Sex-Gender Differences in Diabetes Vascular Complications and Treatment

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Abstract: Diabetes mellitus and cardiovascular diseases act as two sides of the same coin: diabetes is an important risk factor for cardiovascular disease while patients with ischemic cardiovascular diseases often have diabetes or pre-diabetes. As firstly shown by Framingham study, diabetic women have an increased cardiovascular risk about 3.5 fold higher than non diabetic women, against an increase of "only" 2.1 fold found in male subjects. In view of the impact of sexual hormones on glucose homeostasis, the molecular pathways involved in insulin resistance suggest a sex-gender specificity mechanism in the development of diabetic complications leading to the unmet need of sex-gender therapeutic approaches. This has also been seen in other diabetic complications such as renal diseases, which seems to progress at a faster rate in females compared with males and women benefit less from treatment than do men. Of note, none of the trials done so far are primarily designed to assess sex-gender differences in the benefit from a specific intervention strategy, de facto excluding fertile women from experimentation. In order to provide a more evidence based medicine for women and to reach equity between men and women, sex-gender epidemiological reports, preclinical and clinical research are mandatory to evaluate the impact of gender on the outcomes and to improve sex-gender awareness and competency in the health care system. Future studies should consider sex-gender differences in the setting of randomized controlled trials with drugs.

Keywords: Cardiovascular diseases, diabetic complications, diabetes mellitus, risk factors, sex-gender differences, therapy.

INTRODUCTION

Gender is considered a social construct that generally transforms a female in woman and a male in man, whereas sex is generally considered the biological aspect of femininity and masculinity. In view of the numerous interactions existing between sex and gender, that some of us have already discussed [1 and literature cited therein], sometimes it is difficult to divide sex from gender, therefore we prefer to adopt sex-gender. In fact, differences and inequalities in health status often derive from both biological differences and social, cultural and political arrangements in society (Fig. (1)).

Historically, most experimental, clinical and epidemiological studies are performed in men and the results are simply applied to women [2]. Consequentially, much of the human data found in medical texts represent the environment in which the testing has been conducted and the largest number of ''healthy'' individuals have been provided in medical schools and military institutions. Therefore, most of the data present in physiology textbooks represent young healthy, 70-kg Caucasian males [3] and literature cited therein]. Consequently, most modern guidelines are based on studies predominantly conducted in Caucasian adult men or, at the best, mostly post-menopausal women.

Actually, it is emerging that causes, risk factors, clinical manifestations, prognosis, therapeutics and outcomes are highly influenced by sex-gender [4] suggesting that a wider sex-gender-sensitive knowledge is necessary to provide the basis for specific evidence-based interventions both for men and women. Here, we address sex and gender-specific aspects in diabetes mellitus (DM) and its vascular complications, which represents an increasing burden of this century and a great challenge to public health.
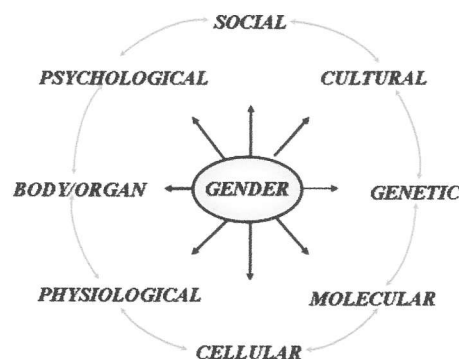

Fig. (1). Biological, psychological and social generators of sex-gender differences in humans.

EPIDEMIOLOGY AND DRIVING FORCES BEHIND DM2 EPIDEMIC DIFFUSION

Epidemiology

A classical example of sex-gender differences is the so called idiopathic diabetes, which has a very high (75%) male

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predominance [5]. Regarding, the more common forms of DM: type 1 and type 2 DM (DM1 and DM2) [6], it is important to recall that DM1 is characterized by a female: male ratio that is approaching 1:1 with a slight predominance of men [7]. Notably, the male predominance starts after puberty [5]. Importantly, the frequency of antibodies against glutamic acid decarboxylase (GADA) depends on sex, with female patients having higher levels of GADA and a more severe loss of β cell function than male patients with the same age at diagnosis [8].

DM2 is the most common endocrine disease with steadily increasing incidence reaching epidemic proportions [9]. It is estimated that by the year 2030 about 366 million people will have DM2 and, despite all the efforts to control it, the number of patients will increase from the present 2.8% to 4.4% of the human population [10]. The total number of women with DM2 is 10% higher than in men, as well as the number of women with impaired glucose tolerance (IGT), which is 20% higher than in men [11].

Driving Forces Behind DM2

The driving forces behind the high prevalence of DM2 are family history, age, obesity, unhealthy lifestyle, social and psychological factors.

Obesity/Nature of Adipose Tissue/Metabolic Impact

The WHO report [12] shows comparable rates of overweight individuals between both sexes in Europe, but obesity (body mass index (BMI) >30) ranges between 7 and 36% in women and between 5 and 23% in men. Indeed, men have predominantly visceral adiposity, which is associated with a more adverse metabolic profile and with a higher risk to develop atherosclerosis than the accumulation of subcutaneous fat typical of the female sex [13]. However, in women but not in men, weight changes after 18 years are linearly related to impaired fasting glucose (IFG), a condition related as pre-diabetes [14]. Nevertheless, the predominantly visceral adiposity in men in comparison with women, inflammatory parameters rise only in women, supporting the concept that weight gain triggers clusters of changes in cardiovascular risk factors in a sex-gender dependent way [15]. Additionally, obesity seems to be a more prominent risk factor for the development of DM in women than in men [16].

It is well acknowledged that women, starting from childhood, are usually more sedentary than men and that their lower physical activity may contribute to the increased prevalence of overweight, obesity and insulin resistance [17]. Pregnancy, a condition of insulin resistance, might also contribute to the higher prevalence of obesity in women (see below).

There are no evident sex-gender differences in the prevalence of DM2 but the number of women with DM (+10%) and its precursor IGT (+20%) has been reported to be slightly higher than in men, who more often feature an isolated IFG [18, 19]. The increased prevalence of altered glucose metabolism in women [19] might be, in part, attributable to different glucose, and lipid metabolism observed in men and

women [1] literature cited therein] and to the higher rate of DM and of pre-diabetes (in particular IGT) in elderly women [20]. Additionally, women are more frequently characterized by postprandial hyperglycaemia than men [19, 20], a condition, typical of IGT, which is associated with increased oxidative stress and a higher cardiovascular risk as stated in Framingham Offspring Study [21] and in successive study [22]. It has been suggested that a prolonged gut absorption might contribute to the higher prevalence of postprandial hyperglycaemia in women as compared to men [23].

Few data are available on sex and gender-related differences in insulin sensitivity and insulin secretion. However, men with IFG or normal glucose tolerance have a more pronounced insulin resistance as compared to women with comparable glucose tolerance status [24, 25]. In contrast, females more often exhibit isolated IGT [19, 20], which is characterized by more prominent defects in first and late phases of insulin secretion [24]. These data are in line with a Danish study showing women to be characterized by higher insulin and lower glucose levels at fasting (-7%) as well as by an increased glucose disappearance rate indicating better insulin sensitivity [26]. Women also show a higher disposition index (the product of insulin sensitivity and insulin secretion). Much of the previous differences in insulin sensitivity depend on body fat, maximal aerobic capacity and use of oral contraceptives [27]. Sex and gender-related differences in the prevalence of the two forms of pre-diabetes (IFG or IGT) reflect in sex-gender specificity of the respective diagnostic tests for the detection of pre-diabetes and also DM2 see below.

It is important to recall that in young age DM2 is far more common in girls than in boys [28-30]. Increasing evidences suggest that girls are more insulin resistant than boys at birth and through early and late childhood [31-34], puberty and adolescence [35-37].

Insulin resistance is considered to be the main cause of the metabolic syndrome characterized by dyslipidemia, hypertension and visceral obesity, and has become a worldwide health issue [38]. Sex-gender differences in metabolic syndrome have been recently reviewed by Regitz-Zagrosek *et al.* [39].

It is believed that the main factor disrupting glucose homeostasis in DM2 is insulin resistance [40], although β cell insulin secretion must be impaired in order to develop DM2.

Hormonal Factors and Aging

There are numerous interactions between sex/reproduction and energy metabolism being energy metabolism differently regulated in men and in women and it is believed that the circulating androgen and estrogen play a role [41]. The increase in life time leads male and women to live part of their life in age-related estrogen or androgen deficiency, which predisposes to metabolic syndrome and DM2 [41].

Testosterone has sexual dimorphic effects on the incidence of DM2: high levels are protective against DM2 in men but have the opposite effect in women, while low levels of testosterone and sex hormone-binding globulin are

associated with the development of DM2 in men [11]. In particular, the prevalence of hypogonadism in men with DM2 is 20% to 60% [42, 43]. Testosterone replacement therapy in hypogonadal men improves insulin sensitivity, decreases abdominal fat mass and disturbances in lipid and glucose metabolism, and has a multidimensional favourable effect on cardiovascular risk profile [44-46], although this has been recently questioned in a special population [47]. On the other hand, hyperandrogenic women develop DM2 (see polycystic ovarian syndrome section), however women with complete androgen insensitivity syndrome have increased total fat mass compared with both female and male age matched control subjects [41].

Social/Psychological Factors

Socio-economic status is an important determinant of health. An association has been evidenced between poverty and DM2 [48-51]. Furthermore an association has been found among deprivation and trauma and DM2 [52] and it has also been suggested that the association is stronger for men than for women [53].

The higher prevalence of DM2 in the low economic status could be attributable to a variety of factors such as obesity and physical inactivity [54, 55]. However, the differences are not fully dependent on differences in obesity and physical activity indicating that other factors are involved [56]. At this regard, it could be important low birth weight, a known risk factor for DM2 [57], that is associated with poverty [57].

Importantly, mental illness is often associated with DM. The prevalence of DM has been reported to be two to four times higher in people with schizophrenia than the general population [58]. A recent Chinese study shows that the overall DM2 prevalence is 20% and 27% in men and in women, respectively, being the increase in body mass index, abdominal obesity and antipsychotic types predictors of DM2 [59]. Indeed, Chinese female schizophrenics have a 1.4 fold greater risk than males for antipsychotic-associated DM2.

The prevalence of DM is also higher in depressed patients. Several investigations have documented that people with DM experience depression from 1.3 to 3 times as often as those without the disorder [60-62]. The association of DM and depression elevates the risks of work loss [63], functional disability [64] and micro- [65] and macrovascular complications [66] increasing health care costs [65]. The depression and DM association is also linked with poorer adherence to medications and self-care activities such as self-monitoring of blood glucose levels and adhering to a proper diet and exercise program [67-70]. In addition, irrespective of their sociodemographic variables, lifestyle or health status, mortality risk is increased among depressed diabetic patients but not among persons without DM [71]. Considering that depression has higher prevalence in women than in men, mental health problem associated with DM could be more relevant in females [72].

A confirmation between DM and mental problems comes also from the association between dementia-Alzheimer's disease (AD) and DM. DM is, in fact, a strong risk factor for

AD [73] and recently it has been proposed to consider AD as a new form of DM: DM3 [74]. The mechanisms for association remain largely unknown, but vascular and brain insulin signaling may contribute to AD progression [75]. Please note that many sex-gender differences are present in AD [76].

Finally, it is relevant to note that in the association between DM2 and mental illness, the disadvantaged social position of patients with mental problems could play a role [50].

HOW DO SEX-GENDER DIFFERENCES IN DM ARISE?

Sexual Hormones and Sex-Gender Differences

The association between estrogens and glucose homeostasis has been debated since 1966, when Wynn and Doar [26] first published their considerations about the effects of oral contraceptives on lipid metabolism and carbohydrate metabolism, which are also sensible to physiological variation of sexual hormones (Fig. (2)). The importance of sexual hormones is confirmed by cyclical variation in plasma lipids and of apolipoproteins during the menstrual cycle in healthy women that has been described by some of us [77]. Therefore, evaluating the lipid risk profile in premenopausal women the phase of the menstrual cycle should be taken into account. Lipids also vary during normal pregnancy and in condition of hormonal stimulation in healthy women [78, 79].
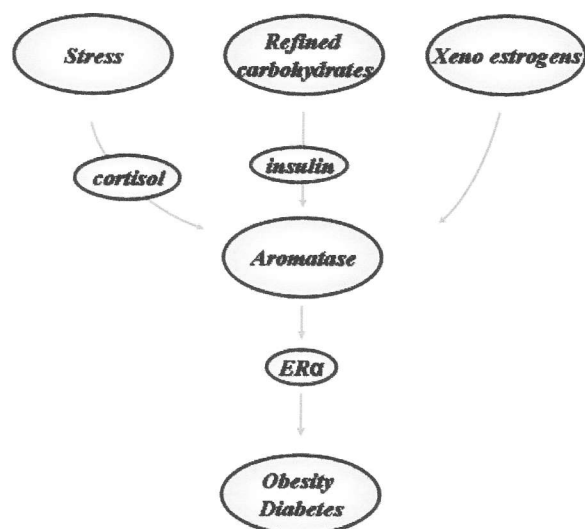

Fig. (2). Role of cortisol, insulin and ERα in the pathogenesis of obesity and DM.

Estrogens influence glucose metabolism (Fig. (3)), which varies during menstrual cycle and pregnancy [80-82] and polycystic ovarian syndrome [83]. Through estrogen receptor (ER) α, estrogens increase the transcription of glucose transporter 4 (GLUT4) and inhibit factors that down regulate GLUT4 [84]. While ERβ has opposite effects, thus the
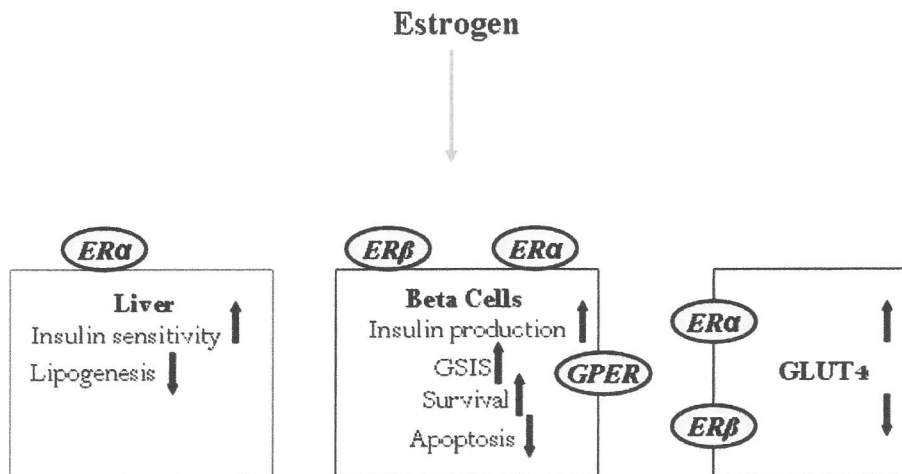
Estrogen

Fig. (3). Schematic representation of some effects of estrogens on glucose metabolism. In liver cells, estrogens through ERα increase insulin sensitivity and decreases lipogenesis. In β cell of pancreas, estrogen through ERβ, ERα and membrane estrogen receptors (GPER) receptors increase insulin production, glucose dependent insulin secretion (GSIS), cell survival and decrease apoptosis. In different cells, estrogens through ERα mediated the increase of GLUT4 transcription and the inhibition of factor for GLUT4 down regulation, while ERβ has the opposite effects.

ratio of ERα/ERβ determines the global effect on GLUT4 expression [11]. Importantly, ERα seems to prevent immunological pancreatic β cell apoptosis and may thus play a role in the development of DM1 [11] (Fig. (4)). A recent human study shows that female sexual hormones may play an important role in the pathogenesis of IFG and IGT, both of which are known to increase the risk of developing DM [85]. The relationship between estrogen and glucose homeostasis is confirmed by the fact that aromatase knockout mice have reduced glucose oxidation, increased adiposity and insulin levels leading to DM2 in the long term [86, 87]. Interestingly, male humans that lack aromatase also have high insulin levels [88]. Briefly, estrogen deficiency may affect glucose regulation and may also increase insulin resistance in estrogen-resistant males as well as in post-menopausal women [11].

Sexual hormones also influence the adipose tissue localization and the secretion of adipokines, which influence the development of insulin resistance [1] and cited literature.
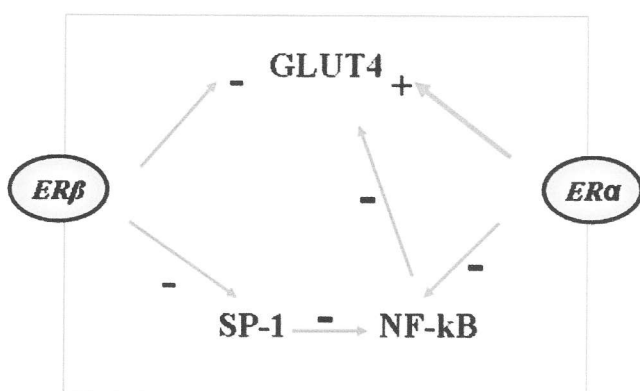

Fig. (4). Schematic representation of estrogen receptors involved in inflammation, insulin resistance and glucose homeostasis (adapted from Szalat, Raz, I, 2008 [11]).

In particular, androgen receptor (AR) is more important in visceral fat, whereas ERα and ERβ are mainly localized in subcutaneous fat [1] and cited literature. In particular, ERα mediate different effects in the two adipose compartment up-regulating antilipolytic a_{2A}-adrenergic receptor in subcutaneous fat but not in visceral fat [11] and cited literature]. The different localization of sexual hormone receptors might explain the different patterns of obesity between men and women [11] and cited literature. The different amount and different distribution of adipose tissue involve the secretion of adipokines such as leptin and adiponectin, which are mainly secreted by subcutaneous fat and both are usually higher in females [11] and cited literature. While visceral fat increases fatty acids and inflammatory cytokines such as tumor necrosis factor-α and interleukin-6, which cause insulin resistance and cardiovascular adverse outcomes resistance [11],1 and cited literature.

Estrogen and testosterone have opposite effect on renin–angiotensin–aldosterone system (RAAS). Estrogen appears to increase angiotensinogen levels and decreases angiotensin receptors type 1 (AT1) renin levels, angiotensin-converting enzyme (ACE) activity, AT1 receptor density, and aldosterone production [11] and cited literature. Additionally, an altered silencing of angiotensin II receptor type 2 (AT2) receptor gene located on X chromosome could induce a different AT2 receptor expression between sex-genders [11] and cited literature and its activity is also estrogen related [11] and cited literature. In fact, estrogen increases AT2 binding in the rat adrenal gland and mouse kidney [48]. In hypertensive rats, AT2 receptor mRNA levels in the kidney are higher in females than in males [11] and cited literature. Importantly, the effect of antagonist of AT1 receptors is greater in females than in males, but this difference is small in AT2 receptor null mice [11] and cited literature. Furthermore, estrogen increases counterparts of the RAAS (*e.g.*, natriuretic peptides, and ANG (1-7). Testosterone effects on RAAS are less clear, however it seems to increase renin

levels and ACE activity [11] and cited literature. Finally, natural progesterone competes with aldosterone for mineral corticoid receptor [89]. The above observation strongly suggests that RAAS function is also controlled by sex hormones.

Genetic Factors

The complexity of inheritance and interaction with the environment makes identification of genes involved with DM2 difficult, however genetic factors also play a role in sex-gender differences in DM. For example, methionine by threonine at amino-acid position 235 (M235T) poly-morphism in the angiotensinogen gene increases the incidence of diabetic nephropathy in male patients with DM2 but not in female patients [90]. AT2 receptor gene is involved in the development of kidney dysfunction and hypertension in DM1 male patients but not in DM1 female patients [91]. In addition, the genetic polymorphisms regarding the thrombospondin 2 gene, the coagulation factor III gene (F3) and the collagen domain containing adiponectin gene and variation in acid phosphatase locus 1 are associated with fasting insulin, and insulin sensitivity in men but not in women [92]. In women, DM is associated with polymorphism of paraoxonase 1 gene [93]. Finally, men, who do not produce endogenous estrogens for a missense mutation in the aromatase gene, develop hypertriglyceridemia and/or insulin resistance, whereas, men with estrogen resistance to ERα deficiency develop hyperinsulinemia and glucose intolerance [5].

The genetic factors should be further explored for a better understanding of their impact on sex-gender difference in DM.

Inflammatory Response

Inflammation is more evident in women with previous gestational diabetes (GD) and DM2. Women with previous GD have, in fact, higher level of plasminogen activator-inhibitor-1 and C-reactive protein [80, 81], while women with DM2 have higher levels of proinflammatory markers (C-reactive protein and interleukin-1 receptor antagonist) than diabetic men. In contrast, no sex-gender differences has been observed in people with normal glucose metabolism [94, 95]. Finally, the adiponectin reduction is significantly more elevated in women than in men when progressing from normal glucose tolerance to prediabetes and DM [96].

Inflammation is also linked to oxidative stress and the control of redox state is a sex-gender process [85] and data indicate that oxidative stress may be more increased in diabetic women than in diabetic men, particularly for what concerns DM1 patients [97-99].

Oxidative stress plays a pivotal role in the development of DM complications, in fact, the diabetic metabolic alterations cause mitochondrial superoxide overproduction in endothelial cells of both large and small vessels, as well as in the myocardium [100]. Reactive oxygen species over-production activates polyol pathway flux, increases formation of advanced glycation end products and expression of the receptor for advanced glycation end products and its activating ligands, produces activation of protein kinase C isoforms and overactivity of the hexosamine pathway and

also directly inhibits endothelial nitric oxide synthase and prostacyclin synthase [100]. These phenomena are involved in the pathogenesis of diabetic complications causing defective angiogenesis in response to ischemia, activating a number of proinflammatory pathways, and causing long-lasting epigenetic activating the so called "hyperglycaemic memory" [100].

Oxidative stress also influences the cell fate including autophagy in a sex-gender specific manner [101-106]. Recently, a defective autophagy has been linked to impaired insulin sensitivity in obesity and DM [107, 108] and upregulating autophagy can combat insulin resistance [109]. Autophagy is inhibited by the insulin amino acid-mTOR signaling pathway *via* both short-term and long-term regulation mechanisms. Short-term inhibition can be produced by mTOR complex 1, which causes phosphorylation and the inhibition of Unc-51-like kinase (ULK1), which is essential for initiation of autophagy [109, 110]. Long-term regulation occurs *via* forkhead transcription factors (FOXO1 and FOX03) [110], which control the transcription of autophagy-related (ATG) genes such as ULK, LC3, which are fundamental for autophagic process, because their activation inhibits insulin induced activation of protein kinase B.

Finally, dysregulation of autophagic process in pancreatic β cell contribute to decrease insulin secretion an indispensable event in the development of DM2 [111]. It appears of interest evaluate whether dysregulation of autophagic process observed in DM2 either in β cells or other tissues linked to obesity and insulin resistance are influenced by sex-gender as occurred in other cells.

SPECIFIC SEX-GENDER RISK FACTORS

In addition, to the largely accepted risk factors for DM2 such as age higher than 45 years, obesity, pre-diabetes, hypertension, hyperlipidemia and vascular diseases, there are other women-specific risk factors such as sex-gender related differences in gene polymorphisms associated with an increased risk of DM2 (see above), ovarian syndrome, previous GD or having delivered a child with birth weight over or equal to 4,500 g [112].

Women Specific Risk Factors

GD

Pregnancy is normally characterized by progressive insulin resistance that begins near mid-pregnancy and progresses through the third trimester to levels that approximate the insulin resistance seen in individuals with DM2 [9]. The fact that insulin resistance rapidly abates following delivery, suggests that the major contributors to this state of resistance are placental hormones, however pancreatic β cells normally increase their insulin secretion to compensate for the insulin resistance of pregnancy [9], if β cells are not able to compensate this insulin resistance, GD develops. In the majority of cases, glucose intolerance disappears after delivery, but up to one third of women will have IFG or DM postpartum [9]. Long-term follow-up studies (over a period of more than 10 years); reveal a stable long-term risk of incidence of DM2 among women with GD ranging from 5% to 50%, depending on the study [113, 114].

Polycystic Ovarian Syndrome

Polycystic ovarian syndrome affects 6–10% of the women of reproductive age, it features an almost three-fold higher risk for the development of GD [115] and is characterized by oligo- or anovulation, ovarian hyper-androgenis and marked insulin resistance independently of the degree of obesity [116]. Metformin, besides the other effects, stimulates GLUT4 translocation [84] and it is able, in some cases, to restore normal ovulatory cycles in women with polycystic ovarian syndrome [117].

Men Specific Risk Factors

In men, factors associated with DM are to be ex-smokers [72] and hypogonadism (see above) and perhaps diabetic mother [118]. GD or pregestational DM could result in growth defects in the offspring. Offspring of diabetic mothers may be macrosomic, small for gestational age and of normal birth weight, depending on the severity of GD, and degree of diabetic control. However, in poorly controlled DM without severe complications, the newborn infants will often be macrosomic [118]. Macrosomic offspring of mothers have at higher risk to develop glucose intolerance later in life [119, 120]. Unfortunately, sex-gender differences are not always reported. However, in a cohort of diabetic pregnancies, some predictors of abnormal birth weight display interaction with the sex of baby and associations are generally more unfavourable to male fetuses [121].

In conclusion, men and women may have specific risk factors and knowing them it is of pivotal importance for health promotion policy and to allow policy makers to draw inferences and conclusions for interventions and planning purposes.

SEX-GENDER SPECIFICITY OF DIAGNOSTIC TESTS

As already mentioned, women have lower prevalence of IFG and higher prevalence of IGT as men, reflecting, as above stated, that in women a prevalence in β cell insulin secretion defect is present [11]. This also occurs in elderly men [11]. Thus screening for DM in women and old men should involve an OGTT with 2-h plasma glucose. Men with IFG have more insulin resistance versus women with IGT who have impaired early and late phases of insulin secretion [11].

CHRONIC COMPLICATIONS

The previous observations *e.g.* the role of sexual hormones in glucose homeostasis suggest that women and men may have different mechanisms to develop diabetic complications. Actually, it is clear that diabetic women lose their normal premenopausal protection against cardio-vascular disease [22, 122] and have more frequent and more severe macrovascular (cardiovascular) complications than men. While the role of sex-gender in the field of micro-vascular complications is still area of uncertainness.

In this review, we will consider sex-gender differences in diabetic microvascular complications only because a) numerous studies have shown a link between micro-and macrovascular disturbances in DM2 patients suggesting a common pathway of developing micro-and macrovascular disturbances [123] b) diabetic nephropathy and diabetic autonomic neuropathy are risk factors for cardiovascular diseases [124-128]. Less is known about the role of retinopathy but recent findings indicate that it is an independent risk factor for the development of the ischemic heart diseases and heart muscle perfusion disturbances [129, 130].

It is also important to recall that nonketotic hyperosmolar coma is diagnosed almost twice in women than men [131], and in another population-based study, the rate of diabetic acidosis in females is 1.5 times that of males [132].

Macrovascular Complications and Cardiac Diseases

DM is not only an endocrine but also a cardiovascular disease. Cardiovascular complications are the leading cause of morbidity and mortality associated with DM, which affects both large and small vessels and hence diabetic complications are broadly classified as microvascular (retinopathy, nephropathy and neuropathy) and macro-vascular (heart disease, stroke and peripheral arterial disease) complications [133-135].

DM confers a markedly increased risk of coronary heart diseases in both women and men [136-139] and importantly diabetic women do not show the decline in cardiovascular mortality that has been observed over the last 30 years in the U.S. population overall and in men with DM [140] and actually the risk for women with DM exceeds that of men [141-143] (see Table 1). In particular, the myocardial infarction mortality rate is 4 times higher in diabetic men and 7 times higher in diabetic women than in individuals without DM [144]. A meta-analysis of 37 prospective studies shows that diabetic women have a 50% increase in cardiovascular mortality compared with men with DM, even after taking into consideration all the cardiovascular risk factors [145].

Table 1. Deaths attributable to DM in different areas of the world (modified from roglic and unwin, 2010 [256]).

Number of Deaths in Males Attributable to DM in the 20-79 Age-Group, 2010	
Africa total males	122,173
Africa total females	210,411
Europe total males	297,600
Europe total females	336,454
America total males	224,500
America total female	260,011
Asia/Pacific Regions total male	1,065,169
Asia/Pacific Regions total female	1,152,700

This situation is not completely explained by traditional biological and psycho-social factors [146, 147] but:

a   in DM1, more girls than boys have a poor DM control contributing to a higher rate of cardiovascular risk factors [148, 149]. This fact might contribute to a higher cardiovascular mortality of diabetic females later in life [150].

b   diabetic females have significantly higher rate of specific risk factors with the exception of smoking and low HDL than males [137].

c   the frequency of nonfatal myocardial infarction is increased before the clinical diagnosis of DM2 [151], women with IGT tend to have a more atherogenic risk profile than men years before the diagnosis of clinical DM [152]. Thus women may stay in a more longstanding atherogenic risk profile before the development of hyperglycaemia [153].

d   diabetic women have a more marked endothelial dysfunction in comparison with diabetic men [154-158]. Importantly, a prospective study shows that E-selectin, ICAM-1, and plasminogen activator inhibitor-1 concentrations are predictive among women but not among men and this is independent of the effects of age, BMI, and homeostasis model assessment–insulin resistance (HOMA-IR), a surrogate index of insulin resistance.

e   inflammation induces great insulin resistance, endothelial dysfunction and oxidative stress and is associated with worse cardiovascular outcomes in women with DM1 [99] and DM2 than in matched men with DM2 [159].

f   diabetic women have a greater degree of fibrinolysis/ thrombosis when compared versus men [146], thus women with DM may be subjected to even more adverse changes in coagulation, vascular function, and cardio-vascular risk factor levels than diabetic men [159-161]. These abnormalities might predispose women to plaque rupture and intraluminal thrombosis, explaining, at least in part, the greater severity and more negative prognosis of ischemic heart disease in diabetic women. Recent clinical trials show that delay in development or prevention of DM is possible, and preventive efforts should occur early in the pre-diabetic state [146, 162, 163].

g   hypertension seems to be more frequent in diabetic women than in diabetic men having a more deleterious effects in women than in men [98, 164] (Fig. (5)). Usually women are less likely than men to achieve blood pressure control, LDL-cholesterol and metabolic control even after a coronary event, underlining the disparity of treatment between the two sexes [165].

h   diabetic dyslipidemia (low HDL, hypertriglyceridemia and increased small LDL particles) seems to be more marked and dangerous in women than in men with DM [98, 164, 165].

i   notably, female diabetic patients do have also an increased prevalence of hypoglycaemic events over the male sex [167] and these phenomena might add justifications of the increased prevalence of cardio-vascular events and mortality among female patients.

j   Framingham Offspring Study evidences the significance of isolated impaired glucose tolerance and postprandial hyperglycaemia for cardiovascular morbidity and mortality [21]. However, there are numerous evidences that isolated impaired glucose tolerance and postprandial hyper-glycaemia are independent cardiovascular risk factors in women only [168].

Thus the stronger effect of DM on the risk of cardiovascular disease in women compared with men might be in part explained by a heavier risk factor burden and a greater effect of blood pressure and atherogenic dyslipidemia in diabetic women. Recent preliminary data suggest that in both men and women with DM the ability to predict the cardiovascular risk is increased using model incorporating HbA1c levels and this effect is far more potent in women [169]. This is in line with another recent paper in which sex-gender differences in HbA1c and fasting plasma glucose are likely to have a true physiopathological background [170]. Without going in details in this discussion if these differences cause an overdiagnosis of DM in female or an underestimation of metabolic control, surely sex-gender
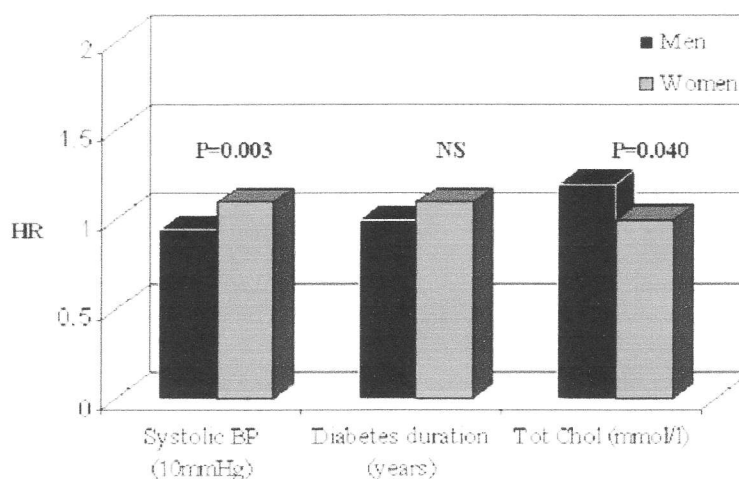

Fig. (5). Sex-gender differences in cardiovascular risk factors in diabetic patients (modified from Juutilainen *et al.*, [166]) BP= blood pressure, HR= hazard ratio, Tot Chol = total cholesterol.

differences in the metabolic parameters do have a role in the different outcomes.

However, it must also be considered nevertheless many therapeutic trials have been conducted, no trials have been conducted into the effects of lowering glucose therapy according to sex-gender [11], thus is questionable of whether all the conclusions that have been obtained in clinical trials conducted in men are equivalent for men and women [11].

If the sex-gender effect is clearly evident on coronary artery diseases, actually it is still disputable the effect of sex-gender on incidence and prognosis of stroke in diabetic patient. A sub-analysis of the United Kingdom Prospective Diabetes Study (UKPDS) and data obtained from a Canadian cohort show that women have less strokes than men with DM2 [171, 172]. However, a British cohort [173] shows an increase in the risk attributable to DM among young women, which decreased with age. A prospective study shows diabetic women having a poorer prognosis with in-hospital mortality rate of 14.9 *vs.* 8.3% in men with DM [174]. Finally, with DM1, there is a higher incidence of stroke in women than in men (26.1 and 17.9%, respectively), not only in the 40–49 years age category but also in other age subgroups [175].

Beyond the classical macroangiopathic complications and hypertension, it is important to recall that DM induces the so called diabetic cardiomyopathy, which appears as a heart failure syndrome and it is still discussing if it is associated with macroangiopathic or macroangiopathic complications or it is derived by direct effect of chronic hyperglycemia that leads to glucotoxicity, which contributes to cardiac injury through multiple mechanisms on cardiomyocytes in absence of hypertension and coronary artery diseases [176]. Sex-gender differences are also seen in diabetic cardiomyopathy and they have been recently reviewed in Ren and Ceylan-Isik AF [177], therefore they are not reported here. Up-to-date, the cellular and molecular basis of intrinsic factors contributing to sex-gender disparity of diabetic cardiomyopathy is essentially unknown. Thus further intensive investigations should be addressed and deserve also in view of the fact that cardiac transplantation is less intensely considered for women [178], however women with dilated cardiomyopathy do as well as men after transplantation.

It is evident that for optimal investigation, diagnosis, prevention and specific treatment of overall cardiac health in diabetic women the previous differences must be acknowledged, planned for, and factored into an effective treatment regimen, which will differ significantly as a function of the patient's sex although further intensive investigations should be addressed.

Microvascular Complications and Sex-Gender Differences

The metabolic alterations linked to DM result also in microvascular complications: retinopathy, neuropathy and nephropathy being the risk to develop them directly proportional to the duration of hyperglycaemia above a certain threshold [110]. Furthermore, in patients with DM, accumulating evidences suggest that small vessel disease is also important for stroke, heart and neurodegenerative diseases such as dementia and AD [179].

Diabetic Neuropathy

This is the most common diabetic complication and as much as 50% of both DM1 and DM2 after 10-15 years of disease might have sign of diabetic neuropathy [180]. Diabetic neuropathy might be autonomic or sensory, while the autonomic form is more associated with cardiovascular mortality, the sensory one may evolve in the diabetic foot with resultant diabetic ulceration and amputation. Few small studies indicate that men with DM2 have more neuropathic complications than women [11, 181-185]. In line with these results, amputation rate in PIMA Indians is more frequent in men compared to women [186]. The age of onset in Caucasian population is more precocious, approximately 4 years earlier, in men than women [187-189]. However, when we look at Asiatic populations (Chinese), the prevalence is higher in women than in men [190] indicating the importance of ethnic factors suggesting the relevance of genes, the contribution of unmeasured environmental factors, or a combination of both. Nevertheless the low prevalence, women seem to have higher mortality associated with diabetes-related amputation [188].

The underlying mechanisms of sex-gender differences are still unknown. Most likely, cultural factors, education and social status, and more hazardous lifestyle of men contribute to such differences in sex-gender ratios in diabetic neuropathy [53, 191, 192]. In turn, a lower economic status could induce unhealthy behaviors, such as smoking and alcohol addiction, overeating, and insufficient physical activities [66, 193]. Additionally, a lower economic status is also linked with poorer access to health care services and self-care practices.

The autonomic neuropathy in DM2 depends on changes in sympathetic innervations, disordered adrenergic receptor expression, and altered catecholamine levels in the myocardium that manifests clinically as resting tachycardia, orthostasis, exercise intolerance, and silent myocardial infarction and myocardiopathy [194]. The autonomic neuropathy partly contribute to induce QT prolongation [194], a parameter controlled by sexual hormones [195-197], which is the result of the total duration of ventricular myocardial depolarization and repolarization. When it is corrected for heart rate (QTc), it is predictive of cardiovascular mortality in apparently healthy people [198] of both sexes [199] as well as in DM [200].

Indeed, prevalence of prolonged QTc interval is higher in people with DM1 and DM2 as compared to non-diabetics [201-203] and prolonged QTc is reported to be an independent marker for coronary heart disease in DM1 and DM2, and has been demonstrated to be highly significant predictor of cardiac death even in newly diagnosed DM2 [204]. Prolongation of QTc interval is often assumed to increase the risk for development of malignant ventricular arrhythmias and has been demonstrated to be highly significant predictor of cardiac death [205, 206]. The cumulative incidence of prolonged QTc in DM1 is significantly different in men (13.9%) versus women (24.5%), even after adjustment for confounding factors, such as age, BMI, physical activity, and blood pressure [207]. This difference could justify the higher risk of cardiovascular

disease and congestive heart failure observed in women with respect to diabetic men. However a metanalysis that includes 4584 patients mainly (92%) affected by DM1 shows that at a given specificity of 86%, prolonged QTc is more sensitive in men than in women [208].

Autonomic diabetic neuropathy is also associated with hypoglycaemic unawareness, a condition by which the subject does not feel the hypoglycaemic state. This effect might increase the severity of the hypoglycaemic events, that in some situations might drive acute cardiovascular events such as stroke or myocardial infarction [209], in women, hypoglycaemia has been described almost 1.5 times that of men [131].

Diabetic Nephropathy

Diabetic nephropathy is a progressive disease caused by angiopathy of capillaries in the kidney glomeruli and is a prime indication for dialysis in many Western countries where sexual hormones and free fatty acids might have a pivotal role in the pathogenesis of glomerulopathy and tubulointerstitial lesions in DM [210].

Sex-gender impact on diabetic nephropathy has been extensively reviewed in [211]. Generally, female have less renal diseases, however the advantage is less evident in diabetic nephropathy than in non-diabetic kidney diseases [212]. However, data on diabetic patients are not univocal because some studies suggest that male gender remains a risk factor for the development of micro- and macroalbuminuria as well as the progression of an established diabetic nephropathy [213]. In particular, renal diabetic injury may be exacerbated by poor glycemic control and elevated systolic blood [214]. Indeed, women aged 60 years or older have greater hypertension prevalence than men [215] and have a lower control of blood pressure than men especially if they are diabetic [216]. Besides, data on metabolic control indicate that, under good metabolic control, DM1 women are more likely to develop diabetic nephropathy than men, whereas the situation is vice-versa under poor metabolic control [217].

The sex-gender differences seems to start at puberty, young girls with DM1 have a higher risk to develop micro-albuminuria than age-matched boys [212] suggesting the importance of sexual hormones. This is confirmed by the oral contraceptives effects. In fact, oral contraceptives containing high doses of estrogens promote the risk of diabetic nephropathy, whereas lower estrogen doses have no influence on renal function [213]. As reported above, sexual hormones largely affect RAAS system, a system that has been involved in the development and progression of diabetic nephropathy [218]. Importantly, at least in young patients with DM1, inhibition of angiotensin converting enzyme declines arterial pressure in men and women, but only women display a reduction in glomerular filtration rate and filtration factor [219].

Ethnic factors are also important in the development of diabetic renal disease. Native Americans, Hispanics (especially Mexican-Americans), and African-Americans have much higher risks of developing end stage renal diseases than non-Hispanic whites with DM2 [220] and it, together with DM duration, metabolic control and hormones

[213, 217], affects interactions between sex-gender and diabetic nephropathy.

Finally, genetic polymorphism could have a role in sexual dimorphism in diabetic renal disease. In the sex-determining region Y-box 2 gene is associated with diabetic nephropathy in female DM1 patients [192]. Whereas the M235T polymorphism in the angiotensinogen gene increases the incidence of nephropathy only in DM2 male patients [90] being the angiotensin II type 2 receptor gene involved in the development of kidney disease in DM1 male patients but not in DM1 women [91].

Interestingly, hyperglycemia induces an attenuation of effective renal plasma flow and renal blood flow as well as an increase in renal vascular resistance and filtration fraction in normoalbuminuric, normotensive DM1 women but not in their male counterparts [219]. This different regulation of renal hemodynamics in hyperglycemic state might, in part, explain the loss of female protection in the presence of DM [219].

Uric acid is independently associated with parameters of glycemic control showing a bell shaped relationship with both HbA1c and fasting glucose levels, whereas the relationship is linear with fasting serum C-peptide and insulin concentrations [221]. Notably, the relationship between uric acid and parameters of glycemic control is stronger among women than men [222]. The association between uric acid levels and kidney disease is nearly linear up to 7 mg dl/l in women and 8 mg dl/l in men [223] above these thresholds, however, the effect of increased uric acid on new-onset-kidney disease is increasing rapidly and, thereby, more pronounced in women as compared to men [223].

A conclusive answer to whether sex-gender plays a role in the development and progression of renal disease in DM is still missing, thus it urges to investigate the effect of sex-gender in a more detail and precise manner also in consideration of the fact that diabetic nephropathy increase the cardiovascular risk [124, 125] and is the first cause of renal dialysis.

Diabetic Retinopathy

Diabetic retinopathy is one of the main causes of visual loss in individuals aged 20-64 years old [224] and is present in more than 77% of patients with DM2 who survive for over 20 years with the disease [10]. It is estimated that 28.5% of U.S. diabetic patients over age 40 have diabetic retinopathy. Diabetic retinopathy is slightly more prevalent among women than men being more severe in men [225-227]. Another study suggests that diabetic women have, on the contrary, a higher probability than diabetic men of suffering from visual impairment [228]. Male sex is independently associated with the presence of diabetic retinopathy, as well as higher HBA1c level, longer duration of diabetes and higher systolic blood pressure [224].

To conclude with diabetic microvascular complications, studies focused on sex-gender differences are scarcely represented either at preclinical or clinical levels. It is therefore mandatory to design studies focalizing on sex-gender differences in order to ameliorate both the specific

outcomes and the eventually associated cardiovascular ones (see above).

THERAPY

Numerous studies demonstrate less than optimal management of DM in the United States. Data from the 1999-2000 National Health and Nutrition Examination Surveys (NHANES) show that only 37% of adults with DM achieve the recommended targets for HbA1c, blood pressure, and cholesterol level [229]. These problems are more evident when groups of vulnerable patients, such as women and racial/ethnic minorities are considered. Correa-de-Araujo *et al.*, [230] report that 28.9% of diabetic women versus 33.9% of diabetic men have received all five recommended services (*i.e.*, HbA1c testing, lipid profile, influenza immunization, eye and foot examination) in the appropriate time frame. Disparities do not decrease although the concern now arising that women are at higher relative risk than men of having complications including diabetic ketoacidosis and cardiovascular diseases [231-236]. Usually women are less likely than men to achieve blood pressure, LDL-cholesterol and HbA1c targets after a coronary event, and this gap does not appear to narrow between 1994 and 2007 [167, 237]. Effects of sex-gender on the outcome are reported in some randomized controlled trial evaluating drug effects on DM risk reduction [238-246]. Subgroup analysis suggestes that in the prevention of progression to overt DM, metformin might be more effective in young obese men and acarbose in older non-obese women [11]. Furthermore, the Irbesartan Type II Diabetic Nephropathy Trial (IDNT) also found that postmenopausal women benefit less from treatment with irbesartan than do men, [247]. Of note, none of these trials were primarily designed to assess sex-gender differences in the benefit from a specific intervention strategy. The lack of trails with sex-gender specific analysis raises the question of whether the conclusions that have been obtained in clinical trials can be translated in women. Evidently, future studies should consider sex-gender differences in the setting of intervention trials in consideration of multiple differences between men and women and they must be performed with all drugs. Indeed many aspects of DM therapy are reviewed in Szalat and Raz [11] whereas the sex-gender safety aspects of cardiovascular therapy are reviewed in Franconi *et al.*, [248], but here we want to recall that the prolongation of QTc induced by sympathetic neuropathy could have important consequences on pharmacological therapy because numerous drugs (more than 100) can prolong QT especially in females [249]. It is evident that diabetic people with QTc prolongation, especially if women should be treated with precautions with drugs that can induces QTc prolongation paying a lot of attention in doing therapeutic associations.

Another important aspect is the different illness orientation of men and women. Women have a larger interest and concern for health appearing more careful to symptoms of illness and seek medical care more frequently than men [250]. This different orientation could have a role in explaining the high incidence of drug adverse effects in women.

Importantly, men and women may have a different adherence to therapeutic treatments. Insulin therapy can induce weight gain either in DM1 or DM2 [251]. The increase in body weight induced by insulin therapy can have dangerous consequences because it has been calculated that for every 1 kg of weight gain after high school, the risk of coronary heart disease increases in women and men of 5.7% and 3.1%, respectively [252]. Indeed, insulin-induced weight gain together with the fear of hypoglycemic crisis may participate in the development of the so called "*psychological insulin resistance*" [252], a syndrome that it is present in about 28% of patients [253] and is more frequent in women [254]. "*Psychological insulin resistance*" may result in the reluctance of patients to both initiate and intensify insulin treatment, leading to delayed treatment initiation.

Treatment strategies should be improved in both sexes, but women with DM may be in need of more aggressive treatment, especially when cardiovascular disease is present.

CONCLUSIONS

sex-gender specific care for people with DM is not widely considered and in our opinion it is important and urgent to consider this point. Between 1971 and 2000, diabetic men have had a 43% relative reduction in the age-adjusted mortality rate (including cardiovascular mortality rate), which is similar to that of men without diabetes. In contrast, diabetic women have no reduction neither in total nor in cardiovascular mortality and the all-cause mortality rate, indeed diabetic women doubled mortality [255]. It is rather well known that women are less likely to be intensively treated, as men are, after an acute coronary event, and it is possible to speculate that even in achieving diabetic control less attention is paid for women in respect to male sex. Thus further insights into the sex-gender differences in the mechanisms that control the cardiovascular function and DM are urgently required to eventually set different therapeutic approaches including sex-gender approach in the all drug development processes. Sex-gender approach from preclinical studies to outcomes is mandatory to provide a more base evidenced medicine for women and to reach equity between men and women and to improve sex-gender awareness and competency in the health care system. In order to do that new preclinical and clinical research is urgently required, but is also necessary to implement education on gender issue to care providers.

ABBREVIATIONS

ACE	=	Angiotensin-converting enzyme
AD	=	Alzheimer's disease
AT 1	=	Angiotensin receptors type 1
AT2	=	Angiotensin receptors type 2
AR	=	Androgen receptor
BMI	=	Body mass index
ER	=	Estrogen receptors
DM	=	Diabetes mellitus
FOXO1 and FOX03	=	Forkhead transcription factors

GADA	=	Glutamic acid decarboxylase
GD	=	Gestational diabetes
GLUT4	=	Glucose transporter 4
GSIS	=	Glucose-dependent insulin secretion
HOMA-IR	=	Homeostasis model assessment–insulin resistance
IFG	=	Impaired fasting glucose
IGT	=	Impaired glucose tolerance
M235T	=	Methionine by threonine at amino-acid position 235
RAAS	=	Renin–angiotensin–aldosterone system
ULK1	=	Unc-51-like kinase

CONFLICT OF INTEREST

All the authors have no conflict of interest associated with the contents of publication.

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REFERENCES

[1]   Marino, M.; Masella, R.; Bulzomi, P.; Campesi, I.; Malorni, W. and Franconi, F. (2011) Nutrition and human health from a sex-gender perspective. *Mol. Aspects Med.*, **32**(1), 1-70.

[2]   Franconi, F.; Brunelleschi, S.; Steardo, L. and Cuomo, V. (2007) Gender differences in drug responses. *Pharmacol. Res.*, **55**(2), 81-95.

[3]   Blair, M. L. (2007) Sex-based differences in physiology: what should we teach in the medical curriculum? *Adv. Physiol. Educ.*, **31**(1), 23-25.

[4]   Legato, M. J. and Bilezikian, J. P. *Principles of gender-specific medicine*. Boston: Elsevier Academic Press: Amsterdam, 2004; p. 1245.

[5]   Liu, S. and Mauvais-Jarvis, F. (2010) Minireview: Estrogenic protection of beta-cell failure in metabolic diseases. *Endocrinology*, **151**(3), 859-864.

[6]   Giuffrida, F. M. and Reis, A. F. (2005) Genetic and clinical characteristics of maturity-onset diabetes of the young. *Diabetes Obes. Metab.*, **7**(4), 318-326.

[7]   Eaton, W. W.; Rose, N. R.; Kalaydjian, A.; Pedersen, M. G. and Mortensen, P. B. (2007) Epidemiology of autoimmune diseases in Denmark. *J. Autoimmun.*, **29**(1), 1-9.

[8]   Lindholm, E.; Hallengren, B. and Agardh, C. D. (2004) Gender differences in GAD antibody-positive diabetes mellitus in relation to age at onset, C-peptide and other endocrine autoimmune diseases. *Diabetes Metab. Res. Rev.*, **20**(2), 158-164.

[9]   Buchanan, T. A. and Xiang, A. H. (2005) Gestational diabetes mellitus. *J. Clin. Invest.*, **115**(3), 485-491.

[10]   Wild, S.; Roglic, G.; Green, A.; Sicree, R. and King, H. (2004) Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care*, **27**(5), 1047-1053.

[11]   Szalat, A. and Raz, I. (2008) Gender-specific care of diabetes mellitus: particular considerations in the management of diabetic women. *Diabetes Obes. Metab.*, **10**(12), 1135-1156.

[12]   World Health Organization. *The challenge of obesity in the WHO European Region and the strategies for response: summary*; Regional Office for Europe: **2007**.

[13]   Blouin, K.; Boivin, A. and Tchernof, A. (2008) Androgens and body fat distribution. *J. Steroid. Biochem. Mol. Biol.*, **108**(3-5), 272-280.

[14]   Seghieri, G.; Tesi, F.; Anichini, R.; De Bellis, A.; Fabbri, G.; Malagoli, R. and Franconi, F. (2008) Gender modulates the relationship between body weight and plasma glucose in overweight or obese subjects. *Diabetes Res. Clin. Pract.*, **80**(1), 134-138.

[15]   Berrahmoune, H.; Herbeth, B.; Samara, A.; Marteau, J. B.; Siest, G. and Visvikis-Siest, S. (2008) Five-year alterations in BMI are associated with clustering of changes in cardiovascular risk factors in a gender-dependant way: the Stanislas study. *Int. J. Obes. (Lond).*, **32**(8), 1279-1288.

[16]   Eckel, R. H.; Grundy, S. M. and Zimmet, P. Z. (2005) The metabolic syndrome. *Lancet*, **365**(9468), 1415-1428.

[17]   Pilote, L.; Dasgupta, K.; Guru, V.; Humphries, K. H.; McGrath, J.; Norris, C.; Rabi, D.; Tremblay, J.; Alamian, A.; Barnett, T.; Cox, J.; Ghali, W. A.; Grace, S.; Hamet, P.; Ho, T.; Kirkland, S.; Lambert, M.; Libersan, D.; O'Loughlin, J.; Paradis, G.; Petrovich, M. and Tagalakis, V. (2007) A comprehensive view of sex-specific issues related to cardiovascular disease. *CMAJ*, **176**(6), S1-44.

[18]   International Diabetes Federation. Prevalence estimates of diabetes mellitus (DM) – European Region. 3rd ed.; Brussels, **2006**.

[19]   Williams, J. W.; Zimmet, P. Z.; Shaw, J. E.; de Courten, M. P.; Cameron, A. J.; Chitson, P.; Tuomilehto, J. and Alberti, K. G. (2003) Gender differences in the prevalence of impaired fasting glycaemia and impaired glucose tolerance in Mauritius. Does sex matter? *Diabet. Med.*, **20**(11), 915-920.

[20]   DECODE Study Group. (2003) Age- and sex-specific prevalences of diabetes and impaired glucose regulation in 13 European cohorts. *Diabetes Care*, **26**(1), 61-69.

[21]   Meigs, J. B.; Nathan, D. M.; D'Agostino, R. B.Sr. and Wilson, P. W. (2002) Fasting and postchallenge glycemia and cardiovascular disease risk: the Framingham Offspring Study. *Diabetes Care*, **25**(10), 1845-1850.

[22]   Kanaya, A. M.; Grady, D. and Barrett-Connor, E. (2002) Explaining the sex difference in coronary heart disease mortality among patients with type 2 diabetes mellitus: a meta-analysis. *Arch. Intern. Med.*, **162**(15), 1737-1745.

[23]   Anderwald, C. H.; Krebs, M.; Promintzer-Schifferl, M.; Luger, A.; Kautzky-Willer, A. and Anderwald-Stadler, M. (2008) Glukoseresorption wa¨hrend des oralen Glukosetoleranztests bei Glukose-toleranten Frauen und Mannern. *Wien Klin. Wochenschr.*, **120**, 3.

[24]   Hanefeld, M.; Koehler, C.; Fuecker, K.; Henkel, E.; Schaper, F. and Temelkova-Kurktschiev, T. (2003) Insulin secretion and insulin sensitivity pattern is different in isolated impaired glucose tolerance and impaired fasting glucose: the risk factor in Impaired Glucose Tolerance for Atherosclerosis and Diabetes study. *Diabetes Care*, **26**(3), 868-874.

[25]   Nuutila, P.; Knuuti, M. J.; Maki, M.; Laine, H.; Ruotsalainen, U.; Teras, M.; Haaparanta, M.; Solin, O. and Yki-Jarvinen, H. (1995) Gender and insulin sensitivity in the heart and in skeletal muscles. Studies using positron emission tomography. *Diabetes*, **44**(1), 31-36.

[26]   Clausen, J. O.; Borch-Johnsen, K.; Ibsen, H.; Bergman, R. N.; Hougaard, P.; Winther, K. and Pedersen, O. (1996) Insulin sensitivity index, acute insulin response, and glucose effectiveness in a population-based sample of 380 young healthy Caucasians. Analysis of the impact of gender, body fat, physical fitness, and life-style factors. *J. Clin. Invest.*, **98**(5), 1195-1209.

[27]   Wynn, J. W.; Doar, J. W. and Mills, G. L. (1966) Some effects of oral contraceptives on serum-lipid and lipoprotein levels. *Lancet*, **2**(7466), 720-723.

[28]   Ehtisham, S.; Hattersley, A. T.; Dunger, D. B. and Barrett, T. G. (2004) First UK survey of paediatric type 2 diabetes and MODY. *Arch. Dis. Child*, **89**(6), 526-529.

[29]   Rosenbloom, A. L.; Joe, J. R.; Young, R. S. and Winter, W. E. (1999) Emerging epidemic of type 2 diabetes in youth. *Diabetes Care*, **22**(2), 345-354.

[30]   Fagot-Campagna, A.; Pettitt, D. J.; Engelgau, M. M.; Burrows, N. R.; Geiss, L. S.; Valdez, R.; Beckles, G. L.; Saaddine, J.; Gregg, E. W.; Williamson, D. F. and Narayan, K. M. (2000) Type 2 diabetes among North American children and adolescents: an epidemiologic review and a public health perspective. *J. Pediatr.*, **136**(5), 664-672.

[31]   Shields, B. M.; Knight, B.; Hopper, H.; Hill, A.; Powell, R. J.; Hattersley, A. T. and Clark, P. M. (2007) Measurement of cord insulin and insulin-related peptides suggests that girls are more insulin resistant than boys at birth. *Diabetes Care*, **30**(10), 2661-2666.

[32]   Murphy, M. J.; Metcalf, B. S.; Voss, L. D.; Jeffery, A. N.; Kirkby, J.; Mallam, K. M. and Wilkin, T. J. (2004) Girls at five are intrinsically more insulin resistant than boys: The Programming Hypotheses Revisited--The EarlyBird Study (EarlyBird 6). *Pediatrics*, **113**(1 Pt 1), 82-86.

[33]   Bavdekar, A.; Yajnik, C. S.; Fall, C. H.; Bapat, S.; Pandit, A. N.; Deshpande, V.; Bhave, S.; Kellingray, S. D. and Joglekar, C. (1999) Insulin resistance syndrome in 8-year-old Indian children: small at birth, big at 8 years, or both? *Diabetes*, **48**(12), 2422-2429.

[34]   Young-Hyman, D.; Schlundt, D. G.; Herman, L.; De Luca, F. and Counts, D. (2001) Evaluation of the insulin resistance syndrome in 5- to 10-year-old overweight/obese African-American children. *Diabetes Care*, **24**(8), 1359-1364.

[35]   Moran, A.; Jacobs, D. R. Jr.; Steinberger, J.; Hong, C. P.; Prineas, R.; Luepker, R. and Sinaiko, A. R. (1999) Insulin resistance during puberty: results from clamp studies in 357 children. *Diabetes*, **48**(10), 2039-2044.

[36]   Travers, S. H.; Jeffers, B. W.; Bloch, C. A.; Hill, J. O. and Eckel, R. H. (1995) Gender and Tanner stage differences in body composition and insulin sensitivity in early pubertal children. *J. Clin. Endocrinol. Metab.*, **80**(1), 172-178.

[37]   Ehtisham, S.; Crabtree, N.; Clark, P.; Shaw, N. and Barrett, T. (2005) Ethnic differences in insulin resistance and body composition in United Kingdom adolescents. *J. Clin. Endocrinol. Metab.*, **90**(7), 3963-3969.

[38]   Alberti, K. G.; Zimmet, P. and Shaw, J. (2005) The metabolic syndrome--a new worldwide definition. *Lancet*, **366**(9491), 1059-1062.

[39]   Regitz-Zagrosek, V.; Lehmkuhl, E. and Mahmoodzadeh, S. (2007) Gender aspects of the role of the metabolic syndrome as a risk factor for cardiovascular disease. *Gend. Med.*, **4** (Suppl B), S162-177.

[40]   Bjornholm, M. and Zierath, J. R. (2005) Insulin signal transduction in human skeletal muscle: identifying the defects in Type II diabetes. *Biochem. Soc. Trans.*, **33**(Pt 2), 354-357.

[41]   Mauvais-Jarvis, F. (2011) Estrogen and androgen receptors: regulators of fuel homeostasis and emerging targets for diabetes and obesity. *Trends Endocrinol. Metab.*, **22**(1), 24-33.

[42]   Dhindsa, S.; Prabhakar, S.; Sethi, M.; Bandyopadhyay, A.; Chaudhuri, A. and Dandona, P. (2004) Frequent occurrence of hypogonadotropic hypogonadism in type 2 diabetes. *J. Clin. Endocrinol. Metab.*, **89**(11), 5462-5468.

[43]   Mulligan, T.; Frick, M. F.; Zuraw, Q. C.; Stemhagen, A. and McWhirter, C. (2006) Prevalence of hypogonadism in males aged at least 45 years: the HIM study. *Int. J. Clin. Pract.*, **60**(7), 762-769.

[44]   Francomano, D.; Bruzziches, R.; Natali, M.; Aversa, A. and Spera, G. (2010) Cardiovascular effect of testosterone replacement therapy in aging male. *Acta. Biomed.*, **81**(Suppl 1), 101-106.

[45]   Haffner, S. M. (1996) Sex hormone-binding protein, hyper-insulinemia, insulin resistance and noninsulin-dependent diabetes. *Horm. Res.*, **45**(3-5), 233-237.

[46]   Marin, P. and Arver, S. (1998) Androgens and abdominal obesity. *Baillieres Clin. Endocrinol. Metab.*, **12**(3), 441-451.

[47]   Basaria, S.; Coviello, A. D.; Travison, T. G.; Storer, T. W.; Farwell, W. R.; Jette, A. M.; Eder, R.; Tennstedt, S.; Ulloor, J.; Zhang, A.; Choong, K.; Lakshman, K. M.; Mazer, N. A.; Miciek, R.; Krasnoff, J.; Elmi, A.; Knapp, P. E.; Brooks, B.; Appleman, E.; Aggarwal, S.; Bhasin, G.; Hede-Brierley, L.; Bhatia, A.; Collins, L.; LeBrasseur, N.; Fiore, L. D. and Bhasin, S. (2010) Adverse events associated with testosterone administration. *N. Engl. J. Med.*, **363**(2), 109-122.

[48]   Meyer, I. H.; Schwartz, S. and Frost, D. M. (2008) Social patterning of stress and coping: does disadvantaged social statuses confer more stress and fewer coping resources? *Soc. Sci. Med.*, **67**(3), 368-379.

[49]   Robbins, J. M.; Vaccarino, V.; Zhang, H. and Kasl, S. V. (2001) Socioeconomic status and type 2 diabetes in African American and non-Hispanic white women and men: evidence from the Third National Health and Nutrition Examination Survey. *Am. J. Public Health*, **91**(1), 76-83.

[50]   Stelmach, W.; Kaczmarczyk-Chalas, K.; Bielecki, W. and Drygas, W. (2005) How education, income, control over life and life style contribute to risk factors for cardiovascular disease among adults in a post-communist country. *Public Health*, **119**(6), 498-508.

[51]   Rabi, D. M.; Edwards, A. L.; Southern, D. A.; Svenson, L. W.; Sargious, P. M.; Norton, P.; Larsen, E. T. and Ghali, W. A. (2006) Association of socio-economic status with diabetes prevalence and utilization of diabetes care services. *BMC Health Serv. Res.*, **6**, 124.

[52]   Tamayo, T.; Christian, H. and Rathmann, W. (2010) Impact of early psychosocial factors (childhood socioeconomic factors and adversities) on future risk of type 2 diabetes, metabolic disturbances and obesity: a systematic review. *BMC Public Health*, **10**, 525.

[53]   Connolly, V.; Unwin, N.; Sherriff, P.; Bilous, R. and Kelly, W. (2000) Diabetes prevalence and socioeconomic status: a population based study showing increased prevalence of type 2 diabetes mellitus in deprived areas. *J. Epidemiol. Community Health*, **54**(3), 173-177.

[54]   World Health Organization. *Prevention of diabetes mellitus*; Geneva, **1994**.

[55]   Colhoun H.; Lampe F. and W.D. Obesity In *Health Survey for England 1994*, P, C. H. a. P.-C., Ed. London, **1995**.

[56]   Unwin, N.; Watson, W. and J., H. (1995) Social class differences in the prevalence of glucose intolerance. *Diabetic Med.*, **12**, s31.

[57]   Hales, C. N.; Barker, D. J.; Clark, P. M.; Cox, L. J.; Fall, C.; Osmond, C. and Winter, P. D. (1991) Fetal and infant growth and impaired glucose tolerance at age 64. *BMJ*, **303**(6809), 1019-1022.

[58]   Smith, M.; Hopkins, D.; Peveler, R. C.; Holt, R. I.; Woodward, M. and Ismail, K. (2008) First- v. second-generation antipsychotics and risk for diabetes in schizophrenia: systematic review and meta-analysis. *Br. J. Psychiatry*, **192**(6), 406-411.

[59]   Chen da, C.; Zhou, M. A.; Zhou, D. H.; Xiu, M. H.; Wu, G. Y.; Kosten, T. R. and Zhang, X. Y. (2011) Gender differences in the prevalence of diabetes mellitus in chronic hospitalized patients with schizophrenia on long-term antipsychotics. *Psychiatry Res.*, **186**(2-3), 451-453.

[60]   Anderson, R. J.; Freedland, K. E.; Clouse, R. E. and Lustman, P. J. (2001) The prevalence of comorbid depression in adults with diabetes: a meta-analysis. *Diabetes Care*, **24**(6), 1069-1078.

[61]   Gavard, J. A.; Lustman, P. J. and Clouse, R. E. (1993) Prevalence of depression in adults with diabetes. An epidemiological evaluation. *Diabetes Care*, **16**(8), 1167-1178.

[62]   Nichols, G. A. and Brown, J. B. (2003) Unadjusted and adjusted prevalence of diagnosed depression in type 2 diabetes. *Diabetes Care*, **26**(3), 744-749.

[63]   Egede, L. E. (2004) Effects of depression on work loss and disability bed days in individuals with diabetes. *Diabetes Care*, **27**(7), 1751-1753.

[64]   Black, S. A.; Markides, K. S. and Ray, L. A. (2003) Depression predicts increased incidence of adverse health outcomes in older Mexican Americans with type 2 diabetes. *Diabetes Care*, **26**(10), 2822-2828.

[65]   Finkelstein, E. A.; Bray, J. W.; Chen, H.; Larson, M. J.; Miller, K.; Tompkins, C.; Keme, A. and Manderscheid, R. (2003) Prevalence and costs of major depression among elderly claimants with diabetes. *Diabetes Care*, **26**(2), 415-420.

[66] de Groot, M.; Anderson, R.; Freedland, K. E.; Clouse, R. E. and Lustman, P. J. (2001) Association of depression and diabetes complications: a meta-analysis. *Psychosom. Med.*, **63**(4), 619-630.

[67] Ciechanowski, P. S.; Katon, W. J. and Russo, J. E. (2000) Depression and diabetes: impact of depressive symptoms on adherence, function, and costs. *Arch. Intern. Med.*, **160**(21), 3278-3285.

[68] Ciechanowski, P. S.; Katon, W. J.; Russo, J. E. and Hirsch, I. B. (2003) The relationship of depressive symptoms to symptom reporting, self-care and glucose control in diabetes. *Gen. Hosp. Psychiatry*, **25**(4), 246-252.

[69] Lin, E. H.; Katon, W.; Von Korff, M.; Rutter, C.; Simon, G. E.; Oliver, M.; Ciechanowski, P.; Ludman, E. J.; Bush, T. and Young, B. (2004) Relationship of depression and diabetes self-care, medication adherence, and preventive care. *Diabetes Care*, **27**(9), 2154-2160.

[70] Lustman, P. J.; Anderson, R. J.; Freedland, K. E.; de Groot, M.; Carney, R. M. and Clouse, R. E. (2000) Depression and poor glycemic control: a meta-analytic review of the literature. *Diabetes Care*, **23**(7), 934-942.

[71] Zhang, X.; Norris, S. L.; Gregg, E. W.; Cheng, Y. J.; Beckles, G. and Kahn, H. S. (2005) Depressive symptoms and mortality among persons with and without diabetes. *Am. J. Epidemiol.*, **161**(7), 652-660.

[72] Grant, J. F.; Hicks, N.; Taylor, A. W.; Chittleborough, C. R. and Phillips, P. J. (2009) Gender-specific epidemiology of diabetes: a representative cross-sectional study. *Int. J. Equity Health*, **8**(1), 6.

[73] Takeda, S.; Sato, N.; Rakugi, H. and Morishita, R. (2011) Molecular mechanisms linking diabetes mellitus and Alzheimer disease: beta-amyloid peptide, insulin signaling, and neuronal function. *Mol. Biosyst.*, **7**(6), 1822-1827.

[74] de la Monte, S. M. and Wands, J. R. (2008) Alzheimer's disease is type 3 diabetes-evidence reviewed. *J. Diabetes Sci. Technol.*, **2**(6), 1101-1113.

[75] Bosco, D.; Fava, A.; Plastino, M.; Montalcini, T. and Pujia, A. (2011) Possible implications of Insulin Resistance and Glucose metabolism in Alzheimer's disease pathogenesis. *J. Cell Mol. Med.*, **15**(9), 1807-1821.

[76] Sinforiani, E.; Citterio, A.; Zucchella, C.; Bono, G.; Corbetta, S.; Merlo, P. and Mauri, M. (2010) Impact of gender differences on the outcome of Alzheimer's disease. *Dement. Geriatr. Cogn. Disord.*, **30**(2), 147-154.

[77] Tonolo, G.; Ciccarese, M.; Brizzi, P.; Milia, S.; Dessole, S.; Puddu, L.; Secchi, G. and Maioli, M. (1995) Cyclical variation of plasma lipids, apolipoproteins, and lipoprotein(a) during menstrual cycle of normal women. *Am. J. Physiol.*, **269** (6 Pt 1), E1101-1105.

[78] Brizzi, P.; Dessole, S.; Tonolo, G.; Capobianco, G.; Milia, L.; Puddu, L. and Nardo, L. G. (2003) Effect of ovarian stimulation on plasma lipid and apolipoprotein concentrations in a population of infertile women undergoing IVF/embryo transfer. *Reprod. Biomed. Online*, **7**(3), 309-312.

[79] Brizzi, P.; Tonolo, G.; Esposito, F.; Puddu, L.; Dessole, S.; Maioli, M. and Milia, S. (1999) Lipoprotein metabolism during normal pregnancy. *Am. J. Obstet. Gynecol.*, **181**(2), 430-434.

[80] Buchanan, T. A.; Metzger, B. E.; Freinkel, N. and Bergman, R. N. (1990) Insulin sensitivity and B-cell responsiveness to glucose during late pregnancy in lean and moderately obese women with normal glucose tolerance or mild gestational diabetes. *Am. J. Obstet. Gynecol.*, **162**(4), 1008-1014.

[81] Case, A. M. and Reid, R. L. (2001) Menstrual cycle effects on common medical conditions. *Compr. Ther.*, **27**(1), 65-71.

[82] Solomon, C. G.; Hu, F. B.; Dunaif, A.; Rich-Edwards, J.; Willett, W. C.; Hunter, D. J.; Colditz, G. A.; Speizer, F. E. and Manson, J. E. (2001) Long or highly irregular menstrual cycles as a marker for risk of type 2 diabetes mellitus. *JAMA*, **286**(19), 2421-2426.

[83] Dunaif, A.; Segal, K. R.; Futterweit, W. and Dobrjansky, A. (1989) Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. *Diabetes*, **38**(9), 1165-1174.

[84] Yang, J. and Holman, G. D. (2006) Long-term metformin treatment stimulates cardiomyocyte glucose transport through an AMP-activated protein kinase-dependent reduction in GLUT4 endocytosis. *Endocrinology*, **147**(6), 2728-2736.

[85] van Genugten, R. E.; Utzschneider, K. M.; Tong, J.; Gerchman, F.; Zraika, S.; Udayasankar, J.; Boyko, E. J.; Fujimoto, W. Y. and Kahn, S. E. (2006) Effects of sex and hormone replacement therapy use on the prevalence of isolated impaired fasting glucose and isolated impaired glucose tolerance in subjects with a family history of type 2 diabetes. *Diabetes*, **55**(12), 3529-3535.

[86] Jones, M. E.; Thorburn, A. W.; Britt, K. L.; Hewitt, K. N.; Wreford, N. G.; Proietto, J.; Oz, O. K.; Leury, B. J.; Robertson, K. M.; Yao, S. and Simpson, E. R. (2000) Aromatase-deficient (ArKO) mice have a phenotype of increased adiposity. *Proc. Natl. Acad. Sci. USA*, **97**(23), 12735-12740.

[87] Takeda, K.; Toda, K.; Saibara, T.; Nakagawa, M.; Saika, K.; Onishi, T.; Sugiura, T. and Shizuta, Y. (2003) Progressive development of insulin resistance phenotype in male mice with complete aromatase (CYP19) deficiency. *J. Endocrinol.*, **176**(2), 237-246.

[88] Faustini-Fustini, M.; Rochira, V. and Carani, C. (1999) Oestrogen deficiency in men: where are we today? *Eur. J. Endocrinol.*, **140**(2), 111-129.

[89] Komukai, K.; Mochizuki, S. and Yoshimura, M. (2010) Gender and the renin-angiotensin-aldosterone system. *Fundam. Clin. Pharmacol.*, **24**(6), 687-698.

[90] Freire, M. B.; Ji, L.; Onuma, T.; Orban, T.; Warram, J. H. and Krolewski, A. S. (1998) Gender-specific association of M235T polymorphism in angiotensinogen gene and diabetic nephropathy in NIDDM. *Hypertension*, **31** (4), 896-899.

[91] Pettersson-Fernholm, K.; Frojdo, S.; Fagerudd, J.; Thomas, M. C.; Forsblom, C.; Wessman, M. and Groop, P. H. (2006) The AT2 gene may have a gender-specific effect on kidney function and pulse pressure in type I diabetic patients. *Kidney Int.*, **69**(10), 1880-1884.

[92] Shu, Y. H.; Hartiala, J.; Xiang, A. H.; Trigo, E.; Lawrence, J. M.; Allayee, H.; Buchanan, T. A.; Bottini, N. and Watanabe, R. M. (2009) Evidence for sex-specific associations between variation in acid phosphatase locus 1 (ACP1) and insulin sensitivity in Mexican-Americans. *J. Clin. Endocrinol. Metab.*, **94**(10), 4094-4102.

[93] Yamaguchi, S.; Yamada, Y.; Matsuo, H.; Segawa, T.; Watanabe, S.; Kato, K.; Yokoi, K.; Ichihara, S.; Metoki, N.; Yoshida, H.; Satoh, K. and Nozawa, Y. (2007) Gender differences in the association of gene polymorphisms with type 2 diabetes mellitus. *Int. J. Mol. Med.*, **19**(4), 631-637.

[94] Winzer, C.; Wagner, O.; Festa, A.; Schneider, B.; Roden, M.; Bancher-Todesca, D.; Pacini, G.; Funahashi, T. and Kautzky-Willer, A. (2004) Plasma adiponectin, insulin sensitivity, and subclinical inflammation in women with prior gestational diabetes mellitus. *Diabetes Care*, **27**(7), 1721-1727.

[95] Farhan, S.; Winzer, C.; Tura, A.; Quehenberger, P.; Bieglmaier, C.; Wagner, O. F.; Huber, K.; Waldhausl, W.; Pacini, G. and Kautzky-Willer, A. (2006) Fibrinolytic dysfunction in insulin-resistant women with previous gestational diabetes. *Eur. J. Clin. Invest.*, **36**(5), 345-352.

[96] Saltevo, J.; Kautiainen, H. and Vanhala, M. (2009) Gender differences in adiponectin and low-grade inflammation among individuals with normal glucose tolerance, prediabetes, and type 2 diabetes. *Gend. Med.*, **6**(3), 463-470.

[97] Evans, R. W. and Orchard, T. J. (1994) Oxidized lipids in insulin-dependent diabetes mellitus: a sex-diabetes interaction? *Metabolism*, **43**(9), 1196-1200.

[98] Legato, M. J.; Gelzer, A.; Goland, R.; Ebner, S. A.; Rajan, S.; Villagra, V. and Kosowski, M. (2006) Gender-specific care of the patient with diabetes: review and recommendations. *Gend. Med.*, **3**(2), 131-158.

[99] Marra, G.; Cotroneo, P.; Pitocco, D.; Manto, A.; Di Leo, M. A.; Ruotolo, V.; Caputo, S.; Giardina, B.; Ghirlanda, G. and Santini, S. A. (2002) Early increase of oxidative stress and reduced anti-oxidant defenses in patients with uncomplicated type 1 diabetes: a case for gender difference. *Diabetes Care*, **25**(2), 370-375.

[100] Giacco, F. and Brownlee, M. (2010) Oxidative stress and diabetic complications. *Circ. Res.*, **107**(9), 1058-1070.

[101] Lista, P.; Straface, E.; Brunelleschi, S.; Franconi, F. and Malorni, W. (2011) On the Role of Autophagy in Human Diseases: a Gender Perspective. *J. Cell Mol. Med.*, **15**(7), 1443-1457

[102] Malorni, W.; Straface, E.; Matarrese, P.; Ascione, B.; Coinu, R.; Canu, S.; Galluzzo, P.; Marino, M. and Franconi, F. (2008) Redox state and gender differences in vascular smooth muscle cells. *FEBS Lett.*, **582**(5), 635-642.

[103] Maselli, A.; Matarrese, P.; Straface, E.; Canu, S.; Franconi, F. and Malorni, W. (2009) Cell sex: a new look at cell fate studies. *FASEB J.*, **23**(4), 978-984.

[104] Ortona, E.; Margutti, P.; Matarrese, P.; Franconi, F. and Malorni, W. (2008) Redox state, cell death and autoimmune diseases: a gender perspective. *Autoimmun. Rev.*, **7**(7), 579-584.

[105] Pierdominici, M.; Ortona, E.; Franconi, F.; Caprio, M.; Straface, E. and Malorni, W. (2011) Gender specific aspects of cell death in the cardiovascular system. *Curr. Pharma Des.*, **17**(11), 1046-1055.

[106] Straface, E.; Vona, R.; Gambardella, L.; Ascione, B.; Marino, M.; Bulzomi, P.; Canu, S.; Coinu, R.; Rosano, G.; Malorni, W. and Franconi, F. (2009) Cell sex determines anoikis resistance in vascular smooth muscle cells. *FEBS Lett.*, **583**(21), 3448-3454.

[107] Hotamisligil, G. S. (2010) Endoplasmic reticulum stress and the inflammatory basis of metabolic disease. *Cell*, **140**(6), 900-917.

[108] Li, S.; Brown, M. S. and Goldstein, J. L. (2010) Bifurcation of insulin signaling pathway in rat liver: mTORC1 required for stimulation of lipogenesis, but not inhibition of gluconeogenesis. *Proc. Natl. Acad. Sci. USA*, **107**(8), 3441-3446.

[109] Yang, L.; Li, P.; Fu, S.; Calay, E. S. and Hotamisligil, G. S. (2010) Defective hepatic autophagy in obesity promotes ER stress and causes insulin resistance. *Cell Metab.*, **11**(6), 467-478.

[110] Liu, H. Y.; Han, J.; Cao, S. Y.; Hong, T.; Zhuo, D.; Shi, J.; Liu, Z. and Cao, W. (2009) Hepatic autophagy is suppressed in the presence of insulin resistance and hyperinsulinemia: inhibition of FoxO1-dependent expression of key autophagy genes by insulin. *J. Biol. Chem.*, **284**(45), 31484-31492.

[111] Hur, K. Y.; Jung, H. S. and Lee, M. S. (2010) Role of autophagy in beta-cell function and mass. *Diabetes Obes. Metab.*, **12**(Suppl 2), 20-26.

[112] American Diabetes Association. (2009) Standards of medical care in diabetes-2009. *Diabetes Care*, **32**(1), S13-61.

[113] Kim, C.; Newton, K. M. and Knopp, R. H. (2002) Gestational diabetes and the incidence of type 2 diabetes: a systematic review. *Diabetes Care*, **25**(10), 1862-1868.

[114] Lee, A. J.; Hiscock, R. J.; Wein, P.; Walker, S. P. and Permezel, M. (2007) Gestational diabetes mellitus: clinical predictors and long-term risk of developing type 2 diabetes: a retrospective cohort study using survival analysis. *Diabetes Care*, **30**(4), 878-883.

[115] Toulis, K. A.; Goulis, D. G.; Kolibianakis, E. M.; Venetis, C. A.; Tarlatzis, B. C. and Papadimas, I. (2009) Risk of gestational diabetes mellitus in women with polycystic ovary syndrome: a systematic review and a meta-analysis. *Fertil. Steril.*, **92**(2), 667-677.

[116] Apridonidze, T.; Essah, P. A.; Iuorno, M. J. and Nestler, J. E. (2005) Prevalence and characteristics of the metabolic syndrome in women with polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.*, **90**(4), 1929-1935.

[117] Eisenhardt, S.; Schwarzmann, N.; Henschel, V.; Germeyer, A.; von Wolff, M.; Hamann, A. and Strowitzki, T. (2006) Early effects of metformin in women with polycystic ovary syndrome: a prospective randomized, double-blind, placebo-controlled trial. *J. Clin. Endocrinol. Metab.*, **91**(3), 946-952.

[118] Ornoy, A. (2011) Prenatal origin of obesity and their complications: Gestational diabetes, maternal overweight and the paradoxical effects of fetal growth restriction and macrosomia. *Reprod. Toxicol.*, **32**(2), 205-212.

[119] Buinauskiene, J.; Baliutaviciene, D. and Zalinkevicius, R. (2004) Glucose tolerance of 2- to 5-yr-old offspring of diabetic mothers. *Pediatr. Diabetes*, **5**(3), 143-146.

[120] Clausen, T. D.; Mathiesen, E. R.; Hansen, T.; Pedersen, O.; Jensen, D. M.; Lauenborg, J. and Damm, P. (2008) High prevalence of type 2 diabetes and pre-diabetes in adult offspring of women with gestational diabetes mellitus or type 1 diabetes: the role of intrauterine hyperglycemia. *Diabetes Care*, **31**(2), 340-346.

[121] Sojo, L.; Garcia-Patterson, A.; Maria, M. A.; Martin, E.; Ubeda, J.; Adelantado, J. M.; de Leiva, A. and Corcoy, R. (2010) Are birth weight predictors in diabetic pregnancy the same in boys and girls? *Eur. J. Obstet. Gynecol. Reprod. Biol.*, **153**(1), 32-37.

[122] Barrett-Connor, E. L.; Cohn, B. A.; Wingard, D. L. and Edelstein, S. L. (1991) Why is diabetes mellitus a stronger risk factor for fatal ischemic heart disease in women than in men? The Rancho Bernardo Study. *JAMA*, **265**(5), 627-631.

[123] Brownlee, M. (2005) The pathobiology of diabetic complications: a unifying mechanism. *Diabetes*, **54**(6), 1615-1625.

[124] Garg, J. P. and Bakris, G. L. (2002) Microalbuminuria: marker of vascular dysfunction, risk factor for cardiovascular disease. *Vasc. Med.*, **7**(1), 35-43.

[125] Klausen, K.; Borch-Johnsen, K.; Feldt-Rasmussen, B.; Jensen, G.; Clausen, P.; Scharling, H.; Appleyard, M. and Jensen, J. S. (2004) Very low levels of microalbuminuria are associated with increased risk of coronary heart disease and death independently of renal function, hypertension, and diabetes. *Circulation*, **110**(1), 32-35.

[126] Veglio, M.; Sivieri, R.; Chinaglia, A.; Scaglione, L. and Cavallo-Perin, P. (2000) QT interval prolongation and mortality in type 1 diabetic patients: a 5-year cohort prospective study. Neuropathy Study Group of the Italian Society of the Study of Diabetes, Piemonte Affiliate. *Diabetes Care*, **23**(9), 1381-1383.

[127] Vinik, A. I.; Maser, R. E.; Mitchell, B. D. and Freeman, R. (2003) Diabetic autonomic neuropathy. *Diabetes Care*, **26**(5), 1553-1579.

[128] Witte, D. R.; Tesfaye, S.; Chaturvedi, N.; Eaton, S. E.; Kempler, P. and Fuller, J. H. (2005) Risk factors for cardiac autonomic neuropathy in type 1 diabetes mellitus. *Diabetologia*, **48**(1), 164-171.

[129] Tryniszewski, W.; Kusmierczyk, J.; Maziarz, Z.; Gos, R.; Mikhailidis, D. P.; Banach, M.; Rysz, J. and Pesudovs, K. (2011) Correlation of the severity of diabetic retinopathy and the heart muscle perfusion in patients with type 2 diabetes. *J. Diabetes Complications.*, **25**(4), 253-257.

[130] Cheung, N.; Tikellis, G. and Wang, J. J. (2007) Diabetic retinopathy. *Ophthalmology*, **114**(11), 2098-2099; author reply 2099.

[131] Fishbein, H. and Palumbo, P. J. Acute metabolic complications in diabetes. In *National Diabetes Data Group. Diabetes in America, 2nd ed*, National Institutes of Health; National Institute of Diabetes and Digestive and Kidney Diseases, Eds. Washington, DC, **1995**; pp. 283-291.

[132] Faich, G. A.; Fishbein, H. A. and Ellis, S. E. (1983) The epidemiology of diabetic acidosis: a population-based study. *Am. J. Epidemiol.*, **117**(5), 551-558.

[133] Akalin, S.; Berntorp, K.; Ceriello, A.; Das, A. K.; Kilpatrick, E. S.; Koblik, T.; Munichoodappa, C. S.; Pan, C. Y.; Rosenthall, W.; Shestakova, M.; Wolnik, B.; Woo, V.; Yang, W. Y. and Yilmaz, M. T. (2009) Intensive glucose therapy and clinical implications of recent data: a consensus statement from the Global Task Force on Glycaemic Control. *Int. J. Clin. Pract.*, **63**(10), 1421-1425.

[134] Stettler, C.; Allemann, S.; Juni, P.; Cull, C. A.; Holman, R. R.; Egger, M.; Krahenbuhl, S. and Diem, P. (2006) Glycemic control and macrovascular disease in types 1 and 2 diabetes mellitus: Meta-analysis of randomized trials. *Am. Heart J.*, **152**(1), 27-38.

[135] Skyler, J. S.; Bergenstal, R.; Bonow, R. O.; Buse, J.; Deedwania, P.; Gale, E. A.; Howard, B. V.; Kirkman, M. S.; Kosiborod, M.; Reaven, P. and Sherwin, R. S. (2009) Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. *Diabetes Care*, **32**(1), 187-192.

[136] Beckman, J. A.; Creager, M. A. and Libby, P. (2002) Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. *JAMA*, **287**(19), 2570-2581.

[137] Haffner, S. M.; Lehto, S.; Ronnemaa, T.; Pyorala, K. and Laakso, M. (1998) Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N. Engl. J. Med.*, **339**(4), 229-234.

[138]   Howard, B. V.; Cowan, L. D.; Go, O.; Welty, T. K.; Robbins, D. C. and Lee, E. T. (1998) Adverse effects of diabetes on multiple cardiovascular disease risk factors in women. The Strong Heart Study. *Diabetes Care*, **21**(8), 1258-1265.

[139]   Hurst, R. T. and Lee, R. W. (2003) Increased incidence of coronary atherosclerosis in type 2 diabetes mellitus: mechanisms and management. *Ann. Intern. Med.*, **139**(10), 824-834.

[140]   Gu, K.; Cowie, C. C. and Harris, M. I. (1999) Diabetes and decline in heart disease mortality in US adults. *JAMA*, **281**(14), 1291-1297.

[141]   Hu, F. B.; Stampfer, M. J.; Solomon, C. G.; Liu, S.; Willett, W. C.; Speizer, F. E.; Nathan, D. M. and Manson, J. E. (2001) The impact of diabetes mellitus on mortality from all causes and coronary heart disease in women: 20 years of follow-up. *Arch. Intern. Med.*, **161**(14), 1717-1723.

[142]   Hu, G. (2003) Gender difference in all-cause and cardiovascular mortality related to hyperglycaemia and newly-diagnosed diabetes. *Diabetologia*, **46**(5), 608-617.

[143]   Lundberg, V.; Stegmayr, B.; Asplund, K.; Eliasson, M. and Huhtasaari, F. (1997) Diabetes as a risk factor for myocardial infarction: population and gender perspectives. *J. Intern. Med.*, **241**(6), 485-492.

[144]   Barrett-Connor, E. and Ferrara, A. (1998) Isolated postchallenge hyperglycemia and the risk of fatal cardiovascular disease in older women and men. The Rancho Bernardo Study. *Diabetes Care*, **21**(8), 1236-1239.

[145]   Huxley, R.; Barzi, F. and Woodward, M. (2006) Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. *BMJ*, **332**(7533), 73-78.

[146]   Donahue, R. P.; Rejman, K.; Rafalson, L. B.; Dmochowski, J.; Stranges, S. and Trevisan, M. (2007) Sex differences in endothelial function markers before conversion to pre-diabetes: does the clock start ticking earlier among women? The Western New York Study. *Diabetes Care*, **30**(2), 354-359.

[147]   Orchard, T. J. (1996) The impact of gender and general risk factors on the occurrence of atherosclerotic vascular disease in non-insulin-dependent diabetes mellitus. *Ann. Med.*, **28**(4), 323-333.

[148]   Schwab, K. O.; Doerfer, J.; Naeke, A.; Rohrer, T.; Wiemann, D.; Marg, W.; Hofer, S. E. and Holl, R. W. (2009) Influence of food intake, age, gender, HbA1c, and BMI levels on plasma cholesterol in 29,979 children and adolescents with type 1 diabetes--reference data from the German diabetes documentation and quality management system (DPV). *Pediatr. Diabetes*, **10**(3), 184-192.

[149]   Soedamah-Muthu, S. S.; Fuller, J. H.; Mulnier, H. E.; Raleigh, V. S.; Lawrenson, R. A. and Colhoun, H. M. (2006) All-cause mortality rates in patients with type 1 diabetes mellitus compared with a non-diabetic population from the UK general practice research database, 1992-1999. *Diabetologia*, **49**(4), 660-666.

[150]   Schwab, K. O.; Doerfer, J.; Marg, W.; Schober, E. and Holl, R. W. (2010) Characterization of 33 488 children and adolescents with type 1 diabetes based on the gender-specific increase of cardiovascular risk factors. *Pediatr Diabetes*, **11**(5), 357-363.

[151]   Hu, F. B.; Stampfer, M. J.; Haffner, S. M.; Solomon, C. G.; Willett, W. C. and Manson, J. E. (2002) Elevated risk of cardiovascular disease prior to clinical diagnosis of type 2 diabetes. *Diabetes Care*, **25**(7), 1129-1134.

[152]   Haffner, S. M.; Miettinen, H. and Stern, M. P. (1997) Relatively more atherogenic coronary heart disease risk factors in prediabetic women than in prediabetic men. *Diabetologia*, **40**(6), 711-717.

[153]   The Diabetes Control and Complications Trial Research Group. (1993) The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N. Engl. J. Med.*, **329**(14), 977-986.

[154]   Festa, A.; D'Agostino, R. Jr.; Tracy, R. P. and Haffner, S. M. (2002) Elevated levels of acute-phase proteins and plasminogen activator inhibitor-1 predict the development of type 2 diabetes: the insulin resistance atherosclerosis study. *Diabetes*, **51**(4), 1131-1137.

[155]   Kuller, L. H.; Tracy, R. P.; Shaten, J. and Meilahn, E. N. (1996) Relation of C-reactive protein and coronary heart disease in the MRFIT nested case-control study. Multiple Risk Factor Intervention Trial. *Am. J. Epidemiol.*, **144**(6), 537-547.

[156]   Meigs, J. B.; Hu, F. B.; Rifai, N. and Manson, J. E. (2004) Biomarkers of endothelial dysfunction and risk of type 2 diabetes mellitus. *JAMA*, **291**(16), 1978-1986.

[157]   Ridker, P. M.; Cushman, M.; Stampfer, M. J.; Tracy, R. P. and Hennekens, C. H. (1997) Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N. Engl. J. Med.*, **336**(14), 973-979.

[158]   Schmidt, M. I.; Duncan, B. B.; Sharrett, A. R.; Lindberg, G.; Savage, P. J.; Offenbacher, S.; Azambuja, M. I.; Tracy, R. P. and Heiss, G. (1999) Markers of inflammation and prediction of diabetes mellitus in adults (Atherosclerosis Risk in Communities study): a cohort study. *Lancet*, **353**(9165), 1649-1652.

[159]   Steinberg, H. O.; Paradisi, G.; Cronin, J.; Crowde, K.; Hempfling, A.; Hook, G. and Baron, A. D. (2000) Type II diabetes abrogates sex differences in endothelial function in premenopausal women. *Circulation*, **101**(17), 2040-2046.

[160]   Ossei-Gerning, N.; Wilson, I. J. and Grant, P. J. (1998) Sex differences in coagulation and fibrinolysis in subjects with coronary artery disease. *Thromb. Haemost.*, **79** (4), 736-740.

[161]   Chan, P. and Pan, W. H. (1995) Coagulation activation in type 2 diabetes mellitus: the higher coronary risk of female diabetic patients. *Diabet. Med.*, **12**(6), 504-507.

[162]   Knowler, W. C.; Barrett-Connor, E.; Fowler, S. E.; Hamman, R. F.; Lachin, J. M.; Walker, E. A. and Nathan, D. M. (2002) Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N. Engl. J. Med.*, **346**(6), 393-403.

[163]   Tuomilehto, J.; Lindstrom, J.; Eriksson, J. G.; Valle, T. T.; Hamalainen, H.; Ilanne-Parikka, P.; Keinanen-Kiukaanniemi, S.; Laakso, M.; Louheranta, A.; Rastas, M.; Salminen, V. and Uusitupa, M. (2001) Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N. Engl. J. Med.*, **344**(18), 1343-1350.

[164]   Barrett-Connor, E.; Giardina, E. G.; Gitt, A. K.; Gudat, U.; Steinberg, H. O. and Tschoepe, D. (2004) Women and heart disease: the role of diabetes and hyperglycemia. *Arch. Intern. Med.*, **164**(9), 934-942.

[165]   Dallongevillle, J.; De Bacquer, D.; Heidrich, J.; De Backer, G.; Prugger, C.; Kotseva, K.; Montaye, M. and Amouyel, P. (2010) Gender differences in the implementation of cardiovascular prevention measures after an acute coronary event. *Heart*, **96**(21), 1744-1749.

[166]   Juutilainen, A.; Kortelainen, S.; Lehto, S.; Ronnemaa, T.; Pyorala, K. and Laakso, M. (2004) Gender difference in the impact of type 2 diabetes on coronary heart disease risk. *Diabetes Care*, **27**(12), 2898-2904.

[167]   Miller, M. E.; Bonds, D. E.; Gerstein, H. C.; Seaquist, E. R.; Bergenstal, R. M.; Calles-Escandon, J.; Childress, R. D.; Craven, T. E.; Cuddihy, R. M.; Dailey, G.; Feinglos, M. N.; Ismail-Beigi, F.; Largay, J. F.; O'Connor, P. J.; Paul, T.; Savage, P. J.; Schubart, U. K.; Sood, A. and Genuth, S. (2010) The effects of baseline characteristics, glycaemia treatment approach, and glycated haemoglobin concentration on the risk of severe hypoglycaemia: post hoc epidemiological analysis of the ACCORD study. *BMJ*, **340**, b5444.

[168]   Cavalot, F.; Petrelli, A.; Traversa, M.; Bonomo, K.; Fiora, E.; Conti, M.; Anfossi, G.; Costa, G. and Trovati, M. (2006) Postprandial blood glucose is a stronger predictor of cardiovascular events than fasting blood glucose in type 2 diabetes mellitus, particularly in women: lessons from the San Luigi Gonzaga Diabetes Study. *J. Clin. Endocrinol. Metab.*, **91**(3), 813-819.

[169]   Paynter, N. P.; Mazer, N. A.; Pradhan, A. D.; Gaziano, J. M.; Ridker, P. M. and Cook, N. R. (2011) Cardiovascular Risk Prediction in Diabetic Men and Women Using Hemoglobin A1c *vs* Diabetes as a High-Risk Equivalent. *Arch. Intern. Med.*, **171**(19), 1712-1718.

[170]   Faerch, K.; Borch-Johnsen, K.; Vaag, A.; Jørgensen, T. and Witte, D. R. (2010) Sex differences in glucose levels: a consequence of

physiology or methodological convenience? The Inter99 study. *Diabetologia*, **53**, 858-865.

[171]   Kothari, V.; Stevens, R. J.; Adler, A. I.; Stratton, I. M.; Manley, S. E.; Neil, H. A. and Holman, R. R. (2002) UKPDS 60: risk of stroke in type 2 diabetes estimated by the UK Prospective Diabetes Study risk engine. *Stroke*, **33**(7), 1776-1781.

[172]   Lin, M.; Chen, Y. and Sigal, R. J. (2007) Stroke associated with diabetes among Canadians: sex and age differences. *Neuroepidemiology*, **28**(1), 46-49.

[173]   Mulnier, H. E.; Seaman, H. E.; Raleigh, V. S.; Soedamah-Muthu, S. S.; Colhoun, H. M.; Lawrenson, R. A. and De Vries, C. S. (2006) Risk of stroke in people with type 2 diabetes in the UK: a study using the General Practice Research Database. *Diabetologia*, **49**(12), 2859-2865.

[174]   Arboix, A.; Milian, M.; Oliveres, M.; Garcia-Eroles, L. and Massons, J. (2006) Impact of female gender on prognosis in type 2 diabetic patients with ischemic stroke. *Eur. Neurol.*, **56**(1), 6-12.

[175]   Sundquist, K. and Li, X. (2006) Type 1 diabetes as a risk factor for stroke in men and women aged 15-49: a nationwide study from Sweden. *Diabet. Med.*, **23**(11), 1261-1267.

[176]   Maisch, B.; Alter, P. and Pankuweit, S. (2011) Diabetic cardiomyopathy-fact or fiction? *Herz.*, **36** (2), 102-115.

[177]   Ren, J. and Ceylan-Isik, A. F. (2004) Diabetic cardiomyopathy: do women differ from men? *Endocrine*, **25**(2), 73-83.

[178]   Regitz-Zagrosek, V.; Petrov, G.; Lehmkuhl, E.; Smits, J. M.; Babitsch, B.; Brunhuber, C.; Jurmann, B.; Stein, J.; Schubert, C.; Merz, N. B.; Lehmkuhl, H. B. and Hetzer, R. (2010) Heart transplantation in women with dilated cardiomyopathy. *Transplantation*, **89**(2), 236-244.

[179]   Holscher, C. (2011) Diabetes as a risk factor for Alzheimer's disease: insulin signalling impairment in the brain as an alternative model of Alzheimer's disease. *Biochem. Soc. Trans.*, **39**(4), 891-897.

[180]   Vinik, A. I.; Holland, M. T.; Le Beau, J. M.; Liuzzi, F. J.; Stansberry, K. B. and Colen, L. B. (1992) Diabetic neuropathies. *Diabetes Care*, **15**(12), 1926-1975.

[181]   Albers, J. W.; Brown, M. B.; Sima, A. A. and Greene, D. A. (1996) Nerve conduction measures in mild diabetic neuropathy in the Early Diabetes Intervention Trial: the effects of age, sex, type of diabetes, disease duration, and anthropometric factors. Tolrestat Study Group for the Early Diabetes Intervention Trial. *Neurology*, **46**(1), 85-91.

[182]   Booya, F.; Bandarian, F.; Larijani, B.; Pajouhi, M.; Nooraei, M. and Lotfi, J. (2005) Potential risk factors for diabetic neuropathy: a case control study. *BMC Neurol.*, **5**, 24.

[183]   Brown, M. J.; Bird, S. J.; Watling, S.; Kaleta, H.; Hayes, L.; Eckert, S. and Foyt, H. L. (2004) Natural progression of diabetic peripheral neuropathy in the Zenarestat study population. *Diabetes Care*, **27**(5), 1153-1159.

[184]   Dyck, P. J.; Litchy, W. J.; Lehman, K. A.; Hokanson, J. L.; Low, P. A. and O'Brien, P. C. (1995) Variables influencing neuropathic endpoints: the Rochester Diabetic Neuropathy Study of Healthy Subjects. *Neurology*, **45**(6), 1115-1121.

[185]   Pop-Busui, R.; Lu, J.; Lopes, N. and Jones, T. L. (2009) Prevalence of diabetic peripheral neuropathy and relation to glycemic control therapies at baseline in the BARI 2D cohort. *J. Peripher. Nerv. Syst.*, **14**(1), 1-13.

[186]   Mayfield, J. A.; Reiber, G. E.; Nelson, R. G. and Greene, T. (1996) A foot risk classification system to predict diabetic amputation in Pima Indians. *Diabetes Care*, **19**(7), 704-709.

[187]   Aaberg, M. L.; Burch, D. M.; Hud, Z. R. and Zacharias, M. P. (2008) Gender differences in the onset of diabetic neuropathy. *J. Diabetes Complications*, **22**(2), 83-87.

[188]   Peek, M. E. (2010) Gender Differences in Diabetes-related Lower Extremity Amputations. *Clin. Orthop. Relat. Res.*, **469**(7), 1951-1955.

[189]   Prompers, L.; Schaper, N.; Apelqvist, J.; Edmonds, M.; Jude, E.; Mauricio, D.; Uccioli, L.; Urbancic, V.; Bakker, K.; Holstein, P.; Jirkovska, A.; Piaggesi, A.; Ragnarson-Tennvall, G.; Reike, H.; Spraul, M.; Van Acker, K.; Van Baal, J.; Van Merode, F.; Ferreira, I. and Huijberts, M. (2008) Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between

individuals with and without peripheral arterial disease. The EURODIALE Study. *Diabetologia*, **51**(5), 747-755.

[190]   Liu, Z.; Fu, C.; Wang, W. and Xu, B. (2010) Prevalence of chronic complications of type 2 diabetes mellitus in outpatients - a cross-sectional hospital based survey in urban China. *Health Qual. Life Outcomes*, **8**, 62.

[191]   Seale, J. P.; Davis-Smith, M. and Okosun, I. (2006) Ethnic and gender differences in lifestyle risk factors in a bi-ethnic primary care sample: prevalence and clinical implications. *Ethn. Dis.*, **16**(2), 460-467.

[192]   Gu, H. F.; Alvarsson, A.; Efendic, S. and Brismar, K. (2009) SOX2 has gender-specific genetic effects on diabetic nephropathy in samples from patients with type 1 diabetes mellitus in the GoKinD study. *Gend. Med.*, **6**(4), 555-564.

[193]   Gonzalez, J. S.; Safren, S. A.; Cagliero, E.; Wexler, D. J.; Delahanty, L.; Wittenberg, E.; Blais, M. A.; Meigs, J. B. and Grant, R. W. (2007) Depression, self-care, and medication adherence in type 2 diabetes: relationships across the full range of symptom severity. *Diabetes Care*, **30**(9), 2222-2227.

[194]   Maser, R. E. and Lenhard, M. J. (2005) Cardiovascular autonomic neuropathy due to diabetes mellitus: clinical manifestations, consequences, and treatment. *J. Clin. Endocrinol. Metab.*, **90**(10), 5896-5903.

[195]   Griffin, M.; Lee, H. W.; Zhao, L. and Eghbali-Webb, M. (2000) Gender-related differences in proliferative response of cardiac fibroblasts to hypoxia: effects of estrogen. *Mol. Cell Biochem.*, **215**(1-2), 21-30.

[196]   Kadokami, T.; McTiernan, C. F.; Kubota, T.; Frye, C. S. and Feldman, A. M. (2000) Sex-related survival differences in murine cardiomyopathy are associated with differences in TNF-receptor expression. *J. Clin. Invest.*, **106**(4), 589-597.

[197]   Peng, S.; Yu, Y.; Hao, K.; Xing, H.; Li, D.; Chen, C.; Huang, A.; Hong, X.; Feng, Y.; Zhang, Y.; Li, J.; Wang, B.; Wu, D.; Wang, X. and Xu, X. (2006) Heart rate-corrected QT interval duration is significantly associated with blood pressure in Chinese hypertensives. *J. Electrocardiol.*, **39**(2), 206-210.

[198]   Schouten, E. G.; Dekker, J. M.; Meppelink, P.; Kok, F. J.; Vandenbroucke, J. P. and Pool, J. (1991) QT interval prolongation predicts cardiovascular mortality in an apparently healthy population. *Circulation*, **84**(4), 1516-1523.

[199]   Dekker, J. M.; Crow, R. S.; Hannan, P. J.; Schouten, E. G. and Folsom, A. R. (2004) Heart rate-corrected QT interval prolongation predicts risk of coronary heart disease in black and white middle-aged men and women: the ARIC study. *J. Am. Coll Cardiol.*, **43**(4), 565-571.

[200]   Okin, P. M.; Devereux, R. B.; Lee, E. T.; Galloway, J. M. and Howard, B. V. (2004) Electrocardiographic repolarization complexity and abnormality predict all-cause and cardiovascular mortality in diabetes: the strong heart study. *Diabetes*, **53**(2), 434-440.

[201]   Veglio, M.; Borra, M.; Stevens, L. K.; Fuller, J. H. and Perin, P. C. (1999) The relation between QTc interval prolongation and diabetic complications. The EURODIAB IDDM Complication Study Group. *Diabetologia*, **42**(1), 68-75.

[202]   Veglio, M.; Bruno, G.; Borra, M.; Macchia, G.; Bargero, G.; D'Errico, N.; Pagano, G. F. and Cavallo-Perin, P. (2002) Prevalence of increased QT interval duration and dispersion in type 2 diabetic patients and its relationship with coronary heart disease: a population-based cohort. *J. Intern. Med.*, **251**(4), 317-324.

[203]   Veglio, M.; Giunti, S.; Stevens, L. K.; Fuller, J. H. and Perin, P. C. (2002) Prevalence of Q-T interval dispersion in type 1 diabetes and its relation with cardiac ischemia : the EURODIAB IDDM Complications Study Group. *Diabetes Care*, **25**(4), 702-707.

[204]   Rana, B. S.; Lim, P. O.; Naas, A. A.; Ogston, S. A.; Newton, R. W.; Jung, R. T.; Morris, A. D. and Struthers, A. D. (2005) QT interval abnormalities are often present at diagnosis in diabetes and are better predictors of cardiac death than ankle brachial pressure index and autonomic function tests. *Heart*, **91**(1), 44-50.

[205]   Akhtar, M. (1990) Clinical spectrum of ventricular tachycardia. *Circulation*, **82**(5), 1561-1573.

[206]   Vlay, S. C.; Mallis, G. I.; Brown, E. J.Jr. and Cohn, P. F. (1984) Documented sudden cardiac death in prolonged QT syndrome. *Arch. Intern. Med.*, **144**(4), 833-835.

[207]   Giunti, S.; Bruno, G.; Lillaz, E.; Gruden, G.; Lolli, V.; Chaturvedi, N.; Fuller, J. H.; Veglio, M. and Cavallo-Perin, P. (2007) Incidence and risk factors of prolonged QTc interval in type 1 diabetes: the EURODIAB Prospective Complications Study. *Diabetes Care*, **30**(8), 2057-2063.

[208]   Whitsel, E. A.; Boyko, E. J. and Siscovick, D. S. (2000) Reassessing the role of QTc in the diagnosis of autonomic failure among patients with diabetes: a meta-analysis. *Diabetes Care*, **23**(2), 241-247.

[209]   Zoungas, S.; Patel, A.; Chalmers, J.; de Galan, B. E.; Li, Q.; Billot, L.; Woodward, M.; Ninomiya, T.; Neal, B.; MacMahon, S.; Grobbee, D. E.; Kengne, A. P.; Marre, M. and Heller, S. (2010) Severe hypoglycemia and risks of vascular events and death. *N. Engl. J. Med.*, **363**(15), 1410-1418.

[210]   Nosadini, R. and Tonolo, G. (2011) Role of oxidized low density lipoproteins and free fatty acids in the pathogenesis of glomerulopathy and tubulointerstitial lesions in type 2 diabetes. *Nutr. Metab. Cardiovasc. Dis.*, **21**(2), 79-85.

[211]   Seliger, S. L.; Davis, C. and Stehman-Breen, C. (2001) Gender and the progression of renal disease. *Curr. Opin. Nephrol. Hypertens.*, **10**(2), 219-225.

[212]   Schultz, C. J.; Konopelska-Bahu, T.; Dalton, R. N.; Carroll, T. A.; Stratton, I.; Gale, E. A.; Neil, A. and Dunger, D. B. (1999) Microalbuminuria prevalence varies with age, sex, and puberty in children with type 1 diabetes followed from diagnosis in a longitudinal study. Oxford Regional Prospective Study Group. *Diabetes Care*, **22**(3), 495-502.

[213]   Maric, C. (2009) Sex, diabetes and the kidney. *Am. J. Physiol. Renal. Physiol.*, **296**(4), F680-688.

[214]   Maric, C. and Hall, J. E. (2011) Obesity, metabolic syndrome and diabetic nephropathy. *Contrib. Nephrol.*, **170**, 28-35.

[215]   Hajjar, I. and Kotchen, T. A. (2003) Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988-2000. *JAMA*, **290**(2), 199-206.

[216]   Thoenes, M.; Neuberger, H. R.; Volpe, M.; Khan, B. V.; Kirch, W. and Bohm, M. (2010) Antihypertensive drug therapy and blood pressure control in men and women: an international perspective. *J. Hum. Hypertens.*, **24**(5), 336-344.

[217]   Sibley, S. D.; Thomas, W.; de Boer, I.; Brunzell, J. D. and Steffes, M. W. (2006) Gender and elevated albumin excretion in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) cohort: role of central obesity. *Am. J. Kidney Dis.*, **47**(2), 223-232.

[218]   Gnudi, L. and Goldsmith, D. (2010) Renin angiotensin aldosterone system (RAAS) inhibitors in the prevention of early renal disease in diabetes. *F1000 Med. Rep.*, **2**,. pii: 18.

[219]   Cherney, D. Z.; Sochett, E. B. and Miller, J. A. (2005) Gender differences in renal responses to hyperglycemia and angiotensin-converting enzyme inhibition in diabetes. *Kidney Int.*, **68**(4), 1722-1728.

[220]   Molitch, M. E.; DeFronzo, R. A.; Franz, M. J.; Keane, W. F.; Mogensen, C. E.; Parving, H. H. and Steffes, M. W. (2004) Nephropathy in diabetes. *Diabetes Care*, **27**(Suppl 1), S79-83.

[221]   Niskanen, L.; Laaksonen, D. E.; Lindstrom, J.; Eriksson, J. G.; Keinanen-Kiukaanniemi, S.; Ilanne-Parikka, P.; Aunola, S.; Hamalainen, H.; Tuomilehto, J. and Uusitupa, M. (2006) Serum uric acid as a harbinger of metabolic outcome in subjects with impaired glucose tolerance: the Finnish Diabetes Prevention Study. *Diabetes Care*, **29**(3), 709-711.

[222]   Choi, H. K. and Ford, E. S. (2008) Haemoglobin A1c, fasting glucose, serum C-peptide and insulin resistance in relation to serum uric acid levels--the Third National Health and Nutrition Examination Survey. *Rheumatology (Oxford)*, **47**(5), 713-717.

[223]   Obermayr, R. P.; Temml, C.; Gutjahr, G.; Knechtelsdorfer, M.; Oberbauer, R. and Klauser-Braun, R. (2008) Elevated uric acid increases the risk for kidney disease. *J. Am. Soc. Nephrol.*, **19**(12), 2407-2413.

[224]   Zhang, X.; Saaddine, J. B.; Chou, C. F.; Cotch, M. F.; Cheng, Y. J.; Geiss, L. S.; Gregg, E. W.; Albright, A. L.; Klein, B. E. and Klein, R. (2010) Prevalence of diabetic retinopathy in the United States, 2005-2008. *JAMA*, **304**(6), 649-656.

[225]   Kashani, A. H.; Zimmer-Galler, I. E.; Shah, S. M.; Dustin, L.; Do, D. V.; Eliott, D.; Haller, J. A. and Nguyen, Q. D. (2010) Retinal thickness analysis by race, gender, and age using Stratus OCT. *Am. J. Ophthalmol.*, **149**(3), 496-502 e491.

[226]   Pradeepa, R.; Anitha, B.; Mohan, V.; Ganesan, A. and Rema, M. (2008) Risk factors for diabetic retinopathy in a South Indian Type 2 diabetic population--the Chennai Urban Rural Epidemiology Study (CURES) Eye Study 4. *Diabet. Med.*, **25**(5), 536-542.

[227]   Rani, P. K.; Raman, R.; Chandrakantan, A.; Pal, S. S.; Perumal, G. M. and Sharma, T. (2009) Risk factors for diabetic retinopathy in self-reported rural population with diabetes. *J. Postgrad. Med.*, **55**(2), 92-96.

[228]   Deshpande, A. D.; Harris-Hayes, M. and Schootman, M. (2008) Epidemiology of diabetes and diabetes-related complications. *Phys. Ther.*, **88**(11), 1254-1264.

[229]   Saydah, S. H.; Fradkin, J. and Cowie, C. C. (2004) Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. *JAMA*, **291**(3), 335-342.

[230]   Correa-de-Araujo, R.; McDermott, K. and Moy, E. (2006) Gender differences across racial and ethnic groups in the quality of care for diabetes. *Womens Health Issues*, **16**(2), 56-65.

[231]   AHRQ. *National Healthcare Disparities Report*. Agency for Healthcare Research and Quality: Rockville, 2004.

[232]   Cowie, C. C.; Port, F. K.; Wolfe, R. A.; Savage, P. J.; Moll, P. P. and Hawthorne, V. M. (1989) Disparities in incidence of diabetic end-stage renal disease according to race and type of diabetes. *N. Engl. J. Med.*, **321**(16), 1074-1079.

[233]   Karter, A. J.; Ferrara, A.; Liu, J. Y.; Moffet, H. H.; Ackerson, L. M. and Selby, J. V. (2002) Ethnic disparities in diabetic complications in an insured population. *JAMA*, **287**(19), 2519-2527.

[234]   Lavery, L. A.; van Houtum, W. H.; Ashry, H. R.; Armstrong, D. G. and Pugh, J. A. (1999) Diabetes-related lower-extremity amputations disproportionately affect Blacks and Mexican Americans. *South Med. J.*, **92**(6), 593-599.

[235]   Rostand, S. G.; Kirk, K. A.; Rutsky, E. A. and Pate, B. A. (1982) Racial differences in the incidence of treatment for end-stage renal disease. *N. Engl. J. Med.*, **306**(21), 1276-1279.

[236]   Trivedi, A. N.; Zaslavsky, A. M.; Schneider, E. C. and Ayanian, J. Z. (2005) Trends in the quality of care and racial disparities in Medicare managed care. *N. Engl. J. Med.*, **353**(7), 692-700.

[237]   Jarvie, J. L. and Foody, J. M. (2010) Recognizing and improving health care disparities in the prevention of cardiovascular disease in women. *Curr. Cardiol. Rep.*, **12**(6), 488-496.

[238]   Braunwald, E.; Domanski, M. J.; Fowler, S. E.; Geller, N. L.; Gersh, B. J.; Hsia, J.; Pfeffer, M. A.; Rice, M. M.; Rosenberg, Y. D. and Rouleau, J. L. (2004) Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *N. Engl. J. Med.*, **351**(20), 2058-2068.

[239]   Freeman, D. J.; Norrie, J.; Sattar, N.; Neely, R. D.; Cobbe, S. M.; Ford, I.; Isles, C.; Lorimer, A. R.; Macfarlane, P. W.; McKillop, J. H.; Packard, C. J.; Shepherd, J. and Gaw, A. (2001) Pravastatin and the development of diabetes mellitus: evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study. *Circulation*, **103**(3), 357-362.

[240]   Gerstein, H. C.; Swedberg, K.; Carlsson, J.; McMurray, J. J.; Michelson, E. L.; Olofsson, B.; Pfeffer, M. A. and Yusuf, S. (2008) The hemoglobin A1c level as a progressive risk factor for cardiovascular death, hospitalization for heart failure, or death in patients with chronic heart failure: an analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program. *Arch. Intern. Med.*, **168**(15), 1699-1704.

[241]   Karlsson, J.; Taft, C.; Sjostrom, L.; Torgerson, J. S. and Sullivan, M. (2003) Psychosocial functioning in the obese before and after weight reduction: construct validity and responsiveness of the Obesity-related Problems scale. *Int. J. Obes. Relat. Metab. Disord.*, **27**(5), 617-630.

[242]   Lithell, H.; Hansson, L.; Skoog, I.; Elmfeldt, D.; Hofman, A.; Olofsson, B.; Trenkwalder, P. and Zanchetti, A. (2003) The Study on Cognition and Prognosis in the Elderly (SCOPE): principal

results of a randomized double-blind intervention trial. *J. Hypertens.*, **21**(5), 875-886.

[243]   Torgerson, J. S.; Hauptman, J.; Boldrin, M. N. and Sjostrom, L. (2004) XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care*, **27**(1), 155-161.

[244]   Trenkwalder, P.; Elmfeldt, D.; Hofman, A.; Lithell, H.; Olofsson, B.; Papademetriou, V.; Skoog, I. and Zanchetti, A. (2005) The Study on COgnition and Prognosis in the Elderly (SCOPE) - major CV events and stroke in subgroups of patients. *Blood Press*, **14**(1), 31-37.

[245]   Yusuf, S.; Ostergren, J. B.; Gerstein, H. C.; Pfeffer, M. A.; Swedberg, K.; Granger, C. B.; Olofsson, B.; Probstfield, J. and McMurray, J. V. (2005) Effects of candesartan on the development of a new diagnosis of diabetes mellitus in patients with heart failure. *Circulation*, **112**(1), 48-53.

[246]   Yusuf, S.; Sleight, P.; Pogue, J.; Bosch, J.; Davies, R. and Dagenais, G. (2000) Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N. Engl. J. Med.*, **342**(3), 145-153.

[247]   Lewis, E. J.; Hunsicker, L. G. and Rodby, R. A. (2001) A clinical trial in type 2 diabetic nephropathy. *Am. J. Kidney Dis.*, **38**(4 Suppl 1), S191-194.

[248]   Franconi, F.; Carru, C.; Malorni, W.; Vella, S. and Mercuro, G. (2011) The effect of sex/gender on cardiovascular pharmacology. *Curr. Pharm. Des.*, **17**(11), 1095-1107.

[249]   Franconi, F.; Carru, C.; Malorni, W.; Vella, S. and Mercuro, G. (2011) The effect of gender on cardiovascular pharmacology. *Curr. Pharm. Design.*, **17**(11), 1095-1107.

[250]   Hibbard, J. H. and Pope, C. R. (1983) Gender roles, illness orientation and use of medical services. *Soc. Sci. Med.*, **17**(3), 129-137.

[251]   Russell-Jones, D. and Khan, R. (2007) Insulin-associated weight gain in diabetes--causes, effects and coping strategies. *Diabetes Obes. Metab.*, **9**(6), 799-812.

[252]   Carver, C. (2006) Insulin treatment and the problem of weight gain in type 2 diabetes. *Diabetes Educ.*, **32**(6), 910-917.

[253]   Polonsky, W. H.; Fisher, L.; Guzman, S.; Villa-Caballero, L. and Edelman, S. V. (2005) Psychological insulin resistance in patients with type 2 diabetes: the scope of the problem. *Diabetes Care*, **28**(10), 2543-2545.

[254]   Nam, S.; Chesla, C.; Stotts, N. A.; Kroon, L. and Janson, S. L. (2010) Factors associated with psychological insulin resistance in individuals with type 2 diabetes. *Diabetes Care*, **33**(8), 1747-1749.

[255]   Gregg, E. W.; Gu, Q.; Cheng, Y. J.; Narayan, K. M. and Cowie, C. C. (2007) Mortality trends in men and women with diabetes, 1971 to 2000. *Ann. Intern. Med.*, **147**(3), 149-155.

[256]   Roglic, G. and Unwin, N. (2010) Mortality attributable to diabetes: estimates for the year 2010. *Diabetes Res. Clin. Pract.*, **87**(1), 15-19.