Proceedings of the Nutrition Society (2020), **79**, 210–218 doi:10.1017/S0029665119001022
 First published online 25 July 2019

The Nutrition Society Spring Meeting was held at Abertay University, Scotland, on 1–2 April 2019

Conference on 'Inter-individual differences in the nutrition response: from research to recommendations'
Symposium 2: Sex differences in nutrient availability and health

Different physiological mechanisms underlie an adverse cardiovascular disease risk profile in men and women

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CVD affect about one-third of the population and are the leading cause of mortality. The prevalence of CVD is closely linked to the prevalence of obesity because obesity is commonly associated with metabolic abnormalities that are important risk factors for CVD, including insulin resistance, pre-diabetes, and type-2 diabetes, atherosclerotic dyslipidaemia, endothelial dysfunction and hypertension. Women have a more beneficial traditional CVD risk profile (lower fasting plasma glucose, less atherogenic lipid profile) and a lower absolute risk for CVD than men. However, the relative risk for CVD associated with hyperglycaemia and dyslipidaemia is several-fold higher in women than in men. The reasons for the sex differences in CVD risk associated with metabolic abnormalities are unclear but could be related to differences in the mechanisms that cause hyperglycaemia and dyslipidaemia in men and women, which could influence the pathogenic processes involved in CVD. In the present paper, we review the influence of a person's sex on key aspects of metabolism involved in the cardiometabolic disease process, including insulin action on endogenous glucose production, tissue glucose disposal, and adipose tissue lipolysis, insulin secretion and insulin plasma clearance, postprandial glucose, fatty acid, and triglyceride kinetics, hepatic lipid metabolism and myocardial substrate use. We conclude that there are marked differences in many aspects of metabolism in men and women that are not all attributable to differences in the sex hormone milieu. The mechanisms responsible for these differences and the clinical implications of these observations are unclear and require further investigation.

Insulin resistance: Dyslipidaemia: Metabolic syndrome: Diabetes

CVD, including atherosclerosis, hypertension, myocardial infarction, stroke and heart failure, affect about 10 % of young and middle-aged (<65 years) and about 30 % of older (≥65 years) adults and are the leading causes of mortality, accounting for >25 % of all deaths[1–3]. More than 80 % of CVD-related deaths are due to IHD and stroke[3]. The prevalence of CVD is closely linked to the prevalence of obesity because obesity is commonly associated with metabolic abnormalities that are important risk factors for CVD, including insulin resistance, pre-diabetes, and type-2 diabetes (T2D), atherosclerotic dyslipidaemia, endothelial dysfunction and hypertension[4–13]. Insulin is a key regulator of glucose and lipid metabolism and also regulates sympathetic nerve activity and endothelial function; accordingly, resistance to the effects of insulin is a key pathogenic mechanism involved in CVD[14]. In addition, increases in plasma glucose and TAG *per se* are directly involved in causing the cellular pathogenic changes associated with hypertension and atherosclerosis[15,16].

Premenopausal women have a more beneficial traditional CVD risk profile (lower fasting plasma glucose[17–22] and less atherogenic lipid profile, characterised by lower plasma TAG and Apo-B containing particles, higher HDL-cholesterol, and more large and fewer small HDL particles[19,23]) and a lower

Abbreviations: DNL, *de novo* lipogenesis; IVGTT, intravenous glucose tolerance test; OGTT, oral glucose tolerance test; T2D, type-2 diabetes.
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absolute risk for CVD than men. The observed sex differences in the metabolic CVD risk profile are attributed to the sex hormone milieu, particularly the protective effect of oestradiol, but it is becoming clear that chronological age *per se* has a major and possibly greater influence on cardiometabolic function in women than menopause[24–28]. In addition, the relative risk for CVD associated with hyperglycaemia and dyslipidaemia is several-fold higher in women than in men[5,7,10,12,29–33]. A meta-analysis of sixty four studies, including a total of 858 507 people, found the relative risk for CVD associated with T2D is about 45 % greater in women than in men[29]; another, smaller meta-analysis, which focused on young and middle-aged (<60 years) adults only, found the relative risk for CVD associated with T2D is approximately three times as high in women than men[30]. Moreover, women with atherosclerotic dyslipidaemia (hypertriglyceridaemia and/or low HDL-cholesterol) have a two to four times greater risk for CVD than women with normal plasma lipids whereas atherosclerotic dyslipidaemia increases the risk for CVD by only 25–50 % in men[5,7]. The reasons for the sex differences in absolute CVD risk and CVD risk associated with increased glucose and TAG concentrations are unclear but could be related to differences in the mechanisms that cause hyperglycaemia and dyslipidaemia in men and women, which could influence the pathogenic processes involved in CVD. For example, the CVD risk associated with increased plasma TAG concentration is not simply determined by the total amount of TAG but dependent on the number of circulating TAG-containing lipoprotein particles at any given TAG concentration (i.e. lots of small TAG-poor *v.* few large, TAG-rich particles), and the T2D risk associated with impaired glucose tolerance depends on the shape of the plasma glucose profile after glucose ingestion, which is likely determined by variations in insulin secretion, plasma clearance and target tissue action[34–40]. In the present paper, we will review and highlight important differences in insulin kinetics and action, basal and postprandial glucose and lipid metabolism and myocardial substrate use between men and women.

Regulation of plasma glucose and TAG concentrations

Plasma glucose concentration is maintained by a balance between hepatic, and to a lesser extent, renal glucose production, meal glucose appearance in plasma and tissue glucose uptake. Insulin is a major regulator of endogenous glucose production and tissue glucose uptake (see[41–43] for excellent and detailed reviews). Insulin suppresses endogenous glucose production, both by acting directly on hepatocytes, and indirectly by inhibiting glucagon production and adipose tissue lipolysis[43]. Endogenous glucose production is very sensitive to the inhibitory effect of insulin and small increases in plasma insulin above basal values are sufficient to completely suppress it[44–46]. Insulin stimulates tissue (predominantly muscle) glucose uptake in a dose-dependent manner and the maximal stimulatory effect of insulin on glucose disposal far exceeds the normal postprandial rise in plasma insulin[44]. Insulin is also a potent inhibitor of adipose tissue lipolysis and fatty acid release into plasma, and small increases in plasma insulin above basal values are sufficient to completely suppress it[45,47,48]. Insulin also regulates hepatic TAG synthesis and secretion, both directly and indirectly by regulating adipose tissue lipolysis. Insulin stimulates hepatic *de novo* lipogenesis (DNL), inhibits VLDL-particle (Apo-B-100) and TAG secretion, and regulates the availability of adipose-derived fatty acids for hepatic TAG synthesis[41,49]. In healthy people, insulin secretion, plasma insulin clearance and insulin sensitivity are tightly coordinated and both insulin secretion and insulin clearance often change simultaneously in opposite directions to compensate for changes in insulin sensitivity; relative insulin insufficiency due to an imbalance among insulin secretion, plasma clearance and sensitivity causes an increase in plasma glucose, fatty acid and TAG concentrations, and ultimately pre-diabetes, T2D and atherosclerotic dyslipidaemia[50–52].

Basal plasma glucose concentration and flux in men and women

Plasma glucose concentration after an overnight fast is generally slightly (about 10 %) lower in women than in men[17–22,53], but it is unclear whether this is due to less glucose production or more efficient plasma clearance in women than in men. The results from studies that evaluated basal endogenous glucose production are equivocal. In most studies basal endogenous glucose production, expressed per kg body weight or per kg fat-free mass, was not different in men and women, irrespective of adiposity status and age[54–62]. However, in some studies, basal endogenous glucose production, expressed per kg body weight or fat-free mass was less[18,63] and in others it was greater[64,65] in women compared with age-matched men. The reasons for the differences in results among studies are unclear but are likely related to differences in the prevailing plasma insulin concentration (because insulin is a potent inhibitor of endogenous glucose production[45]) and the duration of fasting, which affects hepatic glucose production differently in men and women[55,66].

Basal plasma NEFA concentration and flux in men and women

Plasma NEFA concentration after an overnight fast is generally greater in women than men[53,67–69]. The difference in NEFA concentration is largely due to the greater fat mass relative to fat-free mass, not differences in adipose tissue lipolytic activity and/or plasma clearance rate (reviewed later), in women than in men. We measured NEFA appearance rate in plasma, an index of adipose tissue lipolytic activity[70], in lean, overweight and obese (including severely obese) men and women and found basal NEFA appearance rate in plasma, is directly related to fat mass, and the relationship between fat mass

https://doi.org/10.1017/S0029665119001022 Published online by Cambridge University Press

and NEFA appearance in plasma is not different in men and women[68]. However, NEFA appearance rate in relationship to fat-free mass, or unit of plasma volume, or resting energy expenditure is approximately 50 % greater in women than in men[68,71,72] because women have more fat mass than men for any given amount of fat-free mass[73], and fat-free mass is the primary determinant of resting energy expenditure[74,75].

Insulin action on glucose metabolism in men and women

Potential sex differences in insulin action on glucose metabolism have been evaluated by using the homoeostasis model assessment of insulin resistance (e.g.[76,77]), the oral glucose tolerance test (OGTT) (e.g.[18,78,79]), the intravenous glucose tolerance test (IVGTT) (e.g.[21,22]) and the gold-standard hyperinsulinaemic-euglycaemic clamp technique, with or without simultaneous glucose tracer infusion (e.g.[18,47,54,57,58,80–83]). We focus on the results from studies that used the hyperinsulinaemic-euglycaemic clamp procedure in conjunction with glucose tracers (stable isotope- or radio-labelled) to distinguish the effects of insulin on glucose production and glucose disposal (not those that only report the *M*-value, i.e. the glucose infusion rate during the clamp) and those that used the arteriovenous balance technique or dynamic positron emission tomography imaging to provide a direct measure of tissue glucose uptake rates. The homoeostasis model assessment of insulin resistance and the IVGTT-derived insulin sensitivity indices do not provide direct information about the effect of insulin on organ-specific glucose kinetics and the OGTT provides a standard 75 g dose of glucose to subjects regardless of body size, which makes the interpretation of the results difficult because women are generally smaller than men[79,84,85].

Insulin action on endogenous glucose production

Endogenous glucose production is very sensitive to changes in plasma insulin and even small increases in plasma insulin concentration above values observed after an overnight fast can almost completely inhibit it[45,86]. A study that used a relatively low-dose insulin infusion rate that sub-maximally suppressed endogenous glucose production found endogenous glucose production was more sensitive to the inhibitory effect of insulin in women than men (greater relative suppression in women)[57]. Several other studies evaluated the effects of higher (near maximally suppressive) doses of insulin on endogenous glucose production and found near maximally suppressed endogenous glucose production rates were not different in men and women[18,54,58].

Insulin action on glucose disposal

Comparing whole body glucose disposal rates in men and women is difficult because of differences in body size and body composition in men and women. In healthy lean men, skeletal muscle accounts for the majority (>75 %) of whole body insulin-stimulated glucose disposal[86,87]. However, both muscle and adipose tissue are highly sensitive to insulin[88–90] and insulin-stimulated tissue glucose uptake rates in various adipose tissue depots range from 25 to >50 % the rates measured in muscle[63]. Accordingly, the contribution of adipose tissue to total (whole body) glucose disposal depends on a person's adiposity. Whole body insulin-stimulated glucose disposal rate expressed per kg fat-free or lean body mass and adjusted for plasma insulin concentration was often not different in men or age-matched (young or older) women[47,57,81] but glucose uptake rate per leg lean mass (arterio-venous-balance technique) or uptake into muscle (assessed by using dynamic positron emission tomography imaging) was greater in lean women than in lean age-matched men[54,82,83].

NEFA-induced insulin resistance of glucose metabolism in men and women

Plasma NEFA are important negative regulators of insulin action in liver and muscle. An experimentally-induced (intravenous lipid and heparin infusion) increase in plasma NEFA concentration before and during a hyperinsulinaemic-euglycaemic clamp impairs insulin action in liver and muscle in a dose-dependent manner[91–94]. The adverse effect of NEFA on insulin action lasts for almost 4 h after cessation of lipid infusion[95]. The observed greater insulin sensitivity of both endogenous glucose production[57] and muscle glucose disposal[54,82,83] in women compared with men is therefore intriguing considering basal NEFA release from adipose tissue in relationship to fat-free mass is markedly greater in women than in men[68,71,72]. Several studies therefore tested the susceptibility of men and women to NEFA-induced insulin resistance. In some studies, women were less susceptible to NEFA-induced insulin resistance of glucose disposal[54,58], whereas others reported no sex difference in NEFA-mediated insulin resistance[94,96]; however, this could have been due to statistical power because a trend for a lower impairment in women than in men (46 *v.* 60 % impairment) was observed[96]. Only one study evaluated the effect of increased plasma NEFA concentration on insulin-mediated suppression of endogenous glucose production and found NEFA impaired it similarly in men and women[58].

Insulin action on adipose tissue lipolysis in men and women

Adipose tissue is very sensitive to the antilipolytic effect of insulin[48], so even small differences in plasma insulin concentration can have marked effects on NEFA appearance in plasma. The results from studies that evaluated the effect of sex on insulin-mediated suppression of NEFA release into the circulation are inconsistent and difficult to interpret because different doses of insulin were used and plasma insulin concentrations were either not reported or markedly (about 30 %) different in men and women[47,97,98]. However, one of these studies

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evaluated the dose–response relationship between plasma insulin concentration and NEFA rate of appearance in plasma in lean and overweight and obese men and women and found the half-maximum effective insulin concentration was not different in men and women but greater in obese than non-obese subjects[47], suggesting no sex differences in insulin sensitivity of adipose tissue lipolysis but obesity-associated insulin-resistance in both men and women.

Insulin secretion in men and women

A large cohort study that included 380 healthy young subjects found plasma C-peptide concentration (an index of insulin secretion) after an overnight fast was greater in women than men[21]. Potential sex differences in glucose-stimulated insulin secretion have been evaluated by using both IVGTT and OGTT. During the IVGTT, a body weight-adjusted dose of glucose is provided, whereas the same standard dose of glucose (75 g) is given to everyone during the OGTT, which makes the interpretation of the results from OGTT difficult, because women are generally smaller than men[79,84,85]. The acute C-peptide response to an intravenous glucose challenge was not different in men and age-matched women[21], but the acute insulin response was greater in women than men[21,22], suggesting similar glucose-induced insulin secretion but impaired insulin clearance in women compared with men (reviewed in more detail later). The interpretation of the results from studies that evaluated insulin secretion after mixed meal ingestion[64,80] is complicated because different meals were used in different studies and meal energy and carbohydrate contents were not always adjusted for differences in body weight and energy expenditure in men and women. One study provided a body weight adjusted meal (41·84 kJ/kg and 1·2 g dextrose/kg) to both young and older men and women[64] and found the early rise in plasma C-peptide was not different in women and men, but women had slightly higher C-peptide concentrations during the later postprandial period (about 60 min after starting the meal).

Insulin clearance in men and women

The effect of sex on plasma insulin clearance is unclear because of conflicting results from different studies. A study that used the hyperinsulinaemic-euglycaemic pancreatic clamp technique in conjunction with arterial and hepatic vein blood sampling in young and older adults found whole body insulin clearance was greater in women than in men, and this was due to greater non-splanchnic insulin clearance in women whereas hepatic/splanchnic insulin clearance was lower in women than in men[99]. Another study reported impaired steady-state insulin clearance during a hyperinsulinaemic-euglycaemic clamp in women compared with men, but insulin clearance was calculated as the insulin infusion rate divided by plasma insulin concentration[80], which ignores residual endogenous insulin secretion during the clamp[100]. Studies that used a mathematical modelling approach to estimate whole body and regional plasma insulin clearance after mixed meal ingestion found postprandial non-splanchnic insulin clearance was greater in young Caucasian women than in men and splanchnic insulin clearance was significantly less or tended to be less in women than in men[64]; however, in young Asian and older Caucasian subjects, plasma insulin clearance rates were not different in women and men[64,80]. Data obtained during an IVGTT suggest impaired insulin clearance in women compared with men because the acute C-peptide response, which provides a measure of insulin secretion, was not different in men and women but insulin concentration was greater in women than in men[21].

Postprandial glucose kinetics in men and women

Postprandial glucose kinetics in young and older men and women were evaluated by using a triple tracer mixed meal metabolic testing protocol[64]. The meal provided 41·84 kJ/kg and contained 1·2 g dextrose/kg. Endogenous glucose production was rapidly and nearly completely suppressed during the first 60 min after meal ingestion and then returned to basal values in both men and women (both young and old). However, meal glucose appearance in plasma was faster in women than in men (both young and old). Differences in glucose absorption in men and women have also been observed during an OGTT[18], but the results cannot be directly compared with the meal test or among men and women because both men and women received 75 g glucose during the OGTT, so women received much more glucose relative to their body weight and metabolic rate than men.

Postprandial fatty acid kinetics in men and women

Postprandial endogenous and meal fatty acid appearance in plasma in men and pre-menopausal women has been evaluated by using a dual tracer (oral and intravenous) mixed meal testing protocol[101]. Meal ingestion suppressed the NEFA rate of appearance in plasma rapidly and nearly completely for almost 4 h in both men and women whereas meal-derived fatty acid appearance in plasma tended to be greater in men than in women[101]. Postprandial lipaemia and the organ distribution and metabolic fate of NEFA entering the systemic circulation from adipose tissue lipolysis and meals are markedly different in men and pre-menopausal women. After an overnight fast, a smaller proportion of plasma NEFA flux is oxidised to CO_2 in women than in men[102], even though women convert plasma NEFA more rapidly to readily oxidised ketones[103]. The greater non-oxidative disposal of NEFA in women appears to be targeted to adipose tissue because a greater proportion of both plasma NEFA and meal-derived fatty acids are stored in subcutaneous adipose tissue in women than in men (about 25 *v.* ≤10 %, respectively) whereas uptake into liver, muscle and visceral fat after mixed or high fat

https://doi.org/10.1017/S0029665119001022 Published online by Cambridge University Press

meal ingestion is not different in men and women[104–108]. The postprandial increase in plasma TAG after consuming a mixed or high fat meal is less in women than in men, even though the same amount of meal fat is oxidised in women and men[108–110] and less meal fat is cleared by splanchnic tissues in women than in men[111]. The difference in postprandial lipaemia between women and men was observed regardless of whether or not the meal was adjusted for individual subject's energy needs and therefore smaller relative to body weight in men than women. These results suggest markedly impaired peripheral TAG clearance after meal intake in men compared with women. In addition, it was found that adding carbohydrates to an oral lipid load decreased postprandial lipaemia in women but not in men[112]. The differences in postprandial lipid metabolism in men and pre-menopausal women are at least in part due to differences in the sex hormone milieu[113–115]. However, an independent effect of chronological age on postprandial lipaemia has also been observed and it was as pronounced, if not more pronounced than that of menopause[25]. Moreover, subcutaneous adipose tissue fatty acid storage is even greater in postmenopausal than premenopausal women[116], suggesting the observed sexual dimorphism in adipose tissue fatty acid storage is not due to differences in female sex steroids.

Basal hepatic lipid metabolism in men and women

In a series of studies, we evaluated VLDL-TAG and VLDL-Apo-B-100 kinetics by using stable isotope labelled tracer techniques in conjunction with compartmental modelling analysis in lean and obese men and women. The results from these studies revealed that a person's sex affects the kinetics of both the particle (Apo-B-100) *per se* and the TAG moiety of particles, often independently suggesting differences in the lipid load of particles. The differences between men and women are not only due to differences in the sex hormone milieu and are dependent on subjects' adiposity status. We found: (i) lean young women produce fewer but TAG-richer VLDL particles than men[69,72,117], (ii) ovarian hormone deficiency after menopause increases VLDL-TAG but not VLDL-Apo-B-100 (VLDL particle) secretion rate[118], (iii) testosterone treatment has no effect on VLDL-TAG and VLDL-Apo-B-100 kinetics, but oestradiol given to postmenopausal women with obesity stimulates VLDL-TAG plasma clearance[119,120], (iv) increased VLDL-TAG concentrations in obese compared with lean men results from over-secretion of VLDL-TAG whereas increased VLDL-TAG concentrations in obese compared with lean women results in part from VLDL-TAG over-secretion but mostly from impaired VLDL-TAG removal from plasma[69,117] and (v) obese women, but not obese men, are resistant to the inhibitory effects of combined hyperglycaemia–hyperinsulinaemia on hepatic VLDL-TAG secretion whereas no differences in the hyperglycaemia–hyperinsulinaemia induced suppression of VLDL-TAG secretion was observed in lean men and women[121]. A higher VLDL-TAG secretion rate in women with abdominal obesity compared with lean women was also observed by others[122] and was mostly due to an increase in the secretion of large and to a lesser extent small VLDL (50 and 12 % increase, respectively). The VLDL-TAG plasma clearance rate in that study was also about 15–20 % less in obese compared with lean women, but the difference did not reach statistical significance[122]. In addition, it was found that menopause increased hepatic TAG secretion specifically in the small VLDL fraction, and decreased or tended to decrease the secretion of both small and large VLDL particles[122]. The observed differences in the VLDL-TAG secretion rate between men and women are most likely due to differences in the incorporation of systemic plasma fatty acids into VLDL-TAG[72], rather than differences in hepatic DNL[110].

Effect of fructose ingestion on hepatic *de novo* lipogenesis in men and women

Fructose stimulates hepatic DNL and high fructose consumption is associated with hepatic steatosis and hypertriglyceridaemia[123–125]. Consumption of a high- compared with a low-fructose drink (containing 100 g sugar with either 60 or 20 % fructose) significantly increased postprandial hepatic DNL in women (peak DNL about 20 % *v.* about 7 %) but not in men (about 7 % after both meals)[126]. This suggests women are more susceptible to fructose-induced hepatic steatosis and non-alcoholic fatty liver disease. It is worth noting that the stimulatory effect of fructose on DNL is most likely a secondary phenomenon because very little fructose is directly converted to fatty acids and fructose-to-fatty acid conversion was only observed in men but not in women[65]. This is consistent with recent findings that suggest fructose metabolism occurs predominantly in the small intestine, where it is converted to glucose, lactate and glycerol[127].

Myocardial substrate utilisation in men and women

A series of elegant studies that used dynamic positron emission tomography imaging have demonstrated marked differences in myocardial substrate use in men and women. Myocardial oxygen consumption is greater in healthy lean women than healthy lean men and women's hearts use less glucose and fewer dietary fatty acids as a source of energy than men[106,128,129]. Obesity reduces myocardial glucose uptake and oxidation in men, but not in women[129]. Insulin-stimulated myocardial glucose uptake rate, conversely, is not different in healthy young men and women[83]. These findings could have important clinical implications, because myocardial perfusion and fuel use are directly linked with cardiac function[130,131].

Conclusion

There are marked differences in many aspects of glucose and lipid metabolism in men and women. Women

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compared with men: (i) are more sensitive to the inhibitory effect of insulin on glucose production and the stimulatory effect of insulin on muscle glucose disposal, (ii) have greater adipose tissue NEFA release relative to fat-free mass and resting energy and are less susceptible to the adverse effect of NEFA on insulin action in muscle, (iii) have altered meal glucose absorption kinetics, possibly due to different gastric emptying rates[132], (iv) have greater basal and postprandial non-oxidative fatty acid disposal and fatty acid storage in adipose tissue and reduced postprandial lipaemia and (v) are more susceptible to fructose-induced DNL. Moreover, hepatic and plasma lipid metabolism is markedly affected by sex and the observed metabolic differences between men and women depend on subjects' adiposity and age. Conversely, no major differences between men and women have been observed for the antilipolytic effect of insulin and acute glucose-induced insulin secretion. The effect of sex on plasma insulin clearance is unclear because of conflicting results from different studies. We conclude that sex needs to be considered when interpreting data reported in the literature and planning new studies. Carefully designed studies are needed to determine the mechanisms responsible for the observed sexual dimorphism in metabolism and to disentangle the effects of chronological and biological (pre/post menopause) age on metabolism in women.

Financial Support

The authors received salary support from NIH grants DK115400, DK121560, DK56341 (Washington University School of Medicine Nutrition and Obesity Research Center), and UL1 TR000448 (Washington University School of Medicine Clinical Translational Science Award), a grant from the American Diabetes Association (ICTS 1-18-ICTS-119) and the Atkins Obesity Award while working on this manuscript.

Conflict of Interest

None.

Authorship

The authors were jointly responsible for all aspects of preparation of this paper.

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