in a large sample of 415,294 T2DM patients (45.3% women) from 236 diabetes outpatient centers in Italy<sup>65</sup>. Women were older and more obese and had a slightly longer diabetes duration, higher T-C, LDL-C and HDL-C serum levels and lower triglyceride levels as compared to men. Lipid profile was monitored in ~75% of subjects, women being monitored less frequently than men, irrespectively of age. More women (+6.2%) did not reach the LDL-C target as compared to men, particularly in the subgroup treated with lipid-lowering medications. Furthermore, this between-genders gap in reaching LDL-C targets increased with age and diabetes duration, favoring men in all groups<sup>65</sup>.

Nevertheless, the most striking finding of this study was that T2DM women were not able to reach the recommended LDL-C targets as men, in spite of a similar rate in the use of medications and a slightly higher use of statins<sup>65</sup>.

It has been commonly recognized that drug registration trials are usually sex-unbalanced, often including smaller group of women, and they rarely take into

account women in different phases of their hormonal pathway, and this also applies to lipid lowering trials with statins. However, meta-analyses have demonstrated that statin therapy is efficacious in reducing LDL-C and CHD risk also in women with or without T2DM<sup>66</sup>. While waiting for *ad hoc* studies that are needed in order to clarify this important issue, to date there is no indication for having a different approach in the prescription of lipid lowering agents in men and women<sup>3</sup>.

### Relative impact of lipid fraction on CVD risk according to gender

Another important issue to consider is whether the relative risk associated with each lipoprotein abnormality may vary according to gender. Several lines of evidence point to a differential role of lipid profile in men and women.

Although LDL-C levels are the primary target for CVD prevention in both men and women, other lipid abnormalities seem to have a stronger impact on CVD risk in the female gender.

The Lipid Research Clinics' Follow-up Study<sup>67</sup> calculated the risk associated with different lipoprotein abnormalities in 1,405 women aged 50-69 years. They noted that low HDL-C (<50 mg/dl) and high triglycerides (>200 mg/dl) were strong predictors of CVD death while LDL-C and T-C were poor predictors.

Furthermore, a meta-analysis evaluating the association between elevated triglycerides and CHD risk showed that elevated triglycerides were associated with an approximately 30% increased risk for men and a 75% increased risk in women<sup>54</sup>.

To date, only few studies have explored the gender differences in the relation between CVD risk and LDL particle size<sup>68-70</sup>. A recent report from the Women's Cardiovascular Health Study, which enrolled young women aged 18 to 44 years, showed up to a 3.5-fold increase in risk of premature myocardial infarction associated with smaller LDL size<sup>68</sup>.

The role of small dense LDL on CHD risk has also been explored in a cohort of T2DM<sup>70</sup>.

After taking into account several potential predictors, including metabolic and lipid profile, as well as fasting plasma levels of total homocysteine, folate, vitamin B12, hsCRP, IL-6, and VCAM-1, impaired renal function and sdLDL were the strongest predictors of CHD risk in this population, whereas no significant association was noted with LDL-C<sup>70</sup>.

All these findings suggest that beyond LDL-C, more subtle alterations of LDL particles, together with other quantitative and qualitative modifications of lipid profile, may be stronger contributors to CHD risk in women as compared with what is observed in men.

Conclusions

Lipid profile differs by sex and age: in men, lipid profile is modified by ageing, in women by ageing and oestrogen status. Menopause has the strongest impact on lipid fractions which shift toward a more atherogenic pattern in terms of both quantity and quality of circulating lipoproteins. While HRT usually reverses lipid abnormalities, this is not translated into a reduction of CHD risk so that health costs/benefits ratio must drive its use. Furthermore, metabolic derangements like those observed in diabetes seem to have a stronger impact on lipid profile in women than in men.

Also genetic background may modulate plasma lipids, their response to diet or drugs, and all these aspects are dependent on multiple genes-gender interactions.

The relative impact of different lipoprotein fractions on CVD risk may also differ by gender: LDL-C appears to be a relatively weaker CHD risk factor, whereas HDL-C/triglycerides have a stronger influence in women as compared to men. Finally, hypolipidemic treatments may be less efficacious in women, at least in diabetic ones, due to lack of adherence or some still unknown biological mechanisms.

It is increasingly clear that it is necessary to consider men and women separately in the CVD risk assessment and prevention, as recently stated by the American Heart Association, which established specific indications for women<sup>71</sup>.

While awaiting an elucidation of the pathophysiological bases of these gender differences in CVD, correction of all modifiable risk factors, first and foremost lipid abnormalities, is still the only strategy for primary and secondary CVD prevention in both men and women.

Key messages

- Gender-differences have been reported in lipid metabolism.
- Physiologically, starting from puberty lipoprotein levels tend to diverge in the two genders.
- Lipid profile changes more dramatically in women than in men, due to complex hormonal modifications, especially those related to pregnancy and menopause.
- Genetic background may influence lipid and lipoprotein plasma concentrations and significant gene-gender interactions in several genetic loci involved in lipid metabolism have been reported.
- The relative risk associated with lipoprotein abnormalities may vary according to gender, with a higher impact of low HDL-C and higher triglycerides on coronary heart disease risk in the female gender.

References

1. Hazzard WR. Why do women live longer than men? Biologic differences that influence longevity. *Postgrad Med* 1989; 85: 271-78.
2. American Heart association, 2001 Heart and Stroke Statistical Update. Dallas: American Heart association, 2000.
3. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation and treatment of High Blood Cholesterol in Adults (Adult treatment Panel III) final report. *Circulation* 2002; 25: 3143-421.
4. Phan BA, Toth PP. Dyslipidemia in women: etiology and management. *Int J Womens Health* 2014; 6: 185-94.
5. Bittner V. Lipoprotein abnormalities related to women's health. *Am J Cardiol* 2002; 90: 77i-84i.
6. Schaefer EJ, Lamon-Fava S, Cohn SD, et al. Effects of age, gender, and menopausal status on plasma low density lipoprotein cholesterol and apolipoprotein B levels in the Framingham Offspring Study. *J Lipid Res* 1994; 35: 779-92.
7. Gardner CD, Winkleby MA, Fortmann SP. Population frequency distribution of non-high-density lipoprotein cholesterol (Third National Health and Nutrition Examination Survey [NHANES III], 1988-1994). *Am J Cardiol* 2000; 86: 299-304.
8. Ericsson S, Eriksson M, Vitols S, Einarsson K, Berglund L, Angelin B. Influence of age on the metabolism of plasma low density lipoproteins in healthy males. *J Clin Invest* 1991; 87: 591-96.
9. Freedman DS, Bowman BA, Otvos JD, Srinivasan SR, Berenson GS. Levels and correlates of LDL and VLDL particle sizes among children: the Bogalusaheart study. *Atherosclerosis* 2000; 152: 441-49.
10. McNamara JR, Campos H, Ordovas JM, Peterson J, Wilson PW, Schaefer EJ. Effect of gender, age, and lipid status on low density lipoprotein subfraction distribution. Results from the Framingham Offspring Study. *Arteriosclerosis* 1987; 7: 483-90.
11. Krauss RM, Burke DJ. Identification of multiple subclasses of plasma low density lipoproteins in normal humans. *J Lipid Res* 1982; 23: 97-104.
12. Kreisberg RA, Kasim S. Cholesterol metabolism and aging. *Am J Med* 1987; 82: 54-60.
13. Freedman DS, Bowman BA, Srinivasan SR, Berenson GS, Otvos JD. Distribution and correlates of high-density lipoprotein subclasses among children and adolescents. *Metabolism* 2001; 50: 370-76.
14. Lippi G, Albiero A, Montagnana M, et al. Lipid and lipoprotein profile in physiological pregnancy. *Clin Lab* 2007; 53: 173-77.
15. Desoye G, Schweditsch MO, Pfeiffer KP, Zechner R, Kostner GM. Correlation of hormones with lipid and lipoprotein levels during normal pregnancy and postpartum. *J Clin Endocrinol Metab* 1987; 64: 704-12.
16. Mazurkiewicz JC, Watts GE, Warburton FG, Slavin BM, Lowy C, Koukkou E. Serum lipids, lipoproteins and apolipoproteins in pregnant non-diabetic patients. *J Clin Pathol* 1994; 47: 728-31.

17. van Stiphout WA, Hofman A, de Bruijn AM. Serum lipids in young women before, during, and after pregnancy. *Am J Epidemiol* 1987; 126: 922-28.
18. Lewis CE, Funkhouser E, Raczyński JM, Sidney S, Bild DE, Howard BV. Adverse effect of pregnancy on high density lipoprotein (HDL) cholesterol in young adult women. The CARDIA Study. *Coronary Artery Risk Development in Young Adults*. *Am J Epidemiol* 1996; 144: 247-54.
19. Foulon T, Payen N, Laporte F, et al. Effects of two low-dose oral contraceptives containing ethinylestradiol and either desogestrel or levonorgestrel on serum lipids and lipoproteins with particular regard to LDL size. *Contraception* 2001; 64: 11-16.
20. Campos H, McNamara JR, Wilson PW, Ordovas JM, Schaefer EJ. Differences in low density lipoprotein subfractions and apolipoproteins in premenopausal and postmenopausal women. *J Clin Endocrinol Metab* 1988; 67: 30-35.
21. Iverius PH, Brunzell JD. Relationship between lipoprotein lipase activity and plasma sex steroid level in obese women. *J Clin Invest* 1988; 82: 1106-12.
22. Mauvais-Jarvis F. Estrogen and androgen receptors: regulators of fuel homeostasis and emerging targets for diabetes and obesity. *Trends Endocrinol Metab* 2011; 22:24-33.
23. Homma H, Kurachi H, Nishio Y, et al. Estrogen suppresses transcription of lipoprotein lipase gene. Existence of a unique estrogen response element on the lipoprotein lipase promoter. *J Biol Chem* 2000; 275: 11404-11.
24. Price TM, O'Brien SN, Welter BH, George R, Anandjiwala J, Kilgore M. Estrogen regulation of adipose tissue lipoprotein lipase--possible mechanism of body fat distribution. *Am J Obstet Gynecol* 1998; 178: 101-7.
25. Pedersen SB, Kristensen K, Hermann PA, Katzenellenbogen JA, Richelsen B. Estrogen controls lipolysis by up-regulating alpha2A-adrenergic receptors directly in human adipose tissue through the estrogen receptor alpha. Implications for the female fat distribution. *J Clin Endocrinol Metab* 2004; 89: 1869-78.
26. Lundholm L, Zang H, Hirschberg AL, Gustafsson JA, Arner P, Dahlman-Wright K. Key lipogenic gene expression can be decreased by estrogen in human adipose tissue. *Fertil Steril* 2008; 90:44-48.
27. Kovanen PT, Brown MS, Goldstein JL. Increased binding of low density lipoprotein to liver membranes from rats treated with 17 alpha-ethinyl estradiol. *J Biol Chem* 1979; 254: 11367-73.
28. Nestel PJ, Hirsch EZ, Couzens EA. The effect of Chlorophenoxyisobutyric acid and Ethinyl estradiol on cholesterol turnover. *J Clin Invest* 1965; 44: 891-96.
29. Kushwaha RS, Hazzard WR. Effect of exogenous estrogens on catabolism of VLDL in cholesterol-fed rabbits. *Am J Physiol* 1981; 241: E372-77.
30. Mattsson C, Olsson T. Estrogens and glucocorticoid hormones in adipose tissue metabolism. *Curr Med Chem* 2007; 14: 2918-24.
31. Pedersen SB, Bruun JM, Hube F, Kristensen K, Hauner H, Richelsen B. Demonstration of estrogen receptor subtypes alpha and beta in human adipose tissue: influences of adipose cell differentiation and fat depot localization. *Mol Cell Endocrinol* 2001; 182: 27-37.
32. Sacks FM, Walsh BW. Sex hormones and lipoprotein metabolism. *Curr Opin Lipidol* 1994; 5: 236-40.
33. Granfone A, Campos H, McNamara JR, et al. Effects of estrogen replacement on plasma lipoproteins and apolipoproteins in postmenopausal, dyslipidemic women. *Metabolism* 1992; 41: 1193-98.
34. Tikkanen MJ, Nikkila EA, Vartiainen E. Natural oestrogen as an effective treatment for type-II hyperlipoproteinaemia in postmenopausal women. *Lancet* 1978; 2: 490-91.
35. Tikkanen MJ, Nikkilä EA, Kuusi T, Sipinen SU. High density lipoprotein-2 and hepatic lipase: reciprocal changes produced by estrogen and norgestrel. *J Clin Endocrinol Metab* 1982; 54: 1113-17.
36. Greenlund KJ, Webber LS, Srinivasan S, Wattigney W, Johnson C, Berenson GS. Associations of oral contraceptive use with serum lipids and lipoproteins in young women: the Bogalusa Heart Study. *Ann Epidemiol* 1997; 7: 561-67.
37. Ordovas JM. Gender, a significant factor in the cross talk between genes, environment, and health. *Gend Med*. 2007; 4 (Suppl)B: S111-22.
38. Ordovas JM, Corella D. Nutritional genomics. *Annu Rev Genomics Hum Genet* 2004; 5:71-118.
39. Corella D, Tucker K, Lahoz C, et al. Alcohol drinking determines the effect of the APOE locus on LDL-cholesterol concentrations in men: the Framingham Offspring Study. *Am J Clin Nutr* 2001; 73:736-45.
40. Ordovas Pedro-Botet J, Schaefer EJ, Bakker-Arkema RG, et al. Apolipoprotein E genotype affects plasma lipid response to atorvastatin in a gender specific manner. *Atherosclerosis* 2001; 158: 183-93.
41. Tsuda M, Sanada M, Nakagawa H, Kodama I, Sakashita T, Ohama K. Phenotype of apolipoprotein E influences the lipid metabolic response of postmenopausal women to hormone replacement therapy. *Maturitas* 2001; 38: 297-304.
42. Talmud PJ, Humphries SE. Apolipoprotein C-III gene variation and dyslipidaemia. *Curr Opin Lipidol* 1997; 8: 154-8.
43. Russo GT, Meigs JB, Cupples LA, et al. Association of the Sst-I polymorphism at the APOC3 gene locus with variations in lipid levels, lipoprotein subclass profiles and coronary heart disease risk: the Framingham offspring study. *Atherosclerosis* 2001; 158: 173-81.
44. Heller DA, de Faire U, Pedersen NL, Dahlen G, McClearn GE. Genetic and environmental influences on serum lipid levels in twins. *N Engl J Med* 1993; 328: 1150-6.
45. Boekholdt SM, Sacks FM, Jukema JW, et al. Cholesteryl ester transfer protein TaqIB variant, high-density lipoprotein cholesterol levels, cardiovascular risk, and efficacy of pravastatin treatment: individual patient meta-analysis of 13,677 subjects. *Circulation* 2005; 111: 278-87.
46. Brousseau ME, O'Connor Jr JJ, Ordovas JM, et al. Cholesteryl ester transfer protein TaqI B2B2 genotype is associated with higher HDL cholesterol levels and lower risk of coronary heart disease end points in men with

- HDL deficiency: Veterans Affairs HDL Cholesterol Intervention Trial. *Arterioscler Thromb Vasc Biol* 2002; 22: 1148-54.
47. Ordoas JM, Cupples LA, Corella D, et al. Association of cholesteryl ester transfer protein-TaqlB polymorphism with variations in lipoprotein subclasses and coronary heart disease risk: the Framingham study. *Arterioscler Thromb Vasc Biol* 2000; 20: 1323-9.
  48. Russo GT, Horvath KV, Di Benedetto A, Giandalia A, Cucinotta D, Asztalos B. Influence of menopause and cholesteryl ester transfer protein (CETP) TaqlB polymorphism on lipid profile and HDL subpopulations distribution in women with and without type 2 diabetes. *Atherosclerosis* 2010; 210: 294-301.
  49. Huxley R, Barzi F, Woodward. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. *MBMJ* 2006; 332: 73-8.
  50. Huxley RR, Peters SA, Mishra GD, Woodward M. Risk of all-cause mortality and vascular events in women versus men with type 1 diabetes: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol* 2015; 3:198-206.
  51. Rivelles AA, Riccardi G, Vaccaro O. Cardiovascular risk in women with diabetes. *Nutr Metab Cardiovasc Dis* 2010; 20(6):474-80.
  52. Kautzky-Willer A, Stich K, Hintersteiner J, et al. Sex-specific-differences in cardiometabolic risk in type 1 diabetes: a cross-sectional study. *Cardiovasc Diabetol* 2013; 12: 78.
  53. Russo GT, Baggio G, Rossi MC, Kautzky-Willer A. Type 2 diabetes and cardiovascular risk in women. *Int J Endocrinol* 2015; 2015: 832484.
  54. Walden CE, Knopp RH, Wahl P, Beach KW, Strandness E Jr. Sex differences in the effect of diabetes mellitus on lipoprotein triglyceride and cholesterol concentrations. *N Engl J Med* 1984; 311: 953-59.
  55. Assmann G, Schulte H, von Eckardstein A, Huang Y. High-density lipoprotein cholesterol as a predictor of coronary heart disease risk. The PROCAM experience and pathophysiological implications for reverse cholesterol transport. *Atherosclerosis* 1996; 124 (Suppl): S11-20.
  56. Gordon T, Castelli WP, Hjortland MC, Kannel WB, Dawber TR. High density lipoprotein as a protective factor against coronary heart disease. The Framingham Study. *Am J Med* 1977; 62: 707-14.
  57. Cheung MC, Brown BG, Wolf AC, Albers JJ. Altered particle size distribution of apolipoprotein A-I-containing lipoproteins in subjects with coronary artery disease. *J Lipid Res* 1991; 32: 383-94.
  58. Asztalos BF, Cupples LA, Demissie S, et al. High-density lipoprotein subpopulation profile and coronary heart disease prevalence in male participants of the Framingham Offspring Study. *Arterioscler Thromb Vasc Biol* 2004; 24: 2181-7.
  59. Norata GD, Pirillo A, Ammirati E, Catapano AL. Emerging role of high density lipoproteins as a player in the immune system. *Atherosclerosis* 2012; 220: 11-21.
  60. Russo GT, Giandalia A, Romeo EL, et al. Markers of Systemic Inflammation and Apo-AI Containing HDL Subpopulations in Women with and without Diabetes. *Int J Endocrinol* 2014;2014:607924.
  61. Turner RC, Millns H, Neil HA, et al. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS: 23). *BMJ* 1998; 7134: 823-8.
  62. Rossi MC, Cristofaro MR, Gentile S, et al.; AMD Annals Study Group. Sex disparities in the quality of diabetes care: biological and cultural factors may play a different role for different outcomes: a cross-sectional observational study from the AMD Annals initiative. *Diabetes Care* 2013; 36:3162-8.
  63. L. Franzini, D. Ardigò, F. Cavalot, et al. Women show worse control of type 2 diabetes and cardiovascular disease risk factors than men: results from the MIND.IT Study Group of the Italian Society of Diabetology. *Nutr Metab Cardiovasc Dis* 2013; 23(3): 235-41.
  64. Penno G, Solini A, Bonora E, et al; Renal Insufficiency And Cardiovascular Events (RIACE) study, group. Gender differences in cardiovascular disease risk factors, treatments and complications in patients with type 2 diabetes: the RIACE Italian multicentre study. *J Intern Med* 2013; 2: 176-91.
  65. Russo G, Pintauro B, Giorda C, et al. Age- and gender-related differences in LDL-cholesterol management in outpatients with type 2 diabetes mellitus. *Int J Endocrinol* 2015; 2015: 957105.
  66. La Rosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. *JAMA* 1999; 282: 2340-6.
  67. Bass KM, Newschaffer CJ, Klag MJ, Bush TL. Plasma lipoprotein levels as predictors of cardiovascular death in women. *Arch Intern Med* 1993; 153: 2209-16.
  68. Kamigaki AS, Siscovick DS, Schwartz SM, et al. Low density lipoprotein particle size and risk of early-onset myocardial infarction in women. *Am J Epidemiol* 2001; 153: 939-45.
  69. Mykkaenen L, Kuusisto J, Haffner SM, Laakso M, Austin MA. LDL size and risk of coronary heart disease in elderly men and women. *Arterioscler Thromb Vasc Biol* 1999; 19: 2742-8.
  70. Russo GT, Giandalia A, Romeo EL, et al. Lipid and non-lipid cardiovascular risk factors in postmenopausal type 2 diabetic women with and without coronary heart disease. *J Endocrinol Invest* 2014; 37: 261-8.
  71. Mosca L, Benjamin EJ, Berra K, et al. American Heart Association. Effectiveness-based guidelines for the prevention of cardiovascular disease in women--2011 update: a guideline from the American Heart Association. *J Am Coll Cardiol* 2011; 57:1404-23.

Correspondence to:

Giuseppina T Russo, MD, Ph.D.

Department of Clinical and Experimental Medicine

University of Messina, Messina, Italy

Tel +39 090 2217172

Fax +39 090 2921554

email Giuseppina.russo@unime.it