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Sex Hormones and Macronutrient Metabolism

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The biological differences between males and females are determined by a different set of genes and by a different reactivity to environmental stimuli, including the diet, in general. These differences are further emphasized and driven by the exposure to a different hormone flux throughout the life.

These differences have not been taken into appropriate consideration by the scientific community. Nutritional sciences are not immune from this "bias" and when nutritional needs are concerned, females are considered only when pregnant, lactating or when their hormonal profile is returning back to "normal," i.e., to the male-like profile.

The authors highlight some of the most evident differences in aspects of biology that are associated with nutrition.

This review presents and describes available data addressing differences and similarities of the "reference man" vs. the "reference woman" in term of metabolic activity and nutritional needs. According to this assumption, available evidences of sex-associated differences of specific biochemical pathways involved in substrate metabolism are reported and discussed. The modulation by sexual hormones affecting glucose, amino acid and protein metabolism and the metabolization of nutritional fats and the distribution of fat depots, is considered targeting a tentative starting up background for a gender concerned nutritional science.

Keywords   Gender, fat, polymorphism, amino acids

INTRODUCTION

There are evidences that both biochemistry and physiology significantly differ between sexes[1], not solely as determined by the exposure to a specific and cyclic exposure to hormones flux.

Every cell of the body has a "sex" determined by the presence of a specific set of sex chromosomes, and this sex is manifested from the very beginning of fetal development in the womb as the final result of the differential expression of specific sets of genes. After birth significant prepubertal differences exist between the structure and function of other organ system of boys and girls, which are eventually further emphasized by hormone activity and driven by a sex-specific reactivity to environmental stimuli, including nutrients and the diet in general.

These differences have not been taken into appropriate consideration by the scientific community for a number of reasons, including the sociological-cultural setting which does not support and favor women equal opportunities, but also as a consequence some "strictly technical" reasons such as the searching for the simplest experimental model. Until recently, most basic and clinical research either was performed exclusively in male subjects or included both sexes but quite often did not differentiate between males and females in the data analysis.

Whatever the underlying cause is, the final result is that men and women are often considered "equivalent." This assumption is evidently not necessarily true.

Thanks to some recent recognition of important sex-based differences in disease, there is now an increasing availability of reports addressing sex-based differences in normal and pathological functions and effects of sex steroid hormones on the function of multiple organ systems in health and disease. In spite of this, several field of science still underscore the importance of sex and in particular nutritional sciences are not immune from this flaw, which is likely to generate a bias in evaluating specific sex-associated needs (Miller and Hay, 2004). For instance,

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[1]According to the recommendation endorsed by the World Health Organization, throughout the text, the terms **Sex** and **Gender**, respectively identify males and females and the biological and physiological characteristics that define maleness and femaleness, the socially constructed roles, behaviors, activities, and attributes that a given society considers appropriate for men and women and the person's self-representation, a uniquely human concept.

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when nutritional advices are concerned (see Dietary Guidelines for Americans, 2005) women are considered and mentioned only when pregnant, lactating or when, after menopause, their hormonal profile is returning back to "normal," i.e., to the male-like profile.

In this review, the current assumptions about the "reference man" *vs.* the "reference woman" in term of metabolic activity and nutritional needs will be presented and discussed. Available evidences of sex-associated differences in specific biochemical pathways involved in substrate metabolism will be described with the aim to identify a tentative starting up background for a nutrition that takes into proper account sex-associated differences together with the organizational and activational effects of sex hormones on food assumption and energy storage in male and female.

BODY COMPOSITION OF "REFERENCE" MAN AND WOMAN AND SEX-SPECIFICITY OF BODY FAT DISTRIBUTION

A very large part of the data presented in scientific literature refers to a young (18–22 years), healthy, 70-kg Caucasian males. In the majority of cases, data were obtained from the army, athlete associations, or European medical students and depending on the variable measured, the degree of overlap between females and males could range from negligible to complete. Under this premises, it appears very difficult to assess whether they accurately reflect the occurrences of both sexes, even within the same age and race (Huxley, 2007).

Starting from the pioneering work of Behnke and co-workers (Behnke, 1953; 1963), several authors (Abe et al., 1998; Mascie-Taylor and Goto, 2007; Peterson et al., 2008; Ritz et al., 2008) attempted to define what reference men and women are, and whether the difference, if any, are substantially due to a smaller size only, rather than to a real difference in the specific composition of each gender.

On the basis of the classical body "compartments," Lean Body Mass (LBM) and Adipose Tissue (AT), it is possible to define a "minimal body weight" which is the minimal body weight achievable without compromising LBM specific for women, composed of sex-specific essential fat (EF) depots, muscle, bones, and organs plus EF. This latter is defined as the fat internally stored in the bone marrow, and around the main organs such as heart, lungs, liver, spleen, kidneys, intestine, muscles, and the lipids rich tissues surrounding the central nervous system (Heymsfield et al., 1997).

Even though the proportional amount of the "average" storage fat in males and females is similar, accounting for about 12% and 15% body weight in men and women, respectively, the total quantity of EF in females, which includes sex-specific fat, is four times higher than in males accounting for 12% vs. about 4% of total body weight. EF is important for childbearing and hormone-related functions and required for normal physiological functioning. In fact, reducing EF below some minimal

amount, such as in the case of extreme dieting and strenuous exercise can significantly impair overall health (Westerterp et al., 1992; Westerterp and Goran, 1997). In women, EF also includes the "sex-specific fat," usually accounting for about 5–9% of total body fat, which is specifically contained in breast and genital regions, lower body subcutaneous fat, and intramuscular depots (Kissebah and Krakower, 1994).

There are several indications that these differences are trans-culturally maintained and common to different ethnicities (Forbes, 2001; Rush et al., 2004; Stone et al., 2008; Rush et al., 2009; Wulan et al., 2010) and, therefore, of biological origin rather than the simple consequence of a different energy balance.

Besides total fat mass, it is evident that a striking difference between men (abdominal or "apple") and women (gluteal-femoral or "pear") in the distribution of body fat depots exists (Shi and Clegg, 2009).

Abdominal AT areas measured by imaging techniques such as computed tomography or magnetic resonance imaging also show a clear sex-related difference. In men, abdominal AT tends to accumulate in the visceral area to a greater extent than in women (Ross et al., 1994; Kuk et al., 2005) and for a similar fat mass, men have on average a twofold higher visceral AT accumulation compared to women (Lemieux et al., 1993). It is generally accepted that sex-specific differences in body proportions and fat distribution differences in adiposity, fat free mass, and bone mass reflect, at least in part, differences in endocrine status, (estrogens, androgens, growth hormone—GH, and Insulin Growth Factor-1—IGF-1) that emerge starting from a prepuberal stage (Mayes and Watson, 2004). The magnitude of the difference between sexes are amplified with maturation, and particularly from late puberty to early adulthood when males gain a more android body shape and females a more gynoid shape (Taylor et al., 2009) clearly suggesting an involvement of sex hormones. Another apparent difference is in the ability of women to protect visceral depots from fat accumulation up to a certain degree of obesity, while men deposit excess fat in this region in parallel with other depots (Bjorntorp, 1991). suggesting that a smaller "available space" exists in male than female AT.

Available data suggest that there is also a definite difference between sexes in age-related changes of whole-body fat distribution, especially in the abdominal fat tissues, and that the accumulation of visceral fat is markedly accelerated after menopause (Toth et al., 2000; Poehlman, 2002; Shi et al., 2009). In fact, after menopause, women tend to accumulate more fat in the visceral depot in a "men fashion" pattern. Cross-sectional studies indicate that the relative abdominal subcutaneous fat volume decreases with age only in male subjects, being about 2.6 times larger in males than in premenopausal females. In agreement with the hypothesis of an endocrine involvement of fat distribution, postmenopausal females show the same trend than male subjects (Kotani et al., 1994).

The mechanisms responsible for the sex-related differences in body fat distribution could be attributable to differences in fatty acid mobilization, oxidation, and storage between

male and female subjects. In fact, it has been reported that significant differences in fat metabolism exist between sexes (Blaak, 2001). The next part of this paper will address the differences in regional fatty acid storage, mobilization, and oxidation between men and women.

HOW DIFFERENCES IN BODY FAT DISTRIBUTION ARISE?

Hormonal and behavioral differences, that surely have an important role in determining differences in body composition, are difficult to evaluate. The major part of differences in metabolism between men and women emerge and become evident during puberty (Loomba-Albrecht and Styne, 2009). Similarly, menopause is associated with significant changes in energy metabolism (Poehlman and Tchernof, 1998; Poehlman, 2002) that reduce the differences between sexes. It is widely accepted that sex steroid hormones play an important role to the build up of sex-specific body composition. It has also been proposed that specifically localized fat stores in women can be necessary to achieve normal reproductive functions and, on the other hand, significant aberration from a normal range of fat stores is associated with the onset of puberty and with the reproductive capacity (Frisch, 1984; de Ridder et al., 1990; Arslanian and Suprasongsin, 1997; Bray, 1997; Roemmich and Rogol, 1999; Kiess et al., 2000; Vizmanos and Marti-Henneberg, 2000; Klentrou and Plyley, 2003). In fact, it is known that obesity induces a variety of alterations in the reproductive system and, similarly, manipulations of the hypothalamic-pituitary-gonadal axis produce changes in food intake, body weight, and fat distribution. Several hormones influence the amount and regional distribution of AT during puberty. Cortisol and insulin promote fat deposition both in experimental animals (Chan et al., 1982) and in humans (Riccardi et al., 2004; Purnell et al., 2009) while steroid hormones (Thakur and Paramanik, 2009) and GH stimulate lipolysis (Sakharova et al., 2008). An altered sensitivity of hypothalamic-pituitary-adrenal axis has been proposed to be at the basis of obesity leading to an unbalance between the lipogenic effects of cortisol and insulin and the lipolytic effects of sex steroids and GH (Roemmich and Rogol, 1999). In this context leptin, which is secreted by AT in proportion relative to the quantity of fat (Bluher and Mantzoros, 2007), acts as a metabolic signal to the hypothalamic areas controlling satiety, energy expenditure, and therefore, regulates cortisol, insulin, sex steroid and GH release. In enlarged fat cells of obese subjects, circulating levels of leptin are increased in proportion to body fat stores (Beckers et al., 2009). *In vitro* studies indicate that insulin and glucocorticoids directly act on AT to upregulate in a synergistic manner leptin mRNA levels (Wabitsch et al., 1996) and rates of leptin secretion in human AT over the long term (Havel, 2001). These observations suggest that increased leptin expression associated to obesity could originate, at least in part, from the chronic hyperinsulinemia and increased cortisol turnover (Fried et al., 2000).

A relationship between body fat distribution and hormonal profiles in the plasma of early pubertal girls has also been reported. de Ridder and co-workers reported that body fat distribution, rather than body fat mass, was associated to the total concentrations of estrone, $(17\beta\text{-E2})$, and testosterone. Therefore, girls with fat predominantly localized on the hips had the highest levels of sex steroids and gonadotropins as the result of their elevated ovarian activity (de Ridder et al., 1990). Girls with predominantly abdominal fat have been also found to be more obese and with increased plasma levels of total estradiol (E2) and a lower androgen to estrogen ratio in plasma. This association suggests a reciprocal relationship involving body fat distribution, plasma sex hormone levels, and availability of sex steroids in early female puberty. These differences are possibly due to an increased activity of aromatase (a cytochrome P450 enzyme—CYP19 that catalyzes the formation of aromatic C18 estrogens from C19 androgens), especially in abdominal AT. According to this hypothesis, the metabolism of androgens in AT has been reported to be affected by the regional distribution of fat, as indicated by the fact that the upper body fat produces a smaller ratio of estrogens to 5-α-reduced androgens than lower body fat (Killinger et al., 1987; McTernan et al., 2002).

It might be interesting to briefly consider the sex-specific fat distribution also under an historical-evolutionary gender perspective. Throughout the history of *H. sapiens*, periods of food shortages have privileged individuals who could effectively save up and store "extra" energy in times of surplus. Genetic traits associated to fatness have, therefore, been selected because they improve the chance of survival when food is scarce. The ability to successfully counter food restriction took a pivotal importance in pregnancy and while breast feeding the offspring. As mentioned above, females seem to possess a lower lipolytic activity in peripheral body fat than men. Moreover, female body fat level increases the life time of reproductive ability, due to the association of an "optimal fatness" with regular menstrual cycle and early onset of puberty. Under this perspective, at least in the ancestral societies, fatness was possibly seen no only as a social advantage, representing health and fertility, but also a "desirable" phenotype by the male counterparts, further encouraging the selection of specific genetic traits. Within this "evolutionary" context, the usual range of human metabolic variation must have produced many female individuals with a predisposition to store energy and becoming obese. Whereas lower body or peripheral obesity has developed as an important survival element for energy storage in those individual expected to be assigned to somehow "sedentary" life style like prehistoric female for childbirth and nursing, the prehistoric males needed abdominal fat. This fat localization, characterized by a high turnover and, therefore, constituting a rapidly available energy store, may have assumed an important role fulfilling the needs of women's highly active hunting partner (Kissebah and Krakower, 1994). However, this "ancestral" attractiveness due to fat accumulation was at least in part counterbalanced by a number of reproductive problems associated to obesity and also with an increased risk of generating an offspring affected in turn by an adult onset of

obesity. On the other hand, in men, low weight to height ratio is not associated with reduced fertility, while the excess body fat leads to a decreased fatty acid availability and oxidation during endurance exercise. This aspect was obviously a disadvantage for our hunter-gatherer forefathers (Power and Schulkin, 2008).

Overall, it is clear that a complex network of behavioral and biological aspects contributed to induce and consolidate the differences in fat accumulation and distribution between men and women and the underlying differences in substrate metabolism associated to sex.

DIFFERENCES IN SUBSTRATE METABOLISM

Sex-Associated Differences in Fatty Acid Metabolism

Differential regulation of regional AT lipolysis could also be an important factor contributing to the differences in body fat distribution associated to sex. Available *in vitro* studies performed on AT biopsies, indicate that the difference in lipolysis mediated by catecholamine between upper body and lower body fat depots are more pronounced in women than in men (Richelsen, 1986). Similarly, Wahrenberg and coworkers (Wahrenberg et al., 1989), in agreement with bioptic data mentioned above, observed that the lipolytic effect of noradrenaline was stronger in abdominal adipocytes than in gluteal fat cells and this regional difference was more pronounced in females than in males. In the same study, $\alpha 2$-adrenoceptor density was found similar in all regions, but in females the affinity of clonidine, a specific $\alpha 2$-adrenergic agonist, was 10–15 times lower in the abdominal fat cells than in gluteal cells. On the basis of these observations, it can be concluded that regional differences in catecholamine-induced lipolysis are due to site-specific variations in β-adrenoceptor density and that variations in the affinity of $\alpha 2$-adrenergic receptor in females explain, at least in part, the stronger lipolytic response induced by catecholamine in women.

Also in agreement with these observations, Guo and co-workers reported that in the lower extremities, catecholamine mediated free fatty acid release is lower in women than in men, while no significant differences between men and women were observed in free fatty acid release from upper body depots (Guo et al., 1997). Taken together, these reports suggest that in women, lipolysis in lower body AT is less sensitive (or responsive) to β-adrenergic stimulation than subcutaneous AT in the upper body.

The rate of free fatty acid release by the upper body subcutaneous fat depots after a meal has been observed to be sex specific, and in particular, significantly higher in men than in women. This difference indicates a higher resistance to the antilipolytic effect of meal ingestion in the upper body fat depots in men. *In vivo* studies (Jensen, 1995) indicated that the systemic rate of fatty acids appearance is more strongly negatively regulated by a meal in women than in men, and that the upper body subcutaneous AT of non-obese men is more resistant to the antilipolytic effects of a meal ingestion. In a different report, the same authors (Jensen et al., 1995) observed that the increase of oxygen consumption after a mixed meal is primarily localized in splanchnic tissues. These data contribute to explain the frequent observation of a greater postprandial response in men than in women, associated with larger fat depots localized at visceral levels (Kuk et al., 2005).

Available data on resting fat oxidation are somehow contrasting. Basal fat utilization (adjusted for fat free mass) has been reported to be lower in females than in males, thereby contributing to a higher fat storage in women. Nagy and co-workers (Nagy et al., 1996) found that both the absolute rate of basal fat oxidation and the rate adjusted for differences in resting energy expenditure are lower in women than in men. The authors also report that fat oxidation is not increased in individuals with a greater fat mass.

In agreement with this observation, Toth and co-workers (Toth et al., 1998) reported that aged men in resting conditions oxidized more fat than aged women. These differences were not related to noradrenaline appearance rate, free fatty acid concentration, body composition, or aerobic capacity. The presence of significant sex-associated differences in the elderly, when the specific effect of played by sex steroid hormones is not any more significant, indicate the presence of a real, estrogen-independent sex dimorphism of postabsorptive fat metabolism.

In contrast to these observations, Horton and others (Horton et al., 1998) observed no differences associated to sex in substrate utilization in resting conditions. On the other hand, the same study reports that during exercise, epinephrine, and norepinephrine levels were significantly higher in men than in women and that significant differences exist in substrate utilization during physical exercise (see also below). In fact, in their study, women obtained a higher proportion of the total energy expended from fat oxidation, whereas men utilized more carbohydrate (Horton et al., 1998).

Postprandial fat storage in subcutaneous AT has been reported to be higher in women than in men, whereas fat storage in visceral AT has been hypothesized to be higher in men. In both sexes, the concentration of fatty acids 24 h after the administration of a test meal has been found significantly higher in abdominal subcutaneous fat than in thigh AT, but within the same localization, no differences were observed between men and women (Romanski et al., 2000). In the same study, the authors observed significant differences in blood flow between sexes within specific regions of AT after meal ingestion, suggesting that a greater fat storage in lower body depots occurs in women (Romanski et al., 2000).

Sex-specific regional differences have also been shown in triglyceride fatty acid uptake after a standard meal (Nguyen et al., 1996). Following the ingestion of small though frequent feedings designed to achieve steady-state chylomicronemia, chylomicron uptake in the splanchnic bed was significantly and largely higher in men than in women (71 $\pm$ 15% of meal triglyceride disappearance and 20 $\pm$ 7% in women, respectively). These differences may obviously reflect a different set

up of the molecular machinery involved in fatty acids handling. The expression of the mRNA encoding for the membrane bound fatty acid transporter-1 FATP-1 has been reported to be significantly higher in lean women than in lean men (Binnert et al., 2000). This observation suggests that the higher fatty acid storage in females skeletal muscle, in both fasting and postprandial conditions, can be due, at least in part, to a sex-specific increase of the expression of fatty acid transport machinery.

All the observations mentioned above provide a robust background to explain the differences in net regional fat storage between men and women. However, the number of *in vivo* studies on sex-related differences in fatty acid metabolism is very limited and most findings still require confirmation.

Adipocytokines are a variety of biologically active molecules, secreted by AT, that interact with metabolic, endocrine, and immune system. Among them, adiponectin is considered to be one of the most important factors in the pathogenesis of metabolic and cardiovascular disease (Stefan and Stumvoll, 2002; Ukkola and Santaniemi, 2002). Adiponectin is abundantly detectable in the circulation (Arita et al., 1999) and its activity has antidiabetic, antiatherogenic effects (Berg et al., 2002) and anti-inflammatory effects (Ouchi et al., 1999). In mice, adiponectin levels dynamically change throughout the sexual maturation (Combs et al., 2003) and correlate with estrogens or testosterone levels (Nishizawa et al., 2002; Combs et al., 2003).

The abrogation of androgen effects through neonatal castration led to increased adiponectin levels comparable to those found in females, whereas ovariectomy does not interfere with the pubertal increase of adiponectin (Combs et al., 2003). Bottner and co-workers (Bottner et al., 2004) observed a similar trend in human adolescent. In their study, a progressive decline in adiponectin levels, strongly associated with androgen levels and associated to physical and pubertal development was observed in boys compared with girls.

Several authors investigated about sex-associated differences in fat utilization during physical exercise and the effect of training in substrate utilization. The effect of endurance training on whole body substrate, glucose, and glycerol utilization during 90 min of exercise at 60% peak of oxygen consumption have been investigated by Carter and co-workers by using stable isotope labeled substrates (Carter et al., 2001). The authors found that the increase in peak oxygen consumption induced by training was significantly higher in women than in men (22% and 17%, respectively) while the respiratory exchange ratio (the ratio of the amount of carbon dioxide produced to the amount of oxygen consumed) was higher in men. These observations indicate that females oxidize proportionately more lipid and less carbohydrate during exercise compared with males both pre- and posttraining. Higher lipid oxidation was accompanied by a faster glycerol appearance and disappearance rate indicating that lipolysis induced by exercise is higher in females than in males. These differences can be accounted for by the lower circulating levels of both norepinephrine and epinephrine observed in females during exercise (Horton et al., 1998). In fact, the raise

of levels of sympathetic hormones and pancreatic polypeptide in response to exercise has been found significantly higher in men than in women (Carter et al., 2001). Conversely, insulin levels have been found to be higher at baseline in men and to fall by a greater amount and reach levels similar to those observed in women during exercise (Davis et al., 2000). Overall, these studies indicate that men exhibit counter-regulatory responses to exercise thank to a more reactive autonomic nervous system (epinephrine, norepinephrine, and pancreatic polypeptide), cardiovascular (systolic and mean arterial pressure), and specific metabolic (carbohydrate oxidation) changes. On the contrary, women show an increased lipolytic (glycerol and nonesterified fatty acids) and ketogenic (β-hydroxybutyrate) response suggesting that the decreased sympathetic nervous system activity during exercise is possibly compensated by an increased lipolytic responses (Davis et al., 2000).

Moreover, long-term endurance exercise training (6 months) is associated to an increases in the expression of mRNA encoding for muscle lipoprotein lipase, peroxisome proliferator-activated receptor-γ coactivator-1α, carnitine palmitoyltransferase-1β, and acid ceramidase in women, but not men, suggesting that only in women endurance exercise plays an important role in ceramide degradation. Accordingly, endurance exercise led to reductions in the mRNA content of the lipogenic factors sterol regulatory element binding protein-1c and serine palmitoyl transferase in men but not in women (Smith et al., 2009). These data suggest that the adaptations to long-term endurance exercise training is sex-specific as concerning the expression of critical lipid metabolism genes in overweight and obese, middle-aged subjects.

Finally, there are evidences indicating that young, normal weight, healthy women have higher levels of plasma free fatty acids and intramyocellular triglycerides content than men, matched by nutritional and lifestyle habits and insulin sensitivity (Perseghin et al., 2001). It can be concluded that nonobese, healthy, young women have an insulin sensitivity similar to men, even though they show higher levels of postabsorptive circulating and tissue-stored fatty acids.

As mentioned above, sex steroids have an important role in the generation of the sexually dimorphic distribution of AT and in the regulation of adiposity and distribution of fat depots in humans. In particular, E2 has been shown to regulate adipocyte metabolism and regional fat distribution. It is know that ER-α and -β are expressed in adipocytes of rodents and humans, where a delicate balance between the activity of these receptors regulates lipoprotein lipase activity (the rate-limiting enzyme controlling lipid-storage process) and lipolysis and modulate preadipocyte proliferation (Wade and Gray, 1978; Cooke and Naaz, 2004; Dieudonne et al., 2004).

In human AT, E2 promotes leptin expression and regulates mRNA expression and the catalytic activity of lipoprotein lipase (Machinal-Quelin et al., 2002). Finally, E2 increases human preadipocyte proliferation *in vitro* and the size of mature adipocytes by affecting lipolysis and lipogenesis (Price and Tisdale, 1998). Mature adipocytes express both ERα and ERβ,

and their levels are not significantly different between subcutaneous and intra-abdominal AT localizations. Even though no sex-associated difference in ERα expression have been reported in AT, ERβ levels are higher in women than in men (Dieudonne et al., 2004). However, it cannot be excluded that a different pattern of expression for nuclear receptor cofactors in AT between men and women can be one of the molecular basis of the sexual dimorphism of body fat distribution as indicated by the observation that ERα gene knockout mice develop obesity, whereas ERβ knockout mice have a normal amount of AT (Heine et al., 2000; Ohlsson et al., 2000).

One important regulator of local E2 activity in extra-hepatic sites is the enzyme estrogen sulfotransferase (EST). An interesting study by Khor and co-workers (Khor et al., 2008) indicates that EST expression in AT is sex specific and that the expression of EST in both AT and liver is differentially regulated in males and females. In mice, EST is expressed in the white fat tissue of male but not of females and its expression is regulated by testosterone. In fact, castration is associated with a lack of EST expression in epididymal fat, whereas the replacement of testosterone restores its expression. Accordingly, EST expression can be artificially induced in females by exogenous testosterone. Similarly, the expression and regulation of *P*-450 aromatase, the enzyme responsible for the conversion of androgens to estrogens, has been reported to be different in the brain, and in the AT of men and women (McTernan et al., 2002). Testosterone treatment leads to a decrease of adipocyte size of subcutaneous abdominal and gluteal depots in female-to-male trans-sexuals. In these subjects, basal lipolysis was significantly increased in abdominal fat but not in gluteal AT (Elbers et al., 1999). A further indication for an involvement of androgen in the regulation of body fat distribution is provided by androgen receptor (AR) knockout mice that develop a late onset of obesity characterized by a visceral localization (Sato et al., 2003; Fan et al., 2005).

Different studies examined adipocyte cell size, lipoprotein lipase, and lipolytic activities after androgen treatment in humans, concluding that the effect of androgens is essentially antiadipogenic. Both in rats (Dieudonne et al., 2000) and in mice (Singh et al., 2006), the androgens testosterone and dihydrotestosterone (DHT) inhibit preadipocyte differentiation. Moreover, castration increases the differentiation of preadipocytes obtained from perirenal fat depot (Lacasa et al., 1993) and inhibits the differentiation of epididymal preadipocytes (Lacasa et al., 1997). The same study indicates that, in rats, castration causes an increase of the activity of mitogen-activated protein kinase in proliferating preadipocytes. This increase provides a mechanism explaining the enhanced preadipocytes proliferation induced by androgens. The responsiveness to androgens has been found to be more pronounced in deep visceral fat depots in comparison to subcutaneous adipose compartments (Lacasa et al., 1997; Dieudonne et al., 2000). The presence of a higher ARs activity in visceral preadipocytes than in subcutaneous preadipocytes in both rats and humans could be one of the possible reasons underlying the observed site-specific regulation of adipogenesis (Dieudonne et al., 1998; Rodriguez-Cuenca et al., 2005) and

the associated differences between fat deposition rate and shape between sexes.

Low plasma sex-hormone binding globulin levels (Tchernof et al., 1995; Couillard et al., 2000; Garaulet et al., 2000) and 5-Dehydroepiandrosterone (5-DHEA)(Tchernof et al., 2004), have been found to be negatively associated with visceral obesity and visceral fat accumulation significantly correlated with low plasma testosterone concentrations (Seidell et al., 1990). In agreement with these observations, women with polycystic ovary syndrome and hyperandrogenism have been reported to be affected by abdominal obesity and hyperinsulinemia (Dunaif, 1997). Similarly, elevated plasma testosterone (total or free) has been found to be associated with abdominal obesity in women (Pedersen et al., 1995). Elbers and co-workers have shown that testosterone administration in female-to-male trans-sexuals is associated with changes in body fat distribution toward a more android pattern and an increase in visceral fat (Elbers et al., 1997).

Sex- Associated Differences in Carbohydrate Metabolism

There are indication that the prevalence of disturbances in glucose homeostasis and tolerance differs between men and women. In general, women have lower fasting glucose levels and higher post load glucose (Pomerleau et al., 1999). Available population studies indicated that even though women are usually more frequently diagnosed for diabetes than men (Shaw et al., 1999; Qiao et al., 2003), the prevalence of early abnormalities of glucose metabolism is three times higher in men than in women (Kuhl et al., 2005). A number of evidences suggest that E2 modulates insulin sensitivity and is involved in glucose homeostasis (Godsland, 2005). E2 plays an important role in glucose homeostasis. In fact, insulin resistance is frequently present in different diseases such as gestational diabetes mellitus and polycystic ovarian syndrome, which are characterized by disturbances in female gonadal hormones. In these cases, insulin resistance is accompanied by disturbed carbohydrate metabolism and compromised glucose homeostasis and by defects in glucose transporter expression (Okuno et al., 1995; Livingstone and Collison, 2002).

Several studies reported that also 5-DHEA, the most abundant human adrenal steroid hormone, which is more elevated in male than in female, modulates glucose uptake in human fibroblasts and rat adipocytes (Nakashima et al., 1995; Kajita et al., 2000). Moreover, the external administration of 5-DHEA to genetically diabetic d*b*–/d*b*– mice induces the remission of hyperglycemia and improves insulin resistance (Coleman et al., 1982). Similarly, the same treatment protects against visceral obesity and muscle insulin resistance in normal rats fed a high-fat diet (Hansen et al., 1997). Others (Aoki et al., 2000) reported that 5-DHEA supplementation decreases the elevated expression of the gene encoding for glucose-6-phosphatase, (G6Pase), a key enzyme involved in the homeostatic regulation of blood glucose, in d*b*–/d*b*– mice, suggesting that this enzyme is a specific

target of the hypoglycemic effect of 5-DHEA (Aoki et al., 2000). Among the hepatic gluconeogenic enzymes, 5-DHEA directly suppresses the enzyme activity, mRNA level and protein expression of G6Pase in the human hepatoma cell line (HepG2). In the same study, the authors observed a down regulation of phosphoenolpyruvate carboxykinase, another key enzyme involved in gluconeogenesis, indicating that this enzyme may be another molecular target for the insulin-sensitizing effect of DHEA.

Finally, the uptake of glucose has been frequently reported to be strongly affected by sex hormones, even though the molecular mechanisms of this activity still remain scarcely known. Facilitate Glucose transporter (Glut) are a group of structurally related proteins that are encoded by a family of genes and expressed in a tissue-specific manner (Lienhard et al., 1992). Many years ago, some authors reported that the hormonal regulation of Gluts is organ-dependent and that, at least in rats, in specific sex organs, glucose uptake is modulated by estrogen in females and by DHT in males, respectively (Mills and Spaziani, 1968; Meier and Garner, 1987). Accordingly, Hart and co-workers reported significant sex-associated differences in glucose uptake and the effects of sex hormones on glucose transport, suggesting that this process may also be involved in the sexual dimorphism in specific organ (lung) development (Hart et al., 1998). The same authors have also demonstrated that in lung explants from male and female rats, 24 h treatment with estrogen significantly increases glucose uptake, Glut 1 protein expression, and Glut-1 mRNA levels. In contrast, 24 h treatment with DHT significantly decreases glucose uptake, Glut 1 protein, and Glut-1 mRNA levels (Hart et al., 1998). In addition to exhibiting higher basal glucose uptake, female rat lung was also more responsive than male lung to E2 treatment (Hart et al., 1998). The molecular basis underlying this difference is not clear: it is possible to hypothesize a sex-specific regulation at the transcriptional, posttranscriptional, or receptor activity level. Additionally, it has been demonstrated that androgens reduce cyclic adenosine monophosphate generation by lung fibroblast and inhibit the production of epidermal growth factor (EGF) which is an important stimulus for glucose uptake (Catterton et al., 1979). Conversely, E2 has been reported to increase the production of EGF and IGF-1, a second important factor involved in the stimulation of glucose uptake in fetal lung (Simmons et al., 1993).

Barros and co-worker (Barros et al., 2009) suggested that Estrogen Receptor-β (ERβ) opposes the effect of Estrogen Receptor-α (ERα) on glucose tolerance, and that an unbalanced activity of ERβ ligands may be diabetogenic as indicated by a substantial reduction of Glut-4 expression in Aromatase knock-out mice treated with 2,3-bis(4-hydroxyphenyl)propionitrile (DPN), a selective ERβ ligand. It is well-known that Glut-4 plays a crucial role in glucose homeostasis, and it is a limiting step in insulin-induced glucose uptake in skeletal muscle. Thus, the treatment with the ERβ ligand DPN, by reducing Glut4, should lead to a decrease of glucose tolerance (Barros et al., 2009).

In parallel with Gluts, trans-cellular glucose trafficking is performed by Sodium-glucose cotransporters (SGLTs), a family of glucose transporter found in the intestinal mucosa (SGLT1) and in the proximal tubule of the nephron (SGLT2 and SGLT1). Sabolić and coworkers (Sabolic et al., 2006) showed that, in castrated rat, the expression of SGLTs is exclusively affected by androgens, whereas E2 and progesterone have no effect. The same authors also found that, at least in rats, the gene encoding for SGLT1 has two androgen receptor elements. According to these observations, providing a background the effects of sexual hormones on glucose metabolism, glucose intolerance, insulin resistance, and diabetes have been reported to display a stronger phenotype in males than in females in different rodent models (Zierath et al., 1997) The interplay between endocrine and metabolic systems and the pivotal role exerted by adiponectin is illustrated in Fig. 1.

Sex-Associated Differences in Protein and Amino Acid Metabolism

Plasma concentrations of large neutral amino acids (LNAAs) is not tightly regulated and fluctuates in response to food consumption and hormone secretion (Wurtman et al., 1968). It is also affected by several pathological conditions such as liver and renal disease (DeFronzo and Felig, 1980), diabetes (Halliday et al., 1981), obesity (Caballero et al., 1988), and in response to stress (Imai et al., 1984).

Significant differences have been described in the plasma concentration of several AA between young adult males and females (Armstrong and Stave, 1973) and a significant increase of all LNAAs, with the exception of tryptophan, occurs in ageing women, but not in men (Caballero et al., 1991). However, no major differences in plasma AA concentrations have been observed between males and females (Armstrong and Stave, 1973; Gregory et al., 1986) indicating that sex-related differences develop after adolescence, as the hormonal differences are more marked.

Another aspect that has been proposed to be associated to sex is the AA handling system. Several isoforms of Na-coupled neutral AA transporters (SNAT), have been described in detail such as SNAT1, SNAT2, and SNAT4 all having a "system A" transport activity (Sugawara et al., 2000; Varoqui et al., 2000; Yao et al., 2000). Many studies have shown that SNAT2 gene expression is induced by E2 but not by progesterone in cultured breast cancer cell (Shennan et al., 2003; Shennan et al., 2004) and in rat mammary gland (Lopez et al., 2006) and that the induction of "system A" by E2 in breast cancer cell lines only occurs in cell lines expressing ERα. In addition, due to the rapid induction of SNAT2 by E2 in the mammary gland explants, there is the possibility that this effect could be mediated by a nongenomic action of the estrogen receptor (Lopez et al., 2006). Some experimental evidences indicate that both *in vivo* and *in vitro* administration of estrogen reduces proline transport in ovariectomised rats and in R3230AC mammary carcinoma
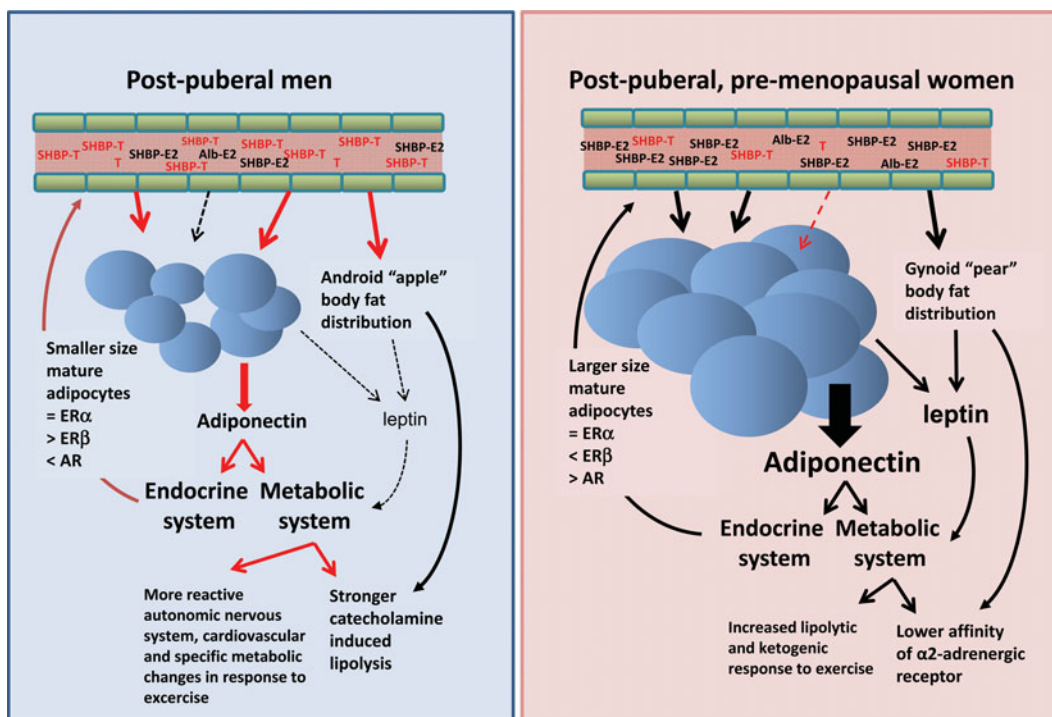
Figure 1 Simplified scheme illustrating some of major differences in fat metabolism associated to gender (see text for more details). Left panel: In males, the relative abundance of circulating android hormone is associated with central body fat depots, usually characterized by small size mature adipocytes expressing high levels of ERβ and high levels of Aromatase. In this setting, adipocytes secrete lower levels of adiponectin and leptin which in turn modulate endocrine system and metabolic rate. Central body fat distribution is usually also characterized by more reactive autonomic nervous system (epinephrine, norepinephrine, and pancreatic polypeptide), cardiovascular (systolic and mean arterial pressure), and specific metabolic (carbohydrate oxidation) changes. Right panel: in women, high levels of circulating Estradiol are associated to lower body fat deposition which is in general characterized by larger size mature adipocytes expressing lower levels of ERβ and higher levels of Aromatase, in comparison to males. Adiponectin and leptin secretion are upregulated. In lower body adipose tissue, lipolysis is less sensitive (or responsive) to β-adrenergic stimulation than subcutaneous adipose tissue in the upper body. Women usually show an increased lipolytic response to exercise in the presence of a lower affinity of adrenergic receptors. SHPB = Steroid hormone binding protein. Alb = Albumin. T = Testosterone. E2 = Estradiol.

(Hissin and Hilf, 1979) respectively. These experimental observations suggest a specificity to the action of E2 on "system A" and that SNAT2 gene expression could be regulated by hormonal changes occurring in female and male during puberty.

A marked sex dimorphism has been reported in the levels of the essential AA, L-Arginine (Arg) in plasma, kidney, and skeletal muscle (Ruzafa et al., 2003). Arg enters in the urea cycle, and serves as a precursor for the synthesis of a number of important biological molecules including Nitric oxide, and guanidine (Reyes et al., 1994; Wu and Morris, 1998; Wu and Meininger, 2002). Dietary Arg restriction induces a marked decrease of plasma and tissues Arg that almost equalizes the sexual dimorphism found in the normal levels of this AA (Morris, 2002). The interaction between dietary Arg and hormone activity is suggested by the observation that Arg dietary restriction affects the activities of enzymes related to the metabolism of Arg and ornithine that are regulated by sex hormones (Ruzafa et al., 2003). Moreover, Arg restriction induces a significant decrease of both body and renal weights in males, but not in females probably due to an interaction between Arg and the mechanism of action of testosterone. This possibility is also supported by the finding that the renal enzyme ornithine decarboxylase, a well-known

target of androgen action in the kidney (Berger, 1989), was dramatically decreased in the kidney of male Arg-deficient mice but not in females. A tentative mechanism for the interaction between Arg and testosterone has been suggested by Cremades and coworker (Cremades et al., 2004) who, based on previously observation (Rosenfeld, 1994), proposed that Arg acts as a scavenger of GH and insulin both in humans and in other mammals. Finally, Arg urinary excretion has been reported to be higher in women than in men (Forte et al., 1998) probably due to estrogen effects (Weiner et al., 1994). Moreover, sex hormones (e.g., estrogen and testosterone) may play an important role in determining gender differences in Arg metabolism as suggested by the observation that, arginase activity is stimulated by testosterone explaining the lowered Arg levels observed in male mice (Kumar and Kalyankar, 1984).

Differently to Arg, the effects of sex on leucine (Leu) metabolism and kinetics is still controversial. During exercise, male subjects oxidize more Leu and have a lower rate of nonoxidative leucine disposal than females (Lamont et al., 2001), but no differences associated to sex have been reported on Leu or lysine kinetics in subjects studied in postabsorptive, resting state. The metabolic mechanism(s) responsible for the lower

Table 1 Some of the more relevant differences in human metabolism associated to sex

Female vs. male	References
Higher postprandial response associated to visceral fat	(Kuk et al., 2005)
Lower basal fat oxidation	(Toth et al., 1998); (Nagy et al., 1996)
Lower epinephrine and norepinephrine during exercise	(Horton et al., 1998)
Higher proportion of energy expended from fat during exercise	(Horton et al., 1998)
Lower catecholamine mediated free fatty acid release in lower estimates	(Guo et al., 1997)
Higher postprandial fat storage in subcutaneous adipose tissue	(Romanski et al., 2000)
Higher blood flow and fat storage in lower body depots	(Nguyen et al., 1996)
Lower chylomicron uptake in splancnic bed and hyperexpression of fatty acid transporter	(Binnert et al., 2000)
Higher utilization of fat and lower utilization of carbohydrates during exercise	(Carter et al., 2001)
Lower reactive nervous system, cardiovascular response, and carbohydrate oxidation during exercise	(Davis et al., 2000)
Higher lipolitic and ketogenic response	(Davis et al., 2000)
Lower fasting glucose levels and higher postload glucose	(Poehlman et al., 1993)
Higher glucose uptake in specific sex organs a result of sex hormones regulation of the expression of specific glucose transporters (Glut-1), IGF-1, and EGF	(Hart et al., 1998)
Lower large rental amino acids plasma concentration	(Caballero et al., 1991)
Higher expression Na-coupled neutral amino acid transporter	(Shennan et al., 2003; Shennan et al., 2004)
Higher protein turnover	(Luiking et al., 2004)

Leu oxidation and protein catabolism in exercising woman also remains scarcely known, but could be related to the observation that women derive more of their needs of energy for exercise from fat, thereby sparing carbohydrate, amino acid, and protein.

Finally, a number of differences in other AA and protein metabolism associated to sex are available in the literature (Volpi et al., 1998), which strongly suggest an implication of sex hormones (Tipton, 2001). It has been estimated that the contribution of protein turnover to the resting metabolic rate is approximately 20% (Welle and Nair, 1990). Thus, it is possible that differences in protein metabolism significantly contribute to the observed differences in energy consumption between women and men. In mice, protein turnover has been reported to be higher in female than in male (Luiking et al., 2004). In basal postabsorptive state, protein oxidation is lower in women than in men, independently on body composition (Volpi et al., 1998). Unfortunately, available literature still reports controversial effects of sex hormones on protein metabolism (Lariviere et al., 1994; Mauras et al., 1994). Burd and co-workers point out that sex-based differences in protein turnover related to exercise exist in young men and women, but these differences are minor. By contrast, older women develop an anabolic resistance to both feeding and exercise, but the reasons are still unknown (Burd et al., 2009).

Overall, the absence of an apparent difference between males and females on either whole body protein synthesis or breakdown suggests that protein turnover, is not different between women and men. Some of the more relevant differences in human metabolism associated to sex are listed in Table 1.

POLYMORPHISMS

A wide spectrum of diseases, if not all, results from the combined effects of a number of genetic variants and environmental factors. The risk of contracting common diseases is likely to be influenced by genetic variants that are relatively common in populations. Variations in DNA sequences can potentially af-

fect the risk to develop diseases and to respond to pathogens, chemicals, drugs, vaccines, and other agents.

At present, available data to evaluate the generality of this association are still scarce but more and more widely distributed genetic variants associated with common diseases are being discovered. On the basis of the analysis of the genome of a sample of 269 individuals, the HapMap project selected several million well-defined SNPs, genotyped the individuals for these SNPs, and published the results (International HapMap Consortium 2005). The goal of the Project was to provide a tool to be used in association studies, where the haplotypes in individuals with a disease are compared to those of a comparable group of individuals without a disease. If a specific haplotype occurs more frequently in affected individuals than in controls, a gene influencing the disease may be located within or near that haplotype. More recently the 1000 Genomes Project (www.1000genomes.org), an international research effort to establish by far the most detailed catalogue of human genetic variation was launched in January 2008 with the objective to sequence the genomes of at least one thousand anonymous participants from a number of different ethnic groups. At present, data simulations suggest that European populations harbor an estimated 19–20 million SNPs, including eight million SNPs with an allele frequency greater than one percent, six million SNPs at between 0.1 and 1% frequency, and 2.5 million singletons. Roughly half of the alleles appear to be specific for each population, pointing to a total estimated of 60 million SNPs.

Specific allelic variants (single nucleotide polymorphisms, SNP), associated with risk factors for disease and substrate kinetics has been often reported to be sex specific (Halsall et al., 2000; Galluzzi et al., 2001; Talmud and Humphries, 2001). Unfortunately, at present, information about the real penetrance into the pathological phenotype and the specific prevalence in males and females are still scarce.

However, this field is in continuous expansion and a significant number of SNPs are identified and filed in public access databases almost daily. We can foresee that in the near future

more precise information will be available allowing the assessment of a sex-specific exposure to disease risk on the basis of presence of a given either a single or a combination of SNPs. In this part of the paper we will briefly mention some of the known association between sex and SNP related to disease risk. Most probably, in the near future this aspect of individual genetic profile will gain more and more relevance and it is not difficult to foresee that will be considered as a major determinant in assessing the so called "personalized nutrition."

There are two possible explanations at the basis of a sex-specific association of SNP concerning the relationship between nutrition and health:

1. The incidence of an SNP within a specific population can be higher in one sex than in the other. This is the case of the hormone-sensitive lipase (HSL) gene (Hoffstedt et al., 2001), which translated for an enzyme that catalyzes the rate-limiting step for lipolysis in fat cells, specifically the breakdown of triglycerides. Magrè and co-workers identified a polymorphism of a dinucleotide repeat including 16 alleles localized within intron 6 of the HSL gene (HSLi6) associated with obesity and diabetes (Magre et al., 1998). The difference in the lipolysis rate between genotypes, and in particular the one associated to allele 5 of the HSLi6 polymorphism, has been found more pronounced in men than in women leading to a more marked decrease in the lipolytic rate of abdominal fat cells. The frequency of allele 5 has been found higher in male than in female (0.68 vs. 0.52). HSLi6 polymorphism is a very important factor in lipolysis and its expression is associated with decreased catecholamine-stimulated lipolysis in abdominal subcutaneous AT. This is more apparent in men than in women. The reason underlying this difference is unknown. However, given the well-known difference in body fat distribution between men and women, it is not surprising that sex-related factors (e.g., sex hormones) may also interact with the genotype and cause different phenotypic effects in men and women.
2. Alternatively, the incidence of an allelic variant could be similar in both genders, but present a preferentially higher "penetrance" into the phenotype in one sex than in the other. We will briefly provide an example of both cases related to the risk of CVD.

A number of studies have shown that the prevalence and onset of coronary heart disease (CHD) is sex-dependent and that CHD prevalence is lower in women than in men at all ages (Perez-Lopez et al., 2010). Furthermore, women's age of CHD onset appears on average about 10 years later. This is widely attributed to the fact that men have less favorable CHD risk factors (e.g., plasma lipid profile) compared to women. Mean levels of protective high-density lipoprotein cholesterol are lower, while triglyceride levels are higher in men than in women.

It is possible that number of genes involved in lipid metabolism, such as Apolipoprotein (Apo) E, as well as their SNP, may be expressed in a sexually dimorphic manner (Kolovou et al., 2009). It has recently been reported that sex-specific polymorphisms exist, associated to lipid metabolism and adiponectin activity (Ordovas, 2007; Anagnostopoulou et al., 2009; Kallio et al., 2009). Some of these differences associated to sex are probably not directly related to the activity sex hormones, as suggested by the fact that their effects have been also observed in postmenopausal women (Perez-Lopez et al., 2010).

Among the polymorphisms that have been reported to have sex-specific characteristics, few are of particular nutritional interest such as the allelic variants encoding for Cholesteryl ester transfer protein (CETP, TaqIB, and 1405V)(Anagnostopoulou et al., 2009), Lipoprotein Lipase (LPL, S447X) (Anagnostopoulou et al., 2009), peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α, Gly482Ser) (Okauchi et al., 2008), Insulin-like growth factor binding protein 5 (IGFBP5, rs9341234, rs3276, and rs11575134) (Kallio et al., 2009), Apolipoprotein A1 (APOA1), and Apolipoprotein E (APOE)(Kolovou et al., 2009).

The real penetrance of these allelic variant in sex-specific risk of disease is still controversial. An illustrative example is PGC-1α, which was first identified as a coactivator of PPARγ a transcription factor involved in the regulation of adaptive thermogenesis (Puigserver et al., 1998) and other aspects related to energy metabolism, such as the control mitochondrial biogenesis, the oxidative breakdown of energy substrates and glucose homeostasis (Soyal et al., 2006). In particular, the Gly482Ser polymorphism of PGC-1α has been found to be associated with type 2 diabetes, obesity, and hypertension. The strength of this association has been reported to be significantly sex-dependent (Esterbauer et al., 2002; Andersen et al., 2005). It has been reported that the Gly482Ser variant of PGC-1α gene affects plasma adiponectin levels in men, but not in women (Okauchi et al., 2008). In this study, no differences in adiponectin levels were observed between women bearing the Gly482Ser allele and

Table 2 Allelic variants having either a different penetrance or a different prevalence between sexes

Gender genes	SNP	References
Hormone sensitive lipase	HSLi6	(Hoffstedt et al., 2001), (Magre et al., 1998)
Apolipoprotein E	$\varepsilon1, \varepsilon2, \varepsilon3$	(Kolovou et al., 2009)
Cholesterylester transfer protein (CTEP)	TaqIB, 150V	(Anagnostopoulou et al., 2009)
Lipoprotein lipase (LPL)	S447X	(Anagnostopoulou et al., 2009)
Insulin-like growth factor binding protein 5 (IGFBP5)	rs9341234, rs3276, rs11575134	(Kallio et al., 2009)
Peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α)	Gly482Ser	(Okauchi et al., 2008)

those bearing the "wild type." On the other hand, a significant influence of Gly482Ser polymorphism on plasma adiponectin level in men, was observed and in particular, the Ser variant was associated with lower adiponectin levels. Even though the Gly482Ser variant is present at the approximately same frequency in men and in women, its effects are only expressed in men. This might indicate either a role for hormones or the involvement of a Y-chromosome-linked modulation. A similar gender-specific effect has been observed for other SNPs including a male-specific association of the *APOE2* and *APOE4* alleles with cardiovascular disease (Lahoz et al., 2001). Some of the allelic variants having either a different penetrance or a different prevalence between sexes are listed in Figure 2.

In conclusion, the effect of specific polymorphisms could be the result of a complex interaction involving genes, environmental factors and sex hormones. Unfortunately, in spite of some clear evidence, available data addressing sex-specific effects of polymorphisms involved in metabolism and disease risk are scarce and do not allow a robust evaluation of this aspect.

CONCLUSIONS

Men and women are different in many ways besides their obvious roles in reproduction. Differences clearly exist, related to a differential expression of specific genes acting throughout the whole life and to the drifting effect of sexual hormones, mainly acting from sexual development to menopause. This review considered the large number of evidences indicating significant sex-related differences in energy and macronutrient metabolism within many tissues and organs resulting in a distinct metabolic profile associated with different risk of disease and possibly with sex-specific nutritional requirements. Despite these indications we propose that the lack of a specific sex-oriented approach has significantly affected and probably biased nutritional sciences.

The striking difference between sexes clearly appears to be not only the expression of cultural and behavioral bias, but also the effect of significant differences at biochemical and physiological level. In spite of this evidence, nutritional sciences seem so far to have underestimated the effect of sex in biochemical and physiological mechanisms related to nutrient utilization. As consequence of this weakness, nutritional, and educational policies addressing the optimal nutrition for the reduction of disease risk that are very rarely gender-oriented and are usually limited to pregnant and lactating women.

Throughout this review, we have tried to highlight some of the aspects related to nutrient metabolism and affected by sex, either specifically concerning the effect of sex hormones or determined by sex-specific differences in metabolic pathways independent on their activity.

Some of the major aspects concerning the involvement of sexual hormones in many of these differences have been considered and in particular the metabolization of nutritional fats and in the distribution of fat depots, glucose homeostasis, and amino acid transport and protein metabolism. Moreover, in some of these sex specific events and in the nutrition-health relationship, also the effect of epigenetic response to environmental and nutritional factors and genetic variants (SNPs) and having either a different penetrance or a different prevalence between sexes are probably involved.

We hope that some nutritional aspect associated with the complexity of the biological system "female" together with the scarcity of data in the literature, clearly emerged.

Further investigations on the potential role of gender with the final target of improving human health are warranted. High throughput methodologies in association with "*Omic*" and system biology approaches will obviously play a pivotal role in this context, providing a tool to carry over a "problem driven" research, taking into account the combined complexity of the interaction between gender-associated differences in the genome, nutrition and health.

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