Sex Differences in Lipid and Lipoprotein Metabolism: It's Not Just about Sex Hormones

Xuewen Wang, Faidon Magkos, and Bettina Mittendorfer

Center for Human Nutrition (X.W., B.M.), Washington University School of Medicine, St. Louis, Missouri 63110; Division of Endocrinology, Diabetes, and Metabolism (F.M.), Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts 02215; and Department of Nutrition and Dietetics (F.M.), Harokopio University, Athens 17671, Greece

It is commonly thought that sex hormones are important regulators of plasma lipid kinetics and are responsible for sexual dimorphism in the plasma lipid profile. Here we discuss the findings from studies evaluating lipid and lipoprotein kinetics in men and women in the context of what we know about the effects of exogenous sex hormone administration, and we conclude that it is more complicated than that. It has become clear that normal physiological alterations in the hormonal milieu (*i.e.* due to menopause or throughout the menstrual cycle) do not significantly affect plasma lipid homeostasis. Furthermore, parenterally administered estrogens have either no effect or only very small beneficial effects, whereas orally administered estrogens raise plasma triglyceride concentrations—a phenomenon that is not consistent with the observed sex differences and likely results from the hepatic "first-pass effect." The effects of progestogens and androgens mimic only in part the differences in plasma lipids between men and women. Thus, the underlying physiological modulators of plasma lipid metabolism responsible for the differences between men and women remain to be elucidated. **(*J Clin Endocrinol Metab* 96: 885–893, 2011)**

Premenopausal women have a less proatherogenic plasma lipid profile than men. Specifically, they have greater high-density lipoprotein (HDL) cholesterol concentration and lower low-density lipoprotein (LDL) cholesterol, very low-density lipoprotein (VLDL) cholesterol, total plasma triglyceride, and VLDL triglyceride concentrations (both during fasted and fed conditions) than age-matched men (1–8). Furthermore, both the concentration and average size of circulating VLDL are smaller (due to lower concentrations of large and medium VLDL) (9–15), whereas the concentration of LDL is smaller but the average size of LDL is larger (due to a shift toward large at the expense of small LDL) (9–15) in women than in men. The concentration of circulating HDL is not different in men and women, but women have larger HDL particles than men (due to a shift toward large and cholesterol-rich HDL) (10–12, 16, 17). These differences in plasma lipid concentrations and lipoprotein particle concentrations, subclass distributions, and sizes likely account for at least part of the cardioprotective effect of female sex (9, 10).

Sex Differences in Lipid Metabolism and Lipoprotein Kinetics

The kinetic mechanisms underlying the differences in the plasma lipid profile between men and premenopausal women have only partially been elucidated and are schematically summarized in Table 1. Curiously, the lower concentrations of VLDL triglyceride and LDL particles in plasma in women than in men are associated with accelerated (rather than reduced) VLDL triglyceride and LDL production; enhanced plasma VLDL triglyceride and LDL particle clearance compensates for this and actually results in overall lower steady-state concentrations (18–22). In contrast, the secretion rate of VLDL apolipoprotein B-100 (VLDL particles) is lower in women than in men. Consequently, women produce fewer but (on average) triglyc-

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2010-2061 Received September 1, 2010. Accepted December 20, 2010.

Abbreviations: HDL, High-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; PCOS, polycystic ovary syndrome; VLDL, very low-density lipoprotein.

TABLE 1. Phenotypic differences in lipid and lipoprotein metabolism among premenopausal and postmenopausal women and men

	Sex differences		Effect of menopause in postmenopausal *vs.* premenopausal women
	Premenopausal women *vs.* men	Postmenopausal women *vs.* men	
Estradiol	↑ ↑	↔	↓ ↓
Progesterone	↑	↔	↓
Testosterone	↓ ↓	↓ ↓	↔
Total and VLDL triglyceride concentrations	↓ ↓	↓	↔
VLDL triglyceride production	↑	↔	↑
VLDL triglyceride removal	↑ ↑	↑	↑
VLDL apolipoprotein B-100 production	↓	↓	↔
VLDL apolipoprotein B-100 removal	↔	↔	↔
HDL cholesterol concentration	↑	↑	↔
HDL apolipoprotein A-I production	↑	↔	↔
HDL apolipoprotein A-I removal	↔	↓	↔
HDL apolipoprotein A-II production	↑	↔	↔
HDL apolipoprotein A-II removal	↑	↔	↔
LDL cholesterol concentration	↓	↔	↑
LDL apolipoprotein B-100 production	↑	↔	↔
LDL apolipoprotein B-100 removal	↑ ↑	↔	↓

↑, Greater, ↓, less; ↔, no difference. *Double arrows* indicate more pronounced effects than *single arrows*.

eride-richer VLDL than men (19). The larger average size of nascent VLDL particles likely facilitates the removal of VLDL triglyceride from the circulation by enhancing their susceptibility to hydrolysis by lipoprotein lipase (23). The sex difference in HDL concentration is associated with a greater HDL apolipoprotein A-I synthesis rate (without differences in removal rate) in women than in men and both greater HDL apolipoprotein A-II synthesis and plasma clearance rates (17). There is no information regarding possible sex differences in cholesterol kinetics in the various lipoprotein fractions in human subjects. However, animal studies support an important role of endogenous sex hormones in mediating cholesterol metabolism in a sexually dimorphic manner (24).

The Case for Sex Hormones and Possible Confounders

The factors mediating the sex-specific regulation of plasma lipid kinetics and concentrations are not clear. It is thought that it is largely the influence of sex steroids that mediates sex differences in plasma lipid homeostasis—a concept that gains support from the fact that loss of ovarian function after menopause as well as hyperandrogenemia in women with polycystic ovary syndrome (PCOS) appears to increase plasma triglyceride and LDL cholesterol and decrease HDL cholesterol concentrations (1, 10, 25–27) and delay postprandial chylomicron clearance from plasma (28–30). However, these data are difficult to interpret because of potential confounding due to concomitant changes in total body fat, body fat distribution, and insulin sensitivity that accompany menopause (31), as well as PCOS (27). Healthy women tend to gain total body and intraabdominal fat and become more insulin resistant after menopause (31), and women with PCOS are typically overweight or obese (especially abdominally obese) and insulin resistant (27), and this alone could be responsible for the changes in lipid homeostasis because increased whole-body adiposity and central fat accumulation and decreased insulin sensitivity are associated with increased plasma triglyceride and LDL cholesterol and decreased HDL cholesterol concentrations (32). In fact, the results from several prospective (33–36) and cross-sectional (36–38) studies that were published during the last couple of years indicate that what has traditionally been thought to be menopause-associated dyslipidemia is, for the most part, due to chronological aging rather than the loss of ovarian function. Perhaps the only exception is a modest increase in total and LDL cholesterol and LDL apolipoprotein B-100 concentrations [due to a decrease in the LDL apolipoprotein B-100 fractional catabolic rate (30)], which seems to be specific to the menopausal transition, independent of aging or changes in body fat mass and distribution (33–36, 39). These results confirm the findings from some earlier but smaller longitudinal and cross-sectional studies (16, 30, 39–44) and are also consistent with the observation that surgically induced menopause without hormone replacement therapy has, aside from some modest transient changes, no effect on plasma lipid concentrations and lipoprotein profile when compared with a surgical control group (hysterectomy with conservation of the ovaries) (36, 42, 45). Nevertheless, we

have recently found that VLDL triglyceride turnover (both hepatic VLDL triglyceride secretion and plasma VLDL triglyceride clearance) is faster in postmenopausal compared with well-matched premenopausal women despite similar plasma triglyceride and VLDL triglyceride concentrations in the two groups (46). The exact reasons for this phenomenon are unclear but are likely related to differences in hepatic fatty acid handling and changes in the architecture of nascent VLDL particles that favor more efficient removal (46), which may be further augmented by the increase in adipose tissue lipoprotein lipase activity after menopause (47). However, whether these differences are a direct consequence of the loss of ovarian function is unknown. Likewise, subjects with PCOS who are lean and normoinsulinemic (although these are rare) have a similar plasma lipid profile as healthy, age- and adiposity-matched women (48–51). Furthermore, most studies report little if any variation in plasma lipid and lipoprotein concentrations across the menstrual cycle in women (52–54), and those that do, in fact, report only small (by 5–6%) reductions in LDL cholesterol concentration during the luteal phase (52, 53) but no changes in plasma triglyceride or HDL cholesterol concentrations. Normal physiological alterations in the hormonal milieu therefore do not appear to significantly affect plasma lipid homeostasis. On the other hand, studies that evaluated sex steroid hormone action by administering them in the form of hormone replacement or supplementation therapy indicate that they do affect plasma lipid metabolism but not necessarily in ways that can help us understand the mechanisms responsible for the differences in lipoprotein kinetics and metabolism between men and women.

Insights from Exogenous Sex Hormone Administration

The majority of available data regarding the effect of sex steroid administration on plasma lipid homeostasis come from studies evaluating the effects of hormone replacement therapy in postmenopausal (both natural and surgically induced) women and the effects of oral contraceptive use in healthy premenopausal women and women with PCOS and have been reviewed in detail (55–57). These are schematically summarized in Table 2, along with the results from studies evaluating changes in lipid and lipoprotein kinetics. Estrogens do not appear to reproduce the beneficial effects on the plasma lipid profile one might expect from the differences in plasma lipid concentrations between men and women. Briefly, oral estrogen preparations given to postmenopausal women (55), premenopausal women (56), women with PCOS (57), as well as men with prostatic carcinoma (58), and male-to-female transsexuals (not on antiandrogen therapy) (59) increase total plasma and VLDL triglyceride concentrations, increase HDL cholesterol concentration, and reduce total and LDL cholesterol concentrations. Although these effects are somewhat dose-dependent, it is unlikely that they are solely due to supraphysiological availability of estrogens in these studies; although in premenopausal women and men sex steroids were given in addition to their normal physiological availability (56–59), the doses used in postmenopausal women were considered replacement doses (55). The hypertriglyceridemic effect of oral estrogen preparations (55–59) is largely due to increased hepatic secretion of large, triglyceride-rich VLDL particles (60) and therefore associated with both increased hepatic VLDL apolipoprotein B-100 and VLDL triglyceride secretion rates (61–65). Although the production of small VLDL particles is also increased (mainly from large VLDL rather than direct hepatic secretion), this is counterbalanced by equivalent increases in the direct removal rate and the conversion to intermediate-density lipoproteins (IDLs) (60). Overall VLDL triglyceride and VLDL particle clearance rates are not affected by oral estrogen (61–65) because of accelerated conversion of large to small VLDL particles with a simultaneous slowing of the direct conversion of large VLDL to IDL (60). The rise in plasma HDL cholesterol concentration in response to oral estrogen treatment (55–59) is predominantly due to an increase in the cholesterol content in the large, cholesterol-rich HDL_2 subfraction, likely attributed to augmented production rates of HDL apolipoprotein A-I (with little if any changes in HDL apolipoprotein A-II kinetics) combined with no changes or mild increases in HDL apolipoprotein A-I removal rates (62, 66–68), although a few studies have reported increases in HDL apolipoprotein A-I production rate coupled with reductions in clearance (69, 70). The decrease in plasma LDL cholesterol concentration in response to oral estrogen treatment (55–59) is associated with an increase in the LDL apolipoprotein B-100 fractional catabolic rate in large LDL particles that overcomes a smaller increase in LDL apolipoprotein B-100 production rate (the production of small LDL particles is also increased, but this is counterbalanced by equivalent increases in removal rates) (58, 60, 64, 71) that occurs as a result of increased rate of IDL-to-LDL conversion rather than from direct hepatic LDL production (60). Reduced dietary cholesterol absorption may also contribute to the hypocholesterolemic effect of estrogen (71). Although this effect of estrogen therapy is comparatively small, it has been observed after not only oral but also transdermal administration (71) and may therefore account for the modest increases in LDL cholesterol after menopause (33–36, 39) and during the follicular phase of the menstrual

TABLE 2. Effects of exogenous sex hormones on lipid and lipoprotein metabolism

	Estrogens		Progestogens	Androgens (oral and parenteral)			
				Aromatizable		Nonaromatizable	
	Oral	Parenteral	Oral and parenteral	Men	Women	Men	Women
Total and VLDL triglyceride concentrations	↑ ↑	↔ or ↓	↓	↔	↔/↑[a]	↔	↔
VLDL triglyceride production	↑ ↑	?	↔	?	↑ ↑	?	?
VLDL triglyceride removal	↔	?	↑	?	↑	?	?
VLDL apolipoprotein B-100 production	↑ ↑	↔	↔	↔	?	?	?
VLDL apolipoprotein B-100 removal	↔	↔	↑	↔	?	?	?
HDL cholesterol concentration	↑ ↑	↔ or ↑	↓	↓	↓	↓ ↓	↓ ↓
HDL apolipoprotein A-I production	↑ ↑	↔	↓ ↓	↓	↓	↓ ↓	↓ ↓
HDL apolipoprotein A-I removal	↔	↔	↓	↑	↑	↑ ↑	↑ ↑
HDL apolipoprotein A-II production	↔	?	?	?	?	?	?
HDL apolipoprotein A-II removal	↔	?	?	?	?	?	?
LDL cholesterol concentration	↓ ↓	↔ or ↓	↔ or ↓	↔	↔	↔ or ↑	↔ or ↑
LDL apolipoprotein B-100 production	↑	↔	↔ or ↑	?	?	?	?
LDL apolipoprotein B-100 removal	↑ ↑	↔	↔ or ↑	?	?	?	?

↑, Increase; ↓, decrease; ↔, no effect; ?, unknown. *Double arrows* indicate more pronounced effects than *single arrows*.

[a] Oral preparations increase, whereas parenteral preparations do not increase plasma triglyceride concentrations in women (see text).

cycle (52, 53) when endogenous estrogen availability is low.

Transdermal administration of 17β-estradiol, which better mimics normal endogenous estrogen delivery, has little or no effect on HDL cholesterol concentration (0–5% increase), only modestly decreases (by $<$ 10%) LDL cholesterol concentration, and does not affect or only modestly decreases (by $<$ 10%) plasma triglyceride concentration in premenopausal (56) and postmenopausal women (55), women with PCOS (57), as well as healthy men (72) and men with prostate cancer (73–75). Similarly, transdermal administration of estradiol, in contrast to oral administration, does not alter plasma VLDL triglyceride and VLDL apolipoprotein B-100 (64), HDL apolipoprotein A-I (67), and LDL apolipoprotein B-100 (64, 71) concentrations and kinetics. The amounts of estradiol administered in these studies ranged from supraphysiological [*e.g.* plasma estradiol concentration increased to more than 1000 pmol/liter (73, 74)] to doses that resulted in plasma estradiol concentrations that fall within the range of those in healthy premenopausal women during the normal menstrual cycle (76, 77) [*e.g.* $<$500 pmol/liter (64, 67, 71)]. It is therefore unlikely that estrogens play a major role in regulating plasma lipid kinetics under normal physiological conditions.

Progestogens (given alone or in combination with estrogens) reduce plasma triglyceride concentration but also decrease plasma HDL cholesterol concentration, irrespective of the route of delivery, dose, and administration pattern (cyclic or continuous), in both premenopausal and postmenopausal women (55, 56, 61, 78–86) but appear to have little effect on plasma LDL cholesterol and LDL apolipoprotein B-100 concentrations, although they increase both the production and the removal rates of LDL apolipoprotein B-100 but do not affect the net balance (82, 86). The hypotriglyceridemic effect of progestogens is mediated by enhanced VLDL triglyceride and VLDL apolipoprotein B-100 plasma clearance rates (61, 78), whereas the HDL cholesterol-lowering effect is possibly associated with decreased production of HDL apolipoprotein A-I, which overcomes a simultaneous reduction in clearance (66). Nevertheless, normal physiological fluctuations of progesterone secretion throughout the menstrual cycle do not affect plasma triglyceride and VLDL

triglyceride and VLDL apolipoprotein B-100 concentrations and kinetics (54); there are no studies of LDL and HDL kinetics during the menstrual cycle.

In contrast to the vast amount of information regarding the effect of female sex hormones on lipid metabolism, there are only limited data available with regard to androgens. Evidence so far indicates that androgen receptor activation is most likely responsible for at least part of the sex differences in HDL cholesterol concentration. Testosterone (given orally, transdermally, or im) (87–92) and both aromatizable (*e.g.* androstenediol and androstenedione, given orally) (93–95) and nonaromatizable (*e.g.* stanozolol, given orally) (88, 96–98) androgen derivatives reduce (in a dose-dependent manner) HDL cholesterol and apolipoprotein A-I concentrations [due to a combination of both reduced HDL apolipoprotein A-I production rate and increased fractional catabolic rate (96)] in both men and women (premenopausal and postmenopausal). Stanozolol-induced reductions in HDL cholesterol and apolipoprotein A-I concentrations (30–50%) are considerably greater than those induced by testosterone (8–20%) and aromatizable androgens (5–12%), suggesting that aromatization blunts the unfavorable effects of androgens on HDL metabolism (90). On the other hand, testosterone administration is associated with only modest (<5%) reductions in LDL cholesterol concentration when given to hypogonadal men in replacement doses (90, 91); has no effect on LDL cholesterol concentration in eugonadal men (regardless of dose) (90) and previously untreated female-to-male transsexuals receiving moderate to high doses (87, 89); and may increase LDL cholesterol concentration in peri- and postmenopausal women when given orally but not transdermally (92). Therefore, androgen action is most likely not responsible for the sex differences in plasma LDL cholesterol concentration.

The effects of androgen receptor agonists on plasma triglyceride concentration and metabolism are not entirely clear but may be sex-specific. In healthy young and elderly men, administration of neither testosterone (73, 88, 99–101) nor aromatizable androgen derivatives (95) affects plasma triglyceride concentrations [or VLDL triglyceride concentration and VLDL apolipoprotein B-100 concentration and kinetics (101)], irrespective of the route of delivery (whether oral, transdermal, or im), dose (100), and treatment duration (102). It is possible, but unlikely, that the lack of effect is due to testosterone in these studies being available in excess of needs because testosterone therapy has also no effect on plasma triglyceride concentrations in hypogonadal men (89, 91, 102, 103). In women, aromatizable androgens or testosterone given orally raises plasma triglyceride concentrations (92, 104) due to a robust increase in hepatic triglyceride secretion, which overcomes a simultaneous but less intense increase in plasma triglyceride clearance (104), whereas nonaromatizable androgens given orally or testosterone applied transdermally has no effect on plasma triglyceride concentrations (92, 97). Gains in body weight with androgen treatment were small and similar between studies (<5%) (97, 104) and thus not likely to explain the different outcomes. Hence, although the oral route of administration may be responsible for much of the hypertriglyceridemic effect of androgens in women, these observations suggest that aromatization is also likely to be involved in the apparent sex-specific effect of androgens (hypertriglyceridemia in women not in men), because aromatization takes place predominantly in adipose tissue and women have typically more body fat than men. These results may also provide a possible mechanism responsible for the hypertriglyceridemia in obese women with PCOS, who have more efficient peripheral aromatization of androgens to estrogens (105).

Summary and Conclusions

Understanding sex differences in lipid metabolism and the factors involved in the regulation of lipid kinetics and the plasma lipid profile, a major risk factor for cardiovascular disease, is important because there are significant differences in the ways men and women experience cardiovascular disease. Clearly, the traditional view that the female "advantage" (*i.e.* the cardioprotective lipid profile in premenopausal women) is due to differences in the sex hormone milieu—in particular, the availability of estrogens and androgens (106, 107)— between men and women and premenopausal and postmenopausal women is not entirely supported by the results from studies examining the effects of normal physiological alterations in the hormonal milieu (*i.e.* due to menopause or throughout the menstrual cycle) and those evaluating the effects of exogenous sex steroid administration on plasma lipid kinetics and concentrations (Tables 1 and 2). Parenterally administered estrogens have either no effect or only very small beneficial effects, whereas orally administered estrogens raise plasma triglyceride concentrations, a phenomenon that is not consistent with the observed sex differences and likely results from the hepatic "first-pass effect." Similarly, the effects of progestogens and androgens mimic only in part the differences in plasma lipids between men and women and, at least in the case of androgens, may depend on the sex of the subject. The lack, in many cases, of randomized, placebo-controlled, dose-response studies and the obvious difficulties in reproducing differences between men and women in sex hormonal milieu experimentally (*e.g.* the normal fluctuations of estradiol and progesterone dur-

ing the menstrual cycle or the circadian rhythm of testosterone) limits interpretation of the available data.

Sexual dimorphism in lipid metabolism therefore seems to be the result of a complex network of hormone action in combination with other, possibly sex-specific, direct or indirect modulators of lipid metabolism. The exact nature of these factors is unclear, but there are seemingly many [*e.g.* insulin and adipokines (107), gene expression and imprinting (108), *etc.*] that need to be explored in the future. An obvious candidate would be differences in insulin action between men and women. Insulin is an important regulator of lipid metabolism, and there are differences between the sexes in insulin sensitivity of glucose metabolism in the liver and muscle (109); however, little is known regarding possible sex differences in the regulation of lipid metabolism by insulin (109). It is unlikely that differences in body composition between men and women (110–115), even if these may be causally related to lipid metabolism [*e.g.* by affecting fatty acid availability for VLDL triglyceride synthesis (116–118)], are responsible for this phenomenon because sex differences in the plasma lipid profile persist even when men and women are matched for percentage of body fat (9). Nevertheless, accumulation of excess body fat appears to affect lipid kinetics differently in men and women (2, 119). The underlying physiological modulators of plasma lipid metabolism responsible for the differences between men and women remain to be elucidated.

Acknowledgments

Address all correspondence and requests for reprints to: Bettina Mittendorfer, Ph.D., Washington University School of Medicine, Division of Geriatrics, Nutritional Science, 660 South Euclid Avenue, Campus Box 8031, St. Louis, Missouri 63110. E-mail: mittendb@wustl.edu.

This publication was made possible by National Institutes of Health Grants AG 031297, HD 057796, DK 56341 (Nutrition and Obesity Research Unit), and UL1 RR024992 (Washington University School of Medicine Clinical Translational Science Award).

Disclosure Summary: The authors have nothing to disclose.

References

1. **Abbott RD, Garrison RJ, Wilson PW, Epstein FH, Castelli WP, Feinleib M, LaRue C** 1983 Joint distribution of lipoprotein cholesterol classes. The Framingham study. Arteriosclerosis 3:260–272
2. **Magkos F, Mittendorfer B** 2009 Gender differences in lipid metabolism and the effect of obesity. Obstet Gynecol Clin North Am 36:245–265, vii
3. **Cohn JS, McNamara JR, Cohn SD, Ordovas JM, Schaefer EJ** 1988 Postprandial plasma lipoprotein changes in human subjects of different ages. J Lipid Res 29:469–479
4. **Couillard C, Bergeron N, Prud'homme D, Bergeron J, Tremblay A, Bouchard C, Mauriège P, Després JP** 1999 Gender difference in postprandial lipemia: importance of visceral adipose tissue accumulation. Arterioscler Thromb Vasc Biol 19:2448–2455
5. **Georgopoulos A, Rosengard AM** 1989 Abnormalities in the metabolism of postprandial and fasting triglyceride-rich lipoprotein subfractions in normal and insulin-dependent diabetic subjects: effects of sex. Metabolism 38:781–789
6. **Horton TJ, Commerford SR, Pagliassotti MJ, Bessesen DH** 2002 Postprandial leg uptake of triglyceride is greater in women than in men. Am J Physiol Endocrinol Metab 283:E1192–E1202
7. **Jensen MD** 1995 Gender differences in regional fatty acid metabolism before and after meal ingestion. J Clin Invest 96:2297–2303
8. **Nguyen TT, Hernández Mijares A, Johnson CM, Jensen MD** 1996 Postprandial leg and splanchnic fatty acid metabolism in nonobese men and women. Am J Physiol 271:E965–E972
9. **Magkos F, Mohammed BS, Mittendorfer B** 2008 Effect of obesity on the plasma lipoprotein subclass profile in normoglycemic and normolipidemic men and women. Int J Obes (Lond) 32:1655–1664
10. **Freedman DS, Otvos JD, Jeyarajah EJ, Shalaurova I, Cupples LA, Parise H, D'Agostino RB, Wilson PW, Schaefer EJ** 2004 Sex and age differences in lipoprotein subclasses measured by nuclear magnetic resonance spectroscopy: the Framingham Study. Clin Chem 50:1189–1200
11. **Johnson JL, Slentz CA, Duscha BD, Samsa GP, McCartney JS, Houmard JA, Kraus WE** 2004 Gender and racial differences in lipoprotein subclass distributions: the STRRIDE study. Atherosclerosis 176:371–377
12. **Vaidya D, Dobs A, Gapstur SM, Golden SH, Hankinson A, Liu K, Ouyang P** 2008 The association of endogenous sex hormones with lipoprotein subfraction profile in the Multi-Ethnic Study of Atherosclerosis. Metabolism 57:782–790
13. **Zuniæ G, Jeliæ-Ivanoviæ Z, Spasiæ S, Stojiljkoviæ A, Majkiæ-Singh N** 1992 Reference values for apolipoproteins A-I and B in healthy subjects, by age. Clin Chem 38:566–569
14. **Leino A, Impivaara O, Kaitsaari M, Järvisalo J** 1995 Serum concentrations of apolipoprotein A-I, apolipoprotein B, and lipoprotein(a) in a population sample. Clin Chem 41:1633–1636
15. **Contois JH, McNamara JR, Lammi-Keefe CJ, Wilson PW, Massov T, Schaefer EJ** 1996 Reference intervals for plasma apolipoprotein B determined with a standardized commercial immunoturbidimetric assay: results from the Framingham Offspring Study. Clin Chem 42:515–523
16. **Velez-Carrasco W, Lichtenstein AH, Li Z, Dolnikowski GG, Lamon-Fava S, Welty FK, Schaefer EJ** 2000 Apolipoprotein A-I and A-II kinetic parameters as assessed by endogenous labeling with [(2)H(3)]leucine in middle-aged and elderly men and women. Arterioscler Thromb Vasc Biol 20:801–806
17. **Schaefer EJ, Zech LA, Jenkins LL, Bronzert TJ, Rubalcaba EA, Lindgren FT, Aamodt RL, Brewer Jr HB** 1982 Human apolipoprotein A-I and A-II metabolism. J Lipid Res 23:850–862
18. **Matthan NR, Jalbert SM, Barrett PH, Dolnikowski GG, Schaefer EJ, Lichtenstein AH** 2008 Gender-specific differences in the kinetics of nonfasting TRL, IDL, and LDL apolipoprotein B-100 in men and premenopausal women. Arterioscler Thromb Vasc Biol 28:1838–1843
19. **Magkos F, Patterson BW, Mohammed BS, Klein S, Mittendorfer B** 2007 Women produce fewer but triglyceride-richer very low-density lipoproteins than men. J Clin Endocrinol Metab 92:1311–1318
20. **Nikkilä EA, Kekki M** 1971 Polymorphism of plasma triglyceride kinetics in normal human adult subjects. Acta Med Scand 190:49–59
21. **Olefsky J, Farquhar JW, Reaven GM** 1974 Sex difference in the kinetics of triglyceride metabolism in normal and hypertriglyceridaemic human subjects. Eur J Clin Invest 4:121–127

22. **Watts GF, Moroz P, Barrett PH** 2000 Kinetics of very-low-density lipoprotein apolipoprotein B-100 in normolipidemic subjects: pooled analysis of stable-isotope studies. Metabolism 49:1204–1210
23. **Karpe F, Bickerton AS, Hodson L, Fielding BA, Tan GD, Frayn KN** 2007 Removal of triacylglycerols from chylomicrons and VLDL by capillary beds: the basis of lipoprotein remnant formation. Biochem Soc Trans 35:472–476
24. **Hewitt KN, Boon WC, Murata Y, Jones ME, Simpson ER** 2003 The aromatase knockout mouse presents with a sexually dimorphic disruption to cholesterol homeostasis. Endocrinology 144:3895–3903
25. **Schubert CM, Rogers NL, Remsberg KE, Sun SS, Chumlea WC, Demerath EW, Czerwinski SA, Towne B, Siervogel RM** 2006 Lipids, lipoproteins, lifestyle, adiposity and fat-free mass during middle age: the Fels Longitudinal Study. Int J Obes Lond 30:251–260
26. **Trémollières FA, Pouilles JM, Cauneille C, Ribot C** 1999 Coronary heart disease risk factors and menopause: a study in 1684 French women. Atherosclerosis 142:415–423
27. **Wu FC, von Eckardstein A** 2003 Androgens and coronary artery disease. Endocr Rev 24:183–217
28. **van Beek AP, de Ruijter-Heijstek FC, Erkelens DW, de Bruin TW** 1999 Menopause is associated with reduced protection from postprandial lipemia. Arterioscler Thromb Vasc Biol 19:2737–2741
29. **Masding MG, Stears AJ, Burdge GC, Wootton SA, Sandeman DD** 2003 Premenopausal advantages in postprandial lipid metabolism are lost in women with type 2 diabetes. Diabetes Care 26:3243–3249
30. **Matthan NR, Jalbert SM, Lamon-Fava S, Dolnikowski GG, Welty FK, Barrett HR, Schaefer EJ, Lichtenstein AH** 2005 TRL, IDL, and LDL apolipoprotein B-100 and HDL apolipoprotein A-I kinetics as a function of age and menopausal status. Arterioscler Thromb Vasc Biol 25:1691–1696
31. **Milewicz A, Tworowska U, Demissie M** 2001 Menopausal obesity—myth or fact? Climacteric 4:273–283
32. **Ferrannini E, Balkau B, Coppack SW, Dekker JM, Mari A, Nolan J, Walker M, Natali A, Beck-Nielsen H** 2007 Insulin resistance, insulin response, and obesity as indicators of metabolic risk. J Clin Endocrinol Metab 92:2885–2892
33. **Matthews KA, Crawford SL, Chae CU, Everson-Rose SA, Sowers MF, Sternfeld B, Sutton-Tyrrell K** 2009 Are changes in cardiovascular disease risk factors in midlife women due to chronological aging or to the menopausal transition? J Am Coll Cardiol 54:2366–2373
34. **Derby CA, Crawford SL, Pasternak RC, Sowers M, Sternfeld B, Matthews KA** 2009 Lipid changes during the menopause transition in relation to age and weight: the Study of Women's Health Across the Nation. Am J Epidemiol 169:1352–1361
35. **Soriguer F, Morcillo S, Hernando V, Valdés S, Ruiz de Adana MS, Olveira G, Fuentes EG, González I, Tapia MJ, Esteva I, Rojo-Martínez G** 2009 Type 2 diabetes mellitus and other cardiovascular risk factors are no more common during menopause: longitudinal study. Menopause 16:817–821
36. **Verhoeven MO, van der Mooren MJ, Teerlink T, Verheijen RH, Scheffer PG, Kenemans P** 2009 The influence of physiological and surgical menopause on coronary heart disease risk markers. Menopause 16:37–49
37. **Muscelli E, Kozàkovà M, Flyvbjerg A, Kyriakopoulou K, Astiarraga BD, Glintborg D, Konrad T, Favuzzi A, Petrie J** 2009 The effect of menopause on carotid artery remodeling, insulin sensitivity, and plasma adiponectin in healthy women. Am J Hypertens 22:364–370
38. **Casiglia E, Tikhonoff V, Caffi S, Bascelli A, Schiavon L, Guidotti F, Saugo M, Giacomazzo M, Martini B, Mazza A, D'este D, Pessina AC** 2008 Menopause does not affect blood pressure and risk profile, and menopausal women do not become similar to men. J Hypertens 26:1983–1992
39. **Peters HW, Westendorp IC, Hak AE, Grobbee DE, Stehouwer CD, Hofman A, Witteman JC** 1999 Menopausal status and risk factors for cardiovascular disease. J Intern Med 246:521–528
40. **Ozbey N, Sencer E, Molvalilar S, Orhan Y** 2002 Body fat distribution and cardiovascular disease risk factors in pre- and postmenopausal obese women with similar BMI. Endocr J 49:503–509
41. **Casiglia E, d'Este D, Ginocchio G, Colangeli G, Onesto C, Tramontin P, Ambrosio GB, Pessina AC** 1996 Lack of influence of menopause on blood pressure and cardiovascular risk profile: a 16-year longitudinal study concerning a cohort of 568 women. J Hypertens 14:729–736
42. **Casiglia E, Ginocchio G, Tikhonoff V, D'Este D, Mazza A, Pizziol A, Pavei A, Ambrosio GB, Piccoli A, Pessina AC** 2000 Blood pressure and metabolic profile after surgical menopause: comparison with fertile and naturally-menopausal women. J Hum Hypertens 14:799–805
43. **Fukami K, Koike K, Hirota K, Yoshikawa H, Miyake A** 1995 Perimenopausal changes in serum lipids and lipoproteins: a 7-year longitudinal study. Maturitas 22:193–197
44. **De Oliveira e Silva ER, Kong M, Han Z, Starr C, Kass EM, Juo SH, Foster D, Dansky HM, Merkel M, Cundey K, Brinton EA, Breslow JL, Smith JD** 1999 Metabolic and genetic determinants of HDL metabolism and hepatic lipase activity in normolipidemic females. J Lipid Res 40:1211–1221
45. **Cheung LP, Pang MW, Lam CW, Tomlinson B, Chung TK, Haines CJ** 1998 Acute effects of a surgical menopause on serum concentrations of lipoprotein (a). Climacteric 1:33–41
46. **Magkos F, Fabbrini E, Mohammed BS, Patterson BW, Klein S, Mittendorfer B** 2010 Estrogen deficiency after menopause does not result in male very-low-density lipoprotein metabolism phenotype. J Clin Endocrinol Metab 95:3377–3384
47. **Ferrara CM, Lynch NA, Nicklas BJ, Ryan AS, Berman DM** 2002 Differences in adipose tissue metabolism between postmenopausal and perimenopausal women. J Clin Endocrinol Metab 87:4166–4170
48. **Legro RS, Kunselman AR, Dunaif A** 2001 Prevalence and predictors of dyslipidemia in women with polycystic ovary syndrome. Am J Med 111:607–613
49. **Oh JY, Lee JA, Lee H, Oh JY, Sung YA, Chung H** 2009 Serum C-reactive protein levels in normal-weight polycystic ovary syndrome. Korean J Intern Med 24:350–355
50. **Gen R, Akbay E, Muslu N, Sezer K, Cayan F** 2009 Plasma visfatin level in lean women with PCOS: relation to proinflammatory markers and insulin resistance. Gynecol Endocrinol 25:241–245
51. **Rocha MP, Maranhão RC, Seydell TM, Barcellos CR, Baracat EC, Hayashida SA, Bydlowski SP, Marcondes JA** 2010 Metabolism of triglyceride-rich lipoproteins and lipid transfer to high-density lipoprotein in young obese and normal-weight patients with polycystic ovary syndrome. Fertil Steril 93:1948–1956
52. **Mumford SL, Schisterman EF, Siega-Riz AM, Browne RW, Gaskins AJ, Trevisan M, Steiner AZ, Daniels JL, Zhang C, Perkins NJ, Wactawski-Wende J** 2010 A longitudinal study of serum lipoproteins in relation to endogenous reproductive hormones during the menstrual cycle: findings from the BioCycle study. J Clin Endocrinol Metab 95:E80–E85
53. **Barnett JB, Woods MN, Lamon-Fava S, Schaefer EJ, McNamara JR, Spiegelman D, Hertzmark E, Goldin B, Longcope C, Gorbach SL** 2004 Plasma lipid and lipoprotein levels during the follicular and luteal phases of the menstrual cycle. J Clin Endocrinol Metab 89:776–782
54. **Magkos F, Patterson BW, Mittendorfer B** 2006 No effect of menstrual cycle phase on basal very-low-density lipoprotein triglyceride and apolipoprotein B-100 kinetics. Am J Physiol Endocrinol Metab 291:E1243–E1249
55. **Godsland IF** 2001 Effects of postmenopausal hormone replacement therapy on lipid, lipoprotein, and apolipoprotein (a) concentrations: analysis of studies published from 1974–2000. Fertil Steril 75:898–915
56. **Crook D** 1998 Effects of estrogens and progestogens on plasma

lipids and lipoproteins. In: Fraser IS, Jansen RPS, Lobo RA, Whitehead MI, eds. Estrogens and progestogens in clinical practice. London: Harcourt Brace, Co. Ltd. (Churchill Livingstone); 787–798
57. **Soares GM, Vieira CS, de Paula Martins W, Dos Reis RM, de Sá MF, Ferriani RA** 2009 Metabolic and cardiovascular impact of oral contraceptives in polycystic ovary syndrome. Int J Clin Pract 63: 160–169
58. **Eriksson M, Berglund L, Rudling M, Henriksson P, Angelin B** 1989 Effects of estrogen on low density lipoprotein metabolism in males. Short-term and long-term studies during hormonal treatment of prostatic carcinoma. J Clin Invest 84:802–810
59. **New G, Timmins KL, Duffy SJ, Tran BT, O'Brien RC, Harper RW, Meredith IT** 1997 Long-term estrogen therapy improves vascular function in male to female transsexuals. J Am Coll Cardiol 29: 1437–1444
60. **Campos H, Walsh BW, Judge H, Sacks FM** 1997 Effect of estrogen on very low density lipoprotein and low density lipoprotein subclass metabolism in postmenopausal women. J Clin Endocrinol Metab 82:3955–3963
61. **Kissebah AH, Harrigan P, Wynn V** 1973 Mechanism of hypertriglyceridaemia associated with contraceptive steroids. Horm Metab Res 5:184–190
62. **Schaefer EJ, Foster DM, Zech LA, Lindgren FT, Brewer Jr HB, Levy RI** 1983 The effects of estrogen administration on plasma lipoprotein metabolism in premenopausal females. J Clin Endocrinol Metab 57:262–267
63. **Glueck CJ, Fallat RW, Scheel D** 1975 Effects of estrogenic compounds on triglyceride kinetics. Metabolism 24:537–545
64. **Walsh BW, Schiff I, Rosner B, Greenberg L, Ravnikar V, Sacks FM** 1991 Effects of postmenopausal estrogen replacement on the concentrations and metabolism of plasma lipoproteins. N Engl J Med 325:1196–1204
65. **Tikkanen MJ, Kuusi T, Nikkilä EA, Sane T** 1985 Very low density lipoprotein triglyceride kinetics during hepatic lipase suppression by estrogen. Studies on the physiological role of hepatic endothelial lipase. FEBS Lett 181:160–164
66. **Lamon-Fava S, Postfai B, Diffenderfer M, DeLuca C, O'Connor Jr J, Welty FK, Dolnikowski GG, Barrett PH, Schaefer EJ** 2006 Role of the estrogen and progestin in hormonal replacement therapy on apolipoprotein A-I kinetics in postmenopausal women. Arterioscler Thromb Vasc Biol 26:385–391
67. **Walsh BW, Li H, Sacks FM** 1994 Effects of postmenopausal hormone replacement with oral and transdermal estrogen on high density lipoprotein metabolism. J Lipid Res 35:2083–2093
68. **Brinton EA** 1996 Oral estrogen replacement therapy in postmenopausal women selectively raises levels and production rates of lipoprotein A-I and lowers hepatic lipase activity without lowering the fractional catabolic rate. Arterioscler Thromb Vasc Biol 16: 431–440
69. **Quintão EC, Nakandakare E, Oliveira HC, Rocha JC, Garcia RC, de Melo NR** 1991 Oral estradiol-17 β raises the level of plasma high-density lipoprotein in menopausal women by slowing down its clearance rate. Acta Endocrinol (Copenh) 125:657–661
70. **Hazzard WR, Haffner SM, Kushwaha RS, Applebaum-Bowden D, Foster DM** 1984 Preliminary report: kinetic studies on the modulation of high-density lipoprotein, apolipoprotein, and subfraction metabolism by sex steroids in a postmenopausal woman. Metabolism 33:779–784
71. **Karjalainen A, Heikkinen J, Savolainen MJ, Bäckström AC, Kesäniemi YA** 2000 Mechanisms regulating LDL metabolism in subjects on peroral and transdermal estrogen replacement therapy. Arterioscler Thromb Vasc Biol 20:1101–1106
72. **Lapauw B, Ouwens M, 't Hart LM, Wuyts B, Holst JJ, T'Sjoen G, Kaufman JM, Ruige JB** 2010 Sex steroids affect triglyceride handling, glucose-dependent insulinotropic polypeptide, and insulin sensitivity: a 1-week randomized clinical trial in healthy young men. Diabetes Care 33:1831–1833
73. **Berglund L, Carlström K, Stege R, Gottlieb C, Eriksson M, Angelin B, Henriksson P** 1996 Hormonal regulation of serum lipoprotein (a) levels: effects of parenteral administration of estrogen or testosterone in males. J Clin Endocrinol Metab 81:2633–2637
74. **Purnell JQ, Bland LB, Garzotto M, Lemmon D, Wersinger EM, Ryan CW, Brunzell JD, Beer TM** 2006 Effects of transdermal estrogen on levels of lipids, lipase activity, and inflammatory markers in men with prostate cancer. J Lipid Res 47:349–355
75. **Steg A, Benoit G** 1979 Percutaneous 17 β-estradiol in treatment of cancer of prostate. Urology 14:373–375
76. **Giardina EG, Chen HJ, Sciacca RR, Rabbani LE** 2004 Dynamic variability of hemostatic and fibrinolytic factors in young women. J Clin Endocrinol Metab 89:6179–6184
77. **Stricker R, Eberhart R, Chevailler MC, Quinn FA, Bischof P, Stricker R** 2006 Establishment of detailed reference values for luteinizing hormone, follicle stimulating hormone, estradiol, and progesterone during different phases of the menstrual cycle on the Abbott ARCHITECT analyzer. Clin Chem Lab Med 44:883–887
78. **Wolfe BM, Huff MW** 1993 Effects of low dosage progestin-only administration upon plasma triglycerides and lipoprotein metabolism in postmenopausal women. J Clin Invest 92:456–461
79. **Kandeel KM, Nayel SA, Abaza MS** 1984 The effect of injectable contraceptive on lipid metabolism in women. Biomed Biochim Acta 43:111–115
80. **Wolfe BM, Plunkett ER** 1994 Early effects of continuous low-dosage all-norgestrel administered alone or with estrogen. Maturitas 18:207–219
81. **Kekki M, Nikkilä EA** 1971 Plasma triglyceride turnover during use of oral contraceptives. Metabolism 20:878–889
82. **Walsh BW, Sacks FM** 1993 Effects of low dose oral contraceptives on very low density and low density lipoprotein metabolism. J Clin Invest 91:2126–2132
83. **Wolfe BM, Huff MW** 1989 Effects of combined estrogen and progestin administration on plasma lipoprotein metabolism in postmenopausal women. J Clin Invest 83:40–45
84. **Wolfe BM, Huff MW** 1995 Effects of continuous low-dosage hormonal replacement therapy on lipoprotein metabolism in postmenopausal women. Metabolism 44:410–417
85. **Wolfe BM, Barrett PH, Laurier L, Huff MW** 2000 Effects of continuous conjugated estrogen and micronized progesterone therapy upon lipoprotein metabolism in postmenopausal women. J Lipid Res 41:368–375
86. **Duvillard L, Dautin G, Florentin E, Petit JM, Gambert P, Vergès B** 2010 Changes in apolipoprotein B100-containing lipoprotein metabolism due to an estrogen plus progestin oral contraceptive: a stable isotope kinetic study. J Clin Endocrinol Metab 95:2140–2146
87. **Elbers JM, Giltay EJ, Teerlink T, Scheffer PG, Asscheman H, Seidell JC, Gooren LJ** 2003 Effects of sex steroids on components of the insulin resistance syndrome in transsexual subjects. Clin Endocrinol (Oxf) 58:562–571
88. **Thompson PD, Cullinane EM, Sady SP, Chenevert C, Saritelli AL, Sady MA, Herbert PN** 1989 Contrasting effects of testosterone and stanozolol on serum lipoprotein levels. JAMA 261:1165–1168
89. **Asscheman H, Gooren LJ, Megens JA, Nauta J, Kloosterboer HJ, Eikelboom F** 1994 Serum testosterone level is the major determinant of the male-female differences in serum levels of high-density lipoprotein (HDL) cholesterol and HDL2 cholesterol. Metabolism 43:935–939
90. **Isidori AM, Giannetta E, Greco EA, Gianfrilli D, Bonifacio V, Isidori A, Lenzi A, Fabbri A** 2005 Effects of testosterone on body composition, bone metabolism and serum lipid profile in middle-aged men: a meta-analysis. Clin Endocrinol (Oxf) 63:280–293
91. **Whitsel EA, Boyko EJ, Matsumoto AM, Anawalt BD, Siscovick DS** 2001 Intramuscular testosterone esters and plasma lipids in hypogonadal men: a meta-analysis. Am J Med 111:261–269
92. **Somboonporn W, Davis S, Seif MW, Bell R** 2005 Testosterone for peri- and postmenopausal women. Cochrane Database Syst Rev 4:CD004509

93. **Broeder CE, Quindry J, Brittingham K, Panton L, Thomson J, Appakondu S, Breuel K, Byrd R, Douglas J, Earnest C, Mitchell C, Olson M, Roy T, Yarlagadda C** 2000 The Andro Project: physiological and hormonal influences of androstenedione supplementation in men 35 to 65 years old participating in a high-intensity resistance training program. Arch Intern Med 160:3093–3104
94. **Brown GA, Vukovich MD, Martini ER, Kohut ML, Franke WD, Jackson DA, King DS** 2001 Endocrine and lipid responses to chronic androstenediol-herbal supplementation in 30 to 58 year old men. J Am Coll Nutr 20:520–528
95. **King DS, Sharp RL, Vukovich MD, Brown GA, Reifenrath TA, Uhl NL, Parsons KA** 1999 Effect of oral androstenedione on serum testosterone and adaptations to resistance training in young men: a randomized controlled trial. JAMA 281:2020–2028
96. **Haffner SM, Kushwaha RS, Foster DM, Applebaum-Bowden D, Hazzard WR** 1983 Studies on the metabolic mechanism of reduced high density lipoproteins during anabolic steroid therapy. Metabolism 32:413–420
97. **Taggart HM, Applebaum-Bowden D, Haffner S, Warnick GR, Cheung MC, Albers JJ, Chestnut 3rd CH, Hazzard WR** 1982 Reduction in high density lipoproteins by anabolic steroid (stanozolol) therapy for postmenopausal osteoporosis. Metabolism 31: 1147–1152
98. **Kluft C, Preston FE, Malia RG, Bertina RM, Wijngaards G, Greaves M, Verheijen JH, Dooijewaard G** 1984 Stanozolol-induced changes in fibrinolysis and coagulation in healthy adults. Thromb Haemost 51:157–164
99. **Münzer T, Harman SM, Sorkin JD, Blackman MR** 2009 Growth hormone and sex steroid effects on serum glucose, insulin, and lipid concentrations in healthy older women and men. J Clin Endocrinol Metab 94:3833–3841
100. **Singh AB, Hsia S, Alaupovic P, Sinha-Hikim I, Woodhouse L, Buchanan TA, Shen R, Bross R, Berman N, Bhasin S** 2002 The effects of varying doses of T on insulin sensitivity, plasma lipids, apolipoproteins, and C-reactive protein in healthy young men. J Clin Endocrinol Metab 87:136–143
101. **Giannoulis MG, Jackson N, Shojaee-Moradie F, Sonksen PH, Martin FC, Umpleby AM** 2006 Effects of growth hormone and/or testosterone on very low density lipoprotein apolipoprotein B100 kinetics and plasma lipids in healthy elderly men: a randomised controlled trial. Growth Horm IGF Res 16:308–317
102. **Snyder PJ, Peachey H, Berlin JA, Hannoush P, Haddad G, Dlewati A, Santanna J, Loh L, Lenrow DA, Holmes JH, Kapoor SC, Atkinson LE, Strom BL** 2000 Effects of testosterone replacement in hypogonadal men. J Clin Endocrinol Metab 85:2670–2677
103. **Agledahl I, Hansen JB, Svartberg J** 2008 Impact of testosterone treatment on postprandial triglyceride metabolism in elderly men with subnormal testosterone levels. Scand J Clin Lab Invest 68: 641–648
104. **Kissebah AH, Harrigan P, Adams PW, Wynn V** 1973 Effect of methandienone on free fatty acid and triglyceride turnover in normal females. Horm Metab Res 5:275–279
105. **Diamanti-Kandarakis E, Bergiele A** 2001 The influence of obesity on hyperandrogenism and infertility in the female. Obes Rev 2:231–238
106. **Hazzard WR** 1985 Atherogenesis: why women live longer than men. Geriatrics 40:42–51, 54
107. **Pérez-López FR, Larrad-Mur L, Kallen A, Chedraui P, Taylor HS** 2010 Gender differences in cardiovascular disease: hormonal and biochemical influences. Reprod Sci 17:511–531
108. **Kim AM, Tingen CM, Woodruff TK** 2010 Sex bias in trials and treatment must end. Nature 465:688–689
109. **Magkos F, Wang X, Mittendorfer B** 2010 Metabolic actions of insulin in men and women. Nutrition 26:686–693
110. **Gallagher D, Heymsfield SB, Heo M, Jebb SA, Murgatroyd PR, Sakamoto Y** 2000 Healthy percentage body fat ranges: an approach for developing guidelines based on body mass index. Am J Clin Nutr 72:694–701
111. **Gallagher D, Visser M, Sepúlveda D, Pierson RN, Harris T, Heymsfield SB** 1996 How useful is body mass index for comparison of body fatness across age, sex, and ethnic groups? Am J Epidemiol 143:228–239
112. **Enzi G, Gasparo M, Biondetti PR, Fiore D, Semisa M, Zurlo F** 1986 Subcutaneous and visceral fat distribution according to sex, age, and overweight, evaluated by computed tomography. Am J Clin Nutr 44:739–746
113. **Shen W, Punyanitya M, Silva AM, Chen J, Gallagher D, Sardinha LB, Allison DB, Heymsfield SB** 2009 Sexual dimorphism of adipose tissue distribution across the lifespan: a cross-sectional whole-body magnetic resonance imaging study. Nutr Metab (Lond) 6:17
114. **Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, Grundy SM, Hobbs HH** 2004 Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology 40:1387–1395
115. **Haufe S, Engeli S, Budziarek P, Utz W, Schulz-Menger J, Hermsdorf M, Wiesner S, Otto C, Haas V, de Greiff A, Luft FC, Boschmann M, Jordan J** 2010 Cardiorespiratory fitness and insulin sensitivity in overweight or obese subjects may be linked through intrahepatic lipid content. Diabetes 59:1640–1647
116. **Adiels M, Taskinen MR, Packard C, Caslake MJ, Soro-Paavonen A, Westerbacka J, Vehkavaara S, Häkkinen A, Olofsson SO, Yki-Järvinen H, Borén J** 2006 Overproduction of large VLDL particles is driven by increased liver fat content in man. Diabetologia 49: 755–765
117. **Fabbrini E, Magkos F, Mohammed BS, Pietka T, Abumrad NA, Patterson BW, Okunade A, Klein S** 2009 Intrahepatic fat, not visceral fat, is linked with metabolic complications of obesity. Proc Natl Acad Sci USA 106:15430–15435
118. **Lewis GF** 1997 Fatty acid regulation of very low density lipoprotein production. Curr Opin Lipidol 8:146–153
119. **Mittendorfer B, Patterson BW, Klein S** 2003 Effect of sex and obesity on basal VLDL-triacylglycerol kinetics. Am J Clin Nutr 77:573–579