Gender-specific care of diabetes mellitus: particular considerations in the management of diabetic women

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In the past 30 years, the all-cause mortality and cardiovascular mortality rates for women with diabetes mellitus (DM), in contrast to men, have not declined. Furthermore, the difference between all-cause mortality rates in women with DM and those without DM has more than doubled. This urgently needs addressing. This review will analyse published medical literature relating to the specific management of DM in women and try to identify areas where gender affects care. We have identified specific gender differences in the pathophysiology of glucose homeostasis disorder, diabetes-related complications and any female gender-specific features of women with diabetes, such as contraception and the menopause. These gender-specific features of DM may offer a route to improved care for women and new therapeutic possibilities.

Keywords: cardiovascular risk factors, contraception, depression, diabetes mellitus, endothelial dysfunction, gestational diabetes mellitus, hormone replacement therapy, inflammation, macrovascular complications, metabolic syndrome, microvascular complications, osteoporosis, polycystic ovary syndrome, sex hormones, sex hormone receptors

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Introduction

Gender-specific care for people with diabetes mellitus (DM) is not well developed, but it is important to address this issue. Indeed, a recent study showed that between 1971 and 2000, men with DM 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, women with diabetes had no reduction neither in total nor in cardiovascular mortality and the all-cause mortality rate difference between women with and without diabetes more than doubled [1]. Recent research has focused on the impact of sex hormones on glucose homeostasis, and the pathophysiology section below suggests a gender specificity in the molecular pathway involved in the development of insulin resistance; as a result, the involvement of gender-specific mechanisms is suspected in the development of diabetes-related complications, leading to gender-specific features of DM, which could lead to gender-specific therapeutic possibilities.

This paper will analyse published medical literature relating to the specific management of DM in women and try to identify areas where gender affects care. We have highlighted specific gender differences in the pathophysiology of glucose homeostasis disorder, diabetes-related complications and any female gender-specific features of women with DM, such as contraception and the menopause. Currently, there is only one review of the evidence-based medicine recommendations published [2], and few of the recommendations are of the highest quality of evidence.

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Gender Specificity of Diagnostic Tests for DM

- Women have lower prevalence of isolated impaired fasting glucose (IFG) and higher prevalence of isolated impaired glucose tolerance (IGT) based on pathological 75 g oral glucose tolerance test (OGTT) than men. This is also the case for elderly men.
- Screening for diabetes in women should involve an OGTT with 2-h plasma glucose values as well as fasting glucose values.

There are marked gender differences in the results of fasting plasma glucose (FPG) values or glucose levels after an OGTT for screening and diagnosis of DM [3] as well as for defining two prediabetic situations [4] in individuals: IFG and IGT (table 1).

As shown in table 1, screening for DM using the FPG misses the diagnosis in many women as well as in older men, justifying the use of OGTT in these groups. The significance of IGT and postprandial hyperglycaemia relating to cardiovascular morbidity and mortality was outlined in the Framingham Offspring Study [5] where it was associated with a 40% increase in cardiovascular event; however, there is growing evidence that IGT and postprandial hyperglycaemia are independent cardiovascular risk factors in women only [6]. It is interesting to note that the differing patterns of glucose homeostasis disorders between men and women may be related to different pathophysiological mechanisms, as proposed by Hanefeld et al. [7]. This study showed that men with IFG had more insulin resistance than women with IGT who had impaired early and late phases of insulin secretion; these observations may have clinical significance when considering the use of a preventive pharmacological drug, for example metformin would be more suitable in the former and acarbose in the latter.

The risk factors for developing type 2 DM are, in both genders [8], positive family history, age, elevated body mass index (BMI) and low HDL levels. However, there are also specific gender differences: high daily alcohol intake, regular smoking and elevated systolic blood pressure (BP) in men, and increased uric acid and physical inactivity in women. In another study [9], risk factors for undiagnosed DM were hypertriglyceridaemia in women and increased waist circumference in men. To note, one study involving 68,907 nurses showed that elevated BMI and waist circumference were stronger independent risk factors than physical inactivity [10].

Sex Hormones, Sex Hormone Receptors and the Pathophysiology of Glucose Homeostasis Disorder

- Testosterone has gender dimorphic effects on the incidence of type 2 DM: high levels are protective against DM in men but have the opposite effect in women, while low levels are associated with the development of type 2 DM in men.
- It is believed that oestrogen deficiency may affect glucose regulation and may also increase insulin resistance in oestrogen-resistant males as well as in postmenopausal women.
- Oestrogen receptor (ER)-α is beneficial to glucose homeostasis through its direct genomic effects on glucose transporter 4 (GLUT4) transcription (the protein involved in glucose absorption). It also has an indirect beneficial effect by interacting with the nuclear factor-xB (NF-xB), which naturally down-regulate GLUT4 activity.
- ER-β has opposite effects, and membrane ratios of ER-α/-β determine the global effect on GLUT4 expression. Thus, development of ER-β antagonists might be an area of research to decrease insulin resistance.
- ER-α seems to prevent immunological pancreatic β-cell apoptosis and may thus play a role in the development of type 1 DM.
- Adipose repartition of androgen receptor (more important in visceral adipose tissue) and ER-α and -β, as well as localized antilipolytic effect of ER-α in subcutaneous fat tissue, might explain the different patterns of obesity in men (abdominal) and women (gluteal).
- Women with normal female repartition of adipose tissue benefit from the protective effect of normal secretion of adipokines (leptin and adiponectin) against the development of insulin resistance.
- A small increase in weight (obesity) has a more deleterious effect on the incidence of type 2 DM in women than in men.
- Abdominal obesity leads to proinflammatory status through secretion of cytokines as tumour necrosis factor (TNF)-α and interleukin (IL)-6.
- Inflammation may play a more important role in the pathophysiology of type 2 DM in women than in men.
- Inflammation leads to increased insulin resistance and endothelial dysfunction, with increased cardiovascular morbidity and mortality.
- Endothelial dysfunction seems to be more prevalent in diabetic women than in men, which suggests that this pathophysiological pathway has an important role in increased female cardiovascular morbidity and mortality.
Table 1 Studies with results of FPG and OGTT in men and women

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study</th>
<th>Fasting glucose</th>
<th>2-h postload 75 g glucose</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>[175]</td>
<td>4367 healthy volunteers (25% of women) aged 40–64 years</td>
<td>Significantly lower in women (5.34 mmol/l) than in men (5.6 mmol/l)</td>
<td>Significantly higher in women (6.04 mmol/l) than in men (5.39 mmol/l)</td>
<td>The results were independent of race, BMI and alcohol consumption</td>
</tr>
<tr>
<td>[27]</td>
<td>15 606 patients (54% women) without a history of DM and 1325 patients with diabetes (54% women) aged 30–89 years</td>
<td>Undiagnosed diabetes and IFG defined by isolated fasting hyperglycaemia was more common in men than in women at 30–69 years of age</td>
<td>Significantly higher in women than men in all categories of age except for the fifth decade and particularly higher in elderly population older than 70 years</td>
<td>IGT was also more prevalent in women of all ages than in men</td>
</tr>
<tr>
<td>[7]</td>
<td>664 subjects at high risk for developing type 2 DM, aged 40–70 years</td>
<td>IFG was more prevalent in men (sex ratio 1.4)</td>
<td>IGT was more prevalent in women (sex ratio 1.7)</td>
<td>Subjects with isolated IFG were more insulin resistant than those with IGT. By contrast, subjects with isolated IGT exhibited a more severe deficit in early- and late-phase insulin secretion vs. IFG subjects</td>
</tr>
<tr>
<td>[9]</td>
<td>1485 individuals (48% women), aged 55–74 years (131 with known DM)</td>
<td>IFG was about two times more common in men than in women (9.8 vs. 4.5%) (p &lt; 0.01)</td>
<td>50% of newly diagnosed DM in women vs. 34% of newly diagnosed DM in men</td>
<td>Prevalence of IGT increased with age in both sexes</td>
</tr>
<tr>
<td>[5]</td>
<td>3370 individuals (54% women)</td>
<td>The prevalence of isolated postchallenge hyperglycaemia was slightly higher comparing women with men without fasting hyperglycaemia (1.9% in women vs. 1.4% in men)</td>
<td>Elevated glucose levels 2 h after oral challenge increased RR for incident CVD by up to 40%, 2 h PG levels identify individuals at an increased risk for CVD events</td>
<td></td>
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</tbody>
</table>

BMI, body mass index; CVD, cardiovascular disease; DM, diabetes mellitus; FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; RR, relative risk.
Levels of sex hormones and sex hormone–binding globulins (SHBG) have in some studies been associated with the development or the prevention of the occurrence of DM in men and women (table 2).

It appears that testosterone has opposing effects on the occurrence of DM in men (protective) and women (risk factor) and that SHBG are more protective in women than in men. Oestradiol also might have opposing effects on men (risk factor) and women (protective), as in males with oestrogen resistance, insulin resistance might develop, whereas in menopausal women without DM, menopause is a risk factor for elevated FPG [11]. However, oestradiol levels in animal studies are associated with increased insulin resistance and adiposity in both males and females [12], and streptozocin-induced diabetes in mice may be halted by a therapeutic dose of oestradiol, which appears to prevent the beta-cell apoptosis by the involvement of the ER-α [13]. This leads us to consider the role of the sex hormone receptors (SHR) and particularly to consider emerging data in the role of ER-α and -β on various gene expressions involved in glucose homeostasis (figure 1).

Animal studies suggest a repressive role of ER-β on the gene expression of GLUT4, the main protein involved in glucose uptake in skeletal muscle (and thus involved in the development of insulin resistance), whereas ER-α might improve insulin resistance. Moreover, these receptors also have opposite non-genomic effects mediated by interactions with transcriptional factors: ER-α–NF-κB interaction avoids repression of GLUT4 expression, whereas ER-β–specificity protein 1 interaction inhibits the expression of the GLUT4. Ratios of ER-α and -β in membrane cells determine the effects on GLUT4 expression and thus on insulin resistance in specific target organs; the use of ER-β antagonists might thus be a way to decrease insulin resistance and should be an area of research [14].

Sex hormones and SHR not only are directly involved in the glucose homeostasis regulatory system but also influence the adipose tissue repartition and thus the secretion of adipokines, which influence the development of insulin resistance. Indeed, SHR are present both in subcutaneous and in visceral fat [15]. Androgen receptors are more expressed in visceral than in subcutaneous fat, in both men and women, and are upregulated by testosterone [16]. Furthermore, ER-α upregulates the antilipolytic α2A-adrenergic receptor in subcutaneous fat but not in intra-abdominal adipose tissue [17]. These facts offer an explanation for the difference in adiposity patterns between men and women, with peripheral gynoid obesity in women and central android obesity in men.

Moreover, the gender-specific obesity pattern influences the secretion of several adipokines by adipose tissues [18,19]. Leptin and adiponectin are usually higher in women than in men, but obese patients have reduced levels. To note, adiponectin has antiatherosclerotic and anti-inflammatory properties. However, abdominal fat tissue increases fatty acids and inflammatory cytokines, as TNF-α and IL-6, which cause insulin resistance and cardiovascular adverse outcomes [19,20]. Thus, women with abdominal obesity may lose a protective adipokine-related effect and simultaneously gain inflammatory cytokines, which aggravate the tendency to insulin resistance and endothelial dysfunction [21]; in clinical settings, the latter was worse in women with type 1 DM [22] or type 2 DM [23] than in matched men. This may explain how C-reactive protein (CRP) levels are significantly more elevated in women than in men diagnosed with DM [24] and how it can aggravate the cardiovascular outcomes in women with diabetes.

### Table 2. Studies which showed relationship between testosterone, oestradiol and SHBG and the occurrence of DM in men and women

<table>
<thead>
<tr>
<th>Reference</th>
<th>Gender</th>
<th>Testosterone</th>
<th>SHBG</th>
<th>Oestradiol</th>
<th>DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>[176]</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>[177]</td>
<td>Men</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Women</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>[178]</td>
<td>Men</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Women</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
</tbody>
</table>

↑, increased risk; ↓, decreased risk; DM, diabetes mellitus; SHBG, sex hormone–binding globulins.
Epidemiology

Type 2 DM accounts for 85–95% of all diabetes in developed countries and even more so in developing countries. The prevalence of DM is directly correlated to the increasing age of the population and is higher in urban than in rural areas. The total number of women with DM is 10% higher than in men, as well as the number of women with IGT, which is 20% higher than in men [25].

In the USA [26] and Europe [27], there is no significant difference in the prevalence of DM between men and women, other than in older people and in minorities. One can hypothesize that menopause-related oestrogen changes are the cause of increased insulin resistance and prevalence of DM in older women.

The estimate of the prevalence of type 1 DM worldwide in children younger than 14 years is 0.02%, with variations between countries and ethnicities [25]. A prospective study conducted in Europe for 2 years found a 1.5 male/female ratio in the 25–29 years age group, a higher ratio than 1 in the 14–25 years age group, whereas the ratio was 1/1 in the 0–14 years age group (except in Slovakia where there was a higher incidence of type 1 DM in male children) [28].

Complications of DM and Related Co-morbidities

Looking at the data related to the impact of sex hormones on glucose homeostasis and their role in increased inflammation and thus endothelial dysfunction in women in comparison with men, one could ascertain that the same level of glucose disorder in women renders them prone to more microvascular and macrovascular complications. This is an area of future research because recommended therapeutic target levels of glucose are for now similar in men and women with diabetes [29]. Table 3 summarizes the differences observed between men and women with DM.

Gender Specificity of Microvascular Complications

Optthalmological Complications

We found only one publication that specifically assessed the impact of gender on diabetic retinopathy in type 1 DM patients [30]: prevalence of retinopathy in women was significantly higher than that in men, but men had higher prevalence of severe retinopathy. Prevalence in women older than 50 years increased with age, whereas it decreased in men. In type 2 DM, retinopathy is an independent predictor of mortality, especially cardio-vascular, in both sexes; however, non-proliferative diabetic retinopathy was more strongly associated with cardiovascular mortality in women with diabetes than in men [31]; this finding is corroborated by three other studies [32–34]. To note, diabetic retinopathy can worsen spontaneously during pregnancy in direct correlation not only with the pregestational severity of the retinopathy but also with the glucose levels before conception and the magnitude of improvement of glucose homeostasis in the first trimester [35]; use of the analogue insulin lispro during pregnancy is controversial because some cases of severe diabetic retinopathy were described [36], whereas a prospective study did not confirm a causal effect [37].

Kidney Complications

Gender impact on diabetic nephropathy is a topic that was reviewed in 2001 [38]. There are contradictory studies on both type 1 DM–related nephropathy and type 2 DM–related nephropathy. However, female gender has not been found to be associated with an increased incidence of nephropathy or a worse renal prognosis. Analysis of the sex-related influence on incidence and prevalence of nephropathy is probably biased by other risk factors such as hypertension (HTN) and duration of diabetes. The opposing impact of oestrogen and testosterone on the kidney might explain gender differences in nephropathy [2]. For example, oestrogen reduces proliferation of mesangial cells and the activity of the renin–angiotensin–aldosterone system (RAAS), whereas testosterone increases both. Moreover, oestrogen increases the activity of metalloproteinase enzymes and nitric oxide (NO) synthesis, whereas it decreases collagen synthesis by mesangial cells. The effect of testosterone on the three latter systems is unknown. Finally, genetic factors might be associated with gender differences in the occurrence of nephropathy. The M235T polymorphism in the angiotensinogen gene increases the incidence of diabetic nephropathy in male patients with type 2 DM but not in female patients [39]. The angiotensin II type 2 receptor gene is involved in the development of kidney dysfunction and HTN in type 1 DM male patients but not in type 1 DM female patients [40]. These genetic factors should be further explored for a better understanding of their impact on gender difference in diabetic nephropathy.

Diabetic Neuropathy

Some small studies considered gender as a risk factor for diabetic neuropathy. In a study involving 191 patients (57% of women) with type 2 DM, men had more distal
Table 3 Differences observed between men and women with DM

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ophthalmological complications</strong></td>
<td>Decreased prevalence after 50 years</td>
<td>Increased prevalence especially above the age of 50 years</td>
</tr>
<tr>
<td></td>
<td>More severe intensity</td>
<td>Non-proliferative retinopathy is more strongly associated with cardiovascular mortality</td>
</tr>
<tr>
<td></td>
<td>Male gender was associated in some studies with a worst renal prognosis</td>
<td>May present a spontaneous aggravation during pregnancy</td>
</tr>
<tr>
<td></td>
<td>M235T polymorphism in the angiotensinogen gene is associated with an increased incidence of nephropathy in male patients with type 2 DM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Angiotensin II type 2 receptor gene is associated with an increased incidence of nephropathy and hypertension in male with type 1 DM</td>
<td></td>
</tr>
<tr>
<td><strong>Kidney complications</strong></td>
<td>Increased occurrence of distal symmetrical polyneuropathy</td>
<td>Female gender is not associated with a worse renal prognosis</td>
</tr>
<tr>
<td></td>
<td>Maybe increased incidence in men</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prolonged QTc is 3.8 more sensitive to predict autonomic neuropathy in men than in women</td>
<td></td>
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<tr>
<td><strong>Cardiovascular</strong></td>
<td>Less aggressively treated</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased mortality and morbidity</td>
<td></td>
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<tr>
<td></td>
<td>Poorer prognosis after MI</td>
<td></td>
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<tr>
<td></td>
<td>Long duration of DM is associated with worse cardiovascular outcomes</td>
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<tr>
<td></td>
<td>Each cardiovascular risk factor alone (hypertension, hyperlipidaemia) and in combination has a more deleterious impact</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overall controversial studies</td>
<td></td>
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<tr>
<td></td>
<td>DM in young women might be a stronger risk factor for a cerebrovascular accident than in men</td>
<td></td>
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<tr>
<td></td>
<td>Women may have higher in-hospital mortality rates than men after an ischaemic stroke</td>
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<tr>
<td><strong>Cerebrovascular complications</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Depression</strong></td>
<td>Higher prevalence in women with type 1 DM aged 20–39 years</td>
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<tr>
<td></td>
<td>Higher prevalence of depression/anxiety in women with type 1 and type 2 DM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stronger correlation between uncontrolled DM and depression in women with type 1 and type 2 DM</td>
<td></td>
</tr>
<tr>
<td><strong>Osteoporosis</strong></td>
<td>Men with type 1 DM have lower values of bone mineral densitometry with increased risk of non-vertebral and hip fractures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased risk of hip fracture in type 1 and type 2 DM, despite higher values of bone mineral densitometry</td>
<td></td>
</tr>
<tr>
<td><strong>Puberty</strong></td>
<td>Pubertal growth retardation in young girls with uncontrolled DM</td>
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</tr>
<tr>
<td></td>
<td>More weight gain and more difficulties to lose overweight</td>
<td></td>
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<tr>
<td></td>
<td>More difficulties to equilibrate DM and higher tendency to develop microvascular complications</td>
<td></td>
</tr>
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</table>

DM, diabetes mellitus; MI, myocardial infarction.
symmetrical polyneuropathy and electromyography-supported neuropathy than women [41]. In a case–control study involving 110 patients (78% of women) with diabetes, men were associated with increased incidence of diabetic neuropathy [42].

According to autonomic diabetic neuropathy, a meta-analysis that included 17 studies with 4584 patients (92% had type 1 DM; 46% women) showed that at a given specificity of 86%, prolonged electrocardiographic QTc was 3.8 more sensitive in men than in women, predicting autonomic failure [43].

**Gender Difference in Macrovascular Complications**

**Cardiovascular Complications**

- Women are less aggressively treated than men at the time of a coronary event.
- Inflammation and endothelial dysfunction are more strongly involved in the pathophysiology of cardiovascular disease (CVD) in women with DM than in men.
- Women with DM have higher morbidity and mortality following an acute coronary syndrome.

There are emerging data that ischaemic heart disease differs between men and women, according to presenting symptoms, ways of diagnosis, evaluation and prognosis [44,45]. Annually, cardiovascular death affects more women than men, and there are no reduced cardiovascular-related mortality rates over the years in women as it is observed in men. An analysis of data published in the American population–based surveys (National Health and Nutrition Examination Survey (NHANES) I, II and III) over the past 30 years reveals that men with DM had a 43% reduction in the overall mortality and cardiovascular mortality rates (similar to the rate observed in the population without diabetes), whereas it did not change in women with DM [1]. Several studies assessed the gender-related impact of DM on cardiovascular mortality and morbidity [46–50]. DM increases the risk of coronary heart disease (CHD) mortality more in women than in men with DM; women with diabetes have a poorer prognosis than men with diabetes after acute myocardial infarction (MI), while long duration of DM is associated with worse cardiovascular outcomes in women but not in men. Overall, in a meta-analysis of 37 prospective studies, women with diabetes had a 50% increase in cardiovascular mortality compared with men with diabetes, even after taking into consideration all the cardiovascular risk factors [47].

The increased cardiovascular morbidity and mortality in women with diabetes may be because of several reasons [44]. First, women are less aggressively treated than men. Second, women may have more combined cardiovascular risk factors than men, which have a worse impact on women than on men and finally cardiovascular risk factors may be more severe in women than in men.

It is of concern that women with DM are less aggressively treated than men at the time of an acute coronary event [51]. Their management is characterized by less frequent use of aspirin, heparin or beta-blockers and delayed used of thrombolytic therapy, with greater incidence of major bleeding, together with less frequent use of cardiac catheterization, percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass graft surgery. Poor outcomes in women with DM after PTCA were found in earlier but not in recent studies, showing an improvement in PTCA outcomes equivalent to those observed in men with diabetes [52,53]. The use of drug-eluting stents appears safe and efficient at 1 year of follow-up, with equivalent comparable outcomes in men and women [54], but a recent meta-analysis showed that the use of sirolimus-eluting stents in patients with DM might be associated with an increased hazard ratio for death in both sexes, warranting a tight follow-up after such a procedure in patients with diabetes [55].

Finally, as previously stated, in the light of endogenous and exogenous hormonal wide impact, women might have worse vascular dysfunction than men, expressed independently of coronary obstruction [44].

In summary, like other authors [23,48,56], we consider that DM removes the protective oestrogen-related benefit on CHD observed in women without diabetes. Therefore, women with DM should be treated as aggressively as men at the time of an acute coronary event.
Cardiovascular Risk Factors: Gender Differences to Explain Worse Cardiovascular Outcomes in Women with DM

- Women are less aggressively treated than men to achieve therapeutic goals of HTN, haemoglobin A1c (HbA1c) for DM, LDL and triglycerides levels for dyslipidaemia in primary and secondary prevention.
- Cardiovascular risk factors have more damaging effects on women than on men.
- Diabetic dyslipidaemia (low HDL, hypertriglyceridaemia and increased small LDL particles) is more severe in women than in men with DM, with a more severe impact as a cardiovascular risk factor.
- HTN is more frequent in women than in men with DM, with more deleterious cardiovascular effects.
- Inflammation has worse impact on endothelial dysfunction in women than in men with DM.
- Obesity in women with DM is associated with a worse cardiovascular prognosis than that in men.
- Metabolic syndrome and CRP levels have a stronger correlation in women than in men, with a worse cardiovascular outcome. Women with DM and the metabolic syndrome should be carefully monitored for ischaemic heart disease as they are at increased risk of ischaemic cardiovascular events and mortality.

In women with DM, the odds ratio (OR) of each cardiovascular risk factor for adverse cardiovascular outcomes is higher than that in men with DM and the non-diabetic population [57]. In women with DM, the impact of individual cardiovascular risk factors is increased and escalates when combined (figure 2). Moreover, it appears that women are less aggressively treated not only during an acute ischaemic event but also in primary and secondary prevention to reach recommended therapeutic goals of HbA1c level, LDL-cholesterol level or BP [58,59].

Inflammation leads to great insulin resistance and endothelial dysfunction and is associated with worse cardiovascular outcomes in women with type 1 DM [22] and obese women with type 2 DM than in matched men with diabetes [23].

Obesity has more impacts on women than on men [60]. Women with type 2 DM might suffer a more negative impact of obesity and fat mass in comparison with men. They develop more easily left ventricular hypertrophy, which is a marker of cardiovascular mortality [61]. Obese women with type 2 DM tend to have worse endothelial dysfunction than men [23].

HTN seems to be more frequent in women than in men with DM, with a more deleterious effect: an increase of 10 mmHg systolic BP might lead to an increase of 30% CHD mortality in women but only 14% in men [2,62].

Diabetic dyslipidaemia (low HDL, hypertriglyceridaemia and increased small LDL particles) seems to be more marked in women than in men with DM, with an increased impact on cardiovascular risk factor. Low HDL levels in women with diabetes are associated with a fourfold increase in CHD mortality compared with women or men without DM at equivalent HDL levels; hypertriglyceridaemia is more deleterious in women than in men [2,48,62].

In women with DM, a diagnosis of metabolic syndrome conveys worse cardiovascular morbidity and mortality because of worse inflammation status determined by higher CRP levels compared with men [63], more arterial stiffness [64], carotid stenosis [65] and more ischaemic strokes [66] than men with the same profile.

Cerebrovascular Complications

There is controversial literature about impact of gender on the incidence of stroke and prognosis. A subanalysis of the United Kingdom Prospective Diabetes Study (UKPDS) showed that women had few strokes than men with type 2 DM [67]. These findings were corroborated in a Canadian cohort study based on 61 327 individuals (55% of women) [68]. However, a British study [69], which involved 41 799 patients with DM and 202 733 control individuals, showed an increase in the risk attributable to
diabetes among young women (Hazard Ratio (HR) 8.18; 95% CI 4.31–15.51), which decreased with age. In a prospective study that involved 261 women and 300 men with diabetes among 2446 patients hospitalized for ischaemic stroke, women with DM had a poorer prognosis with in-hospital mortality rate of 14.9 vs. 8.3% in men with DM [70]. In a study of individuals with type 1 DM, there was 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. In this study, diabetic nephropathy was a strong predictor of stroke [71].

Foot Complications

The term ‘diabetic foot’ includes a vast range of abnormalities and involves macrovascular as well as microvascular diabetic complications. In a large, prospective study, which included 500 848 patients with DM and 500 268 matched subjects, women younger than 45 years had higher incidence of peripheral revascularization than men, and women older than 84 years had higher incidence of both lower extremity amputation and peripheral revascularization procedures than men [72]. There are few relevant publications, which assess gender difference for this complication. A Swedish study showed that health concepts and beliefs, which differ between women and men, can lead to differences in preventing and managing diabetic foot lesions (women were more active than men in seeking and applying professional), thus influencing outcomes [73].

Depression

Patients with DM have co-morbid depression or psychological symptoms more often than healthy individuals. A meta-analysis showed that it affects up to one third of patients with diabetes and that the OR for depression in type 1 and type 2 DM patients doubled compared with that in the non-diabetic population. The OR was higher in women with diabetes than in men, which further exacerbates the higher prevalence of depression in women in the general population [74].

Depression in young people with type 1 DM is three times more prevalent than that in young people without DM. There are controversial data regarding gender difference in the occurrence of depression in young patients with type 1 DM [75]. In a study that involved 53 072 individuals aged 20–64 years [76], involving patients with both type 1 and type 2 DM, it was shown that DM was significantly associated with depression in women aged 20–39 years (OR = 2.52) but not in older women. In another study that involved 825 individuals with type 1 DM (48% females) and 786 with type 2 DM (50% females), there was a higher prevalence of anxiety and depression in women than in men as well as a stronger association of depressive symptoms with uncontrolled diabetes (as assessed by high HbA1c) in women with type 1 and type 2 DM than in men. The authors of this study believed that changes in oestrogen levels might link glycaemic control and depressive symptoms and that women might be more negatively affected by depressive symptoms in regard to behavioural self-care treatment than men [77].

The gender difference of the impact of depression in the diabetic population has not been studied, although depressive symptoms predicted cardiovascular events in type 1 DM women but not in men [78].

We can conclude that women with DM, especially younger ones and those with uncontrolled DM, have an increased risk of depression in comparison with men with diabetes. The pathophysiology of oestrogen involvement in depressive symptoms and glycaemic control is an area for research.

Osteoporosis

Bone mineral densitometry (BMD) value is lower in individuals with type 1 DM [79,80] than in patients without diabetes, in both adult men and women. In a small, retrospective study involving 60 people with type 1 DM (50% females), men had significantly lower vertebral and femoral BMD values, whereas women had only significantly lower femoral BMD in comparison with healthy, age- and sex-matched patients [81]. In children with type 1 DM, a prospective study showed a more marked decrease in bone mass in girls than in boys [82]; however, this finding was not observed in other studies [83,84]. In patients with type 2 DM, BMD was similar [79] or higher [80, 85] than that in patients without diabetes. In one study that involved patients with type 2 DM, BMD values were higher in women and similar in men with DM compared with individuals without DM [86]. Another gender difference to note is a faster BMD loss in older (70 to 79 year old), white women with type 2 DM than in men with type 2 DM or in black women; in the latter, there is no difference in the BMD loss compared with normoglycaemic subjects [87].

The risk of hip fracture in women with type 1 DM was evaluated from 6.4- to 12.25-fold [88–91] in comparison with women without diabetes. Men with type 1 diabetes have a 3.9-fold risk of non-vertebral fracture and a 17.8-fold relative risk of hip fracture in comparison
with normoglycaemic men [90], but another study did not find a significant increase in the rates of fracture in men with type 1 DM [89]. In women with type 2 DM, studies showed a 1.5- to 2.2-fold [88–92] increased relative risk of hip fractures compared with that in normoglycaemic women, despite higher BMD [92,93]. In men with type 2 DM, some studies showed a less significant but still more elevated risk of hip fracture [89,94], whereas other data did not confirm these findings [90].

There is concern about increased fractures and worsening osteoporosis in older women with type 2 DM treated with thiazolidinediones. Schwartz et al. showed that in 69 of 666 patients with DM treated with thiazolidinedione (rosiglitazone, pioglitazone and troglitazone), unlike men, women had a yearly increased total, spine and trochanter bone loss in comparison with patients with DM who did not receive this drug [95]. A review of the safety data of the A Diabetes Outcome Progression Trial (ADOPT) study by GlaxoSmithKlein (Philadelphia, Pennsylvania, USA) and an independent safety committee [96], as well as Takeda Pharmaceuticals (Deerfield, Illinois, USA) [97], found that rosiglitazone and pioglitazone, respectively, led to increased incidence of fractures (hands, humerus and feet) in treated women with type 2 DM in comparison with men. The information has been reviewed by the Food and Drug Administration, which recommends that consideration of the risk of fractures should be made before starting these drugs in women with type 2 DM [98,99].

Gynaecological Considerations in Women with DM

Gender Difference in Puberty in Patients with Type 1 DM

There are specific pubertal issues that affect young girls and female adolescents with type 1 DM. Pubertal growth retardation has been observed in female patients with type 1 DM with elevated HbA1C but not in young male patients [100]. Moreover, young girls with type 1 DM gain more weight than boys with type 1 DM [101–103] and have more difficulty losing weight than male patients [102]. Finally, glucose homeostasis is more difficult to reach in girls with type 1 DM during adolescence than in boys for several reasons. There may be differences in the sensitivity to insulin between boys and girls during puberty [104]. Furthermore, girls are more prone to discontinue insulin therapy to limit weight gain than boys [105], coupled with a higher incidence of eating disorders during puberty than boys [106]. This results in the possibility of girls with type 1 DM developing more microvascular complications than boys [107, 108].

Menstrual Abnormalities, Infertility and Sexual Disorder in DM Women

Irregular Menstruations and Infertility

- Women with type 1 diabetes have an increased prevalence of menstrual disorders compared with non-diabetic women. They also have up to 6 years of reduction in their reproductive period.
- Up to 40% of women with type 1 DM will develop polycystic ovarian syndrome (PCOS), which is associated with infertility disorder and hyperandrogenism.
- Women with type 2 DM have up to a 10-fold increased risk of developing the PCOS, with an increased risk of developing the metabolic syndrome, associated with a worse cardiovascular prognosis.

In a retrospective study [109] that compared 143 women with type 1 DM with their 186 healthy sisters and 158 unrelated healthy controls, type 1 DM was an independent risk factor in menstrual problems (including long cycle length, long menstruation and heavy menstruation) at younger age ranges (20 to 39 year old) but not at older ages. One conclusion of the authors was that menstrual abnormalities in the earlier reproductive years might be more accentuated in women with type 1 DM.

In another cohort study [110], women with type 1 DM had delayed menarche and earlier menopause, which led to a 6-year reduction of their reproductive period. In a systemic review, up to 20% of women with type 1 DM had menstrual irregularities, 20% had hyperandrogenaemia and 30% had hirsutism; these findings indicated a prevalence of the PCOS among women with type 1 diabetes in a range from 12 to 40% [111]. Fifty to 70% of women with PCOS have insulin resistance (in comparison with 10–25% of women of the general population) and thus have a five-fold to 10-fold greater risk of developing type 2 DM: up to 45% of women with PCOS will be diagnosed as having type 2 DM or IGT [112]. The corollary of this is that women with type 2 DM are also at greater risk (5–10 times greater) of developing PCOS than healthy matched cases [112]. Insulin resistance in women with PCOS is associated with an 11-fold increased risk of
developing the metabolic syndrome with lipid profile abnormalities in comparison with age-matched women without PCOS [113]. Thus, there is concern that PCOS is associated with an increased adverse cardiovascular morbidity and mortality. To note, hyperandrogenism in PCOS might also increase the incidence of endometrial carcinoma [114]; the latter is also increased in women with type 1 DM [115], and thus the combination of both factors confers a high risk of endometrial carcinoma in these women, who should be carefully monitored for this occurrence. Abnormal menstruations may be associated with hyperglycaemic or hyperglycaemic events in women with diabetes, without clear explanations [116].

Sexual Disorder

Sexual dysfunction in women with diabetes, contrary to men, is not related to age, BMI, glycaemic control, duration of diabetes and diabetes-related complications (except for chronic renal failure) and is mostly because of psychological factors (depression and poor cognitive adjustment to diabetes).

In men with DM, sexual dysfunction is essentially expressed by erectile dysfunction, which might result from endothelium and smooth muscle disorder as well as from autonomic neuropathy and psychological causes; in women with DM, the pathophysiology, expression, risk factors and severity of sexual disorders are much less studied [117]. In one review, sexual dysfunction in women with diabetes, contrary to men with DM, was not related to age, BMI, control of glucose levels, duration of diabetes and diabetes-related complications (except for chronic renal failure); however, depression had a similar impact on sexual disorder in patients with DM of both genders [117]. Women with either type 1 [118] or type 2 [119] DM have higher prevalence of sexual dysfunction than healthy women. In a questionnaire-based study involving 97 women and 95 men with type 1 DM, predictors of sexual dysfunction in men were both psychological (low-quality partnerships and poor emotional and cognitive adjustment to diabetes) and somatic factors (higher age, higher BMI, poor glycaemic control and diabetes-related complications). In women with type 1 diabetes, depression and poor cognitive adjustment to diabetes were also associated with poor sexual function [120].

In conclusion, sexual dysfunction might radically differ between women and men with DM according to the involved pathophysiological pathways and risk factors and should thus be further studied in the aim to better understand and prevent its occurrence.

Pregnancy and DM

Pregnant women may have pregestational (type 1 or 2) DM (PGDM) or gestational DM (GDM), which is defined by DM diagnosed for the first time during pregnancy.

Complications of maternal hyperglycaemia affect both mother and foetus [121] and can result in increased spontaneous abortions and congenital malformations in women with type 1 and 2 DM [122–125]. Glucose homeostasis is critical till the end of organogenesis, at the 12th week of gestation, to avoid complications [35], and thus tight preconception care is critical and can reduce the rate of congenital abnormalities from 6.5 to 2.5% [126].

Diabetes in pregnant women is of growing concern because of the epidemic of obesity and metabolic syndrome in young women [60,127]. This leads to increased risk in women of fertile age developing GDM or with type 2 PGDM [123]. Thus, screening for GDM has become a public health issue, and there are extensive reviews about the controversies of modalities and cut-off values regarding the screening and diagnostic tests for GDM, beyond the scope of the present work [121,125,128]. The high rate of true type 2 DM following the occurrence of GDM requires screening soon after delivery (and later if negative) [29,125,129].

Diagnosis and treatment of GDM as well as optimal glucose regulation in PGDM are challenging and critical issues; the usual recommended treatment is an intensive insulin therapy, but several studies highlighted safety and efficiency issues relating oral hypoglycaemic agents such as glibenclamide [122,130–134] and metformin [135,136] in GDM or type 2 PGDM. The safety of long-acting analogue insulins during pregnancy has not been proven, and there are concerns, particularly, about insulin glargine because of its increased interaction with the insulin-like growth factor 1 (IGF-I) receptor and potential modification of IGF-I action, which is implicated during early pregnancy in the implantation of the embryo in the endometrium and later regulates foetal growth as a mediator of the human placental growth hormone [137]. There are not enough data currently available on the use of insulin detemir and glargine during pregnancy to conclude on their safety and efficacy during pregnancy [137]. On the contrary, rapid-acting analogue insulins aspart and lispro are considered safe during pregnancy (no placental crossing and no more congenital abnormalities) [137].
Contraception in Women with DM

- Contraception is an important issue in women with DM, and it is vital to consider all the options regarding the hormone-related risk of thrombotic events, uncontrolled HTN, hyperlipidaemia or hyperglycaemia.
- Copper intrauterine device (IUD) is the safest form of contraception for women with DM, although low-dose oestrogen combined oral contraceptive might be adapted in young women without vascular complications, whereas progestin-only IUD might be suitable in women with microvascular or macrovascular complications.
- Progestin-only regimens should not be offered to women with previous GDM because they are associated with an increased incidence of overt type 2 DM.
- Menstrual period may be associated with increased insulin resistance and uncontrolled DM in diabetic women.

The planning of pregnancy in women with DM is crucial to avoid maternal as well as foetal morbidity and mortality, which may result from prolonged gestational hyperglycaemia; however, hormonal contraception in women with DM raises some concern because of the possibility of adverse effects such as disturbance in carbohydrate and lipid metabolism as well as thrombotic events [138,139].

A systematic Cochrane review about hormonal and non-hormonal forms of contraception for women with type 1 and type 2 DM found only three suitable randomized controlled trials [139]. The authors concluded that there was insufficient evidence to assess whether progestin-only and combined oral contraceptives differ from non-hormonal contraceptives in glucose and lipid profiles as well as in long-term complications; however, the safest form of contraception in women with DM appears to be the copper IUD. A prospective study, which was published after the Cochrane review, involving 55 type 2 DM and 58 type 1 DM perimenopausal women showed that women with type 1 DM who received a high-dose combination oestrogen contraceptive [30 mg ethyniloestradiol (EE)/75 mg gestodene)] needed to increase significantly the dose of their insulin therapy without increased HbA1c; lipid profile was transiently altered in women with type 1 DM treated with 20 mg EE/150 mg desogestrel. Although a slight increase in biological thrombotic patterns was observed, which was lowest with the use of low-dose combined oestrogen oral contraception, no adverse clinical events were noted [140].

Progestin-only contraceptive therapy is not recommended for women with previous GDM as it is associated with an increased incidence of type 2 DM in these women [141,142]. A potential benefit of hormonal contraception is that it may lead to a subsequent reduction in ischaemic heart disease severity, independently of other risk factors including DM in postmenopausal women [143]. Finally, the menstruation period can be associated with changes in the usual glycaemic profile of women with diabetes, in the form of changes in eating patterns, increased insulin resistance or hormonal-related changes, which remain to be determined [116].

Postmenopausal Status and Hormone Replacement Therapy in Women with DM

- Postmenopausal women with DM might benefit from the positive metabolic effects of hormone replacement therapy (HRT) in the form of reduced insulin resistance and better glycaemic control and also the limitation of weight gain, reduction of BMI and waist–hip ratio and amelioration in lipid profile.
- Potential adverse cardiovascular effects are concerning because of increased levels of CRP, prothrombotic factors and triglycerides.
- There are controversial results in regard to cardiovascular outcomes in women with DM treated with HRT.
- HRT should not be started to prevent CVD or osteoporosis as better alternative therapies exist. HRT should not be started in patients with DM before an alternative therapy is considered to control vasomotor effects of menopause.
- If HRT is started, short-term, low-dose, transdermal oestrogen is the safest regimen.

HRT is a controversial option for postmenopausal women [144]. Potential adverse outcomes are of serious concern in women with DM who are already at increased risk of cardiovascular event, especially during menopause [145]. Moreover, type 1 DM might be associated with increased incidence of endometrial cancer [115] and thus HRT might further aggravate this occurrence in these patients.

A meta-analysis [146] that included 107 studies suggested that whereas healthy women who received HRT
had reduced androgenic fat, insulin resistance, new-onset of DM, BP, LDL/HDL ratio and procoagulant markers, women with diabetes had only reduced fasting glucose and insulin resistance. In a large, well-designed trial [147], women with DM also had a reduction in weight, waist circumference and waist-hip ratio. Oral HRT (conjugated rather than esterified oestrogen and oestrogen alone rather than combined with progestin) had better metabolic effects than transdermal agents and also led in a dose-dependent association to increased triglycerides and CRP levels as well as decreased protein S levels, whereas transdermal agents did not [146]. The authors concluded that younger postmenopausal women, including women with DM, might benefit from transdermal HRT, without an increase in cardiovascular risks, whereas the risks of oral HRT outweigh the benefits in older women, especially those with CVD.

The potential positive metabolic effects of HRT cannot be translated into straightforward positive clinical cardiovascular effects. Some studies showed cardiovascular benefits of low-dose oestrogens (less than 0.625 mg oestradiol) in women with DM [148,149], which was more marked when combined to progestogens, whereas other studies showed worsening cardiovascular outcomes in women with DM [149,150]. As a result, it is recommended that one should not start HRT for cardiovascular primary nor secondary prevention in postmenopausal women, including recently postmenopausal women because other more effective therapies, such as statins and aspirin, would provide greater benefit [144,151,152]. Other therapeutic alternatives to HRT include bisphosphonates to control osteoporosis, and selective serotonin reuptake inhibitor as venlafaxine or antiepileptics as gabapentin to control vasomotor symptoms related to oestrogen deficiency [153].

Some authors consider that HRT could be given in low-cardiovascular risk postmenopausal women with diabetes (without other contraindication as breast or endometrial cancer) according to a stratification based on age, triglycerides levels and time from beginning of menopausal symptoms to starting HRT [153]; however, as we reviewed previously the worsening outcomes of CVD in women with diabetes, we think that DM excludes the possibility of a low-cardiovascular risk category in affected women.

In conclusion, despite an amelioration of many components of the metabolic syndrome, there is no assurance of protective cardiovascular effects especially in oral oestrogen regimens that elevate CRP and triglycerides levels. Alternative therapies to HRT should be considered first; if the latter is given, it should be transdermal, at low dose, and for a short period of time. Further studies are needed for this major issue.

Pharmacological Considerations

In a study that involved 3849 patients with diabetes (50.7% women) treated in five academic primary care settings, women with or without CVD were significantly less likely than men to be prescribed lipid-lowering medications and aspirin and were less likely to reach HbA1c LDL as well as BP goal levels [58]. There was no analysis of the reasons for such differences in the treatment of DM between men and women as a description of the number of oral drugs or of the frequency of use of insulin was not provided. Nevertheless, women had a poorer glycaemic control. The fact that women are less aggressively treated than men is obvious and can explain in part the increased cardiovascular mortality observed in women with diabetes in comparison with men, but the question remains as to how we change this.

Glucose Regulation in Women with DM

- There are no available data today showing that efficacy of any hypoglycaemic agent differs between men and women to achieve glycaemic control.
- Women with DM may be less aggressively treated than men and have a poorer glycaemic control. They should be more aggressively treated.
- Thiazolidinediones seem to lead to more fractures in women than in men.
- In light of particular physiopathology of glucose homeostasis in women, specific therapeutic options should be assessed: role of CRP-lowering drugs and development of ER-β antagonists and ER-α agonists.
- It would be of particular interest to evaluate if women and men benefit similarly of the same recommended therapeutic goals (fasting glucose and post-prandial glucose (PPG)) for equilibration of DM.

Many therapeutic trials have been conducted into all known pharmacological antidiabetic agents, such as the oral hypoglycaemic agents (biguanide, sulphonylurea, thiazolidinediones and glucosidase inhibitors), new oral dipeptidyl peptidase inhibitor, inhaled insulin, subcutaneous analogue or human insulin and subcutaneous glucagon-like peptide 1. However, the only epidemiological gender-specific considerations to
come out of these trials are data regarding the proportions of men and women involved. The benefits of lowering hyperglycaemia to prevent microvascular complications have been similarly measured according to gender. However, no trials have been conducted into the effects of lowering glucose therapy according to gender. We showed that there are emerging data suggesting gender difference in the pathophysiology as well as in the course of DM. As we already stated, a meta-analysis showed that men but not women with DM have experienced improved all-cause and cardiovascular mortality in the past 30 years [1]. Taken together, this raises the question of whether all the conclusions that have been obtained in clinical trials are equivalent for men and women with DM: are normal hypoglycaemic drugs as efficient in women as in men? Are the secondary effects of drugs the same in women and men? Because of the specific role of inflammation in the pathophysiology of DM and its related complications in women, should we choose anti-inflammatory drugs in their treatment? Should the management of DM be different in men and women, with different therapeutic goals? Indeed, recommended targets for HDL levels are higher in women than in men because of the more negative effects of low HDL in female patients [29], but why not also consider different goals for HTN (which was also shown to be more damaging in women than in men) and for parameters of equilibration of DM as HbA1c, fasting glucose and postprandial glucose?

These questions are not easy to answer. For example, thiazolidinediones, which appeared to reduce CRP levels better than insulin [154], may be a preferred first-line therapy in women; however, the use of thiazolidinediones is associated with more fractures in women than in men with DM [95]. This illustrates the complexity of the pharmacological options for DM and underlines the fact that any hypoglycaemic agent should be assessed according to advantages and disadvantages on glycaemic, cardiovascular and overall effects in women, rather than according to one isolated parameter of amelioration.

Development of new drugs should take into consideration the role of the ER in glucose homeostasis, and some authors consider specific ER-β antagonists and specific ER-α agonists as good options for DM control in women [14]; these possibilities should be carefully evaluated in the future. It was shown that in both male and female mice, oestradiol has a protective effect against the occurrence of pancreatic beta-cell apoptosis through ER-α [13], and this is an area for future research.

### Pharmacological Considerations in Women with DM to Reduce the Cardiovascular Mortality

- Women are less aggressively treated than men to achieve therapeutic goals of HTN, HbA1c, for DM and LDL and triglycerides levels for dyslipidaemia in primary and secondary prevention.
- **Dyslipidaemia**
  - A low-fat diet is less beneficial to women than men in improving lipid profile and cardiovascular outcomes.
  - Statins reduce cardiovascular events in both genders, but women have less reduction in total mortality and stroke events than men.
  - HDL levels are recommended to be ≥50 mg/dl in women and ≥40 mg/dl in men. Elevating HDL drugs might be of particular benefit to diabetic women in ameliorating the more harmful effect of low HDL.
- **HTN**
  - Recommended therapeutic goals for HTN are similar for men and women with DM, but this should be challenged.
  - CRP-reducing antihypertensive drugs might be of particular benefit to women. This issue should be evaluated in clinical trials.
- Inflammation and endothelial dysfunction are more strongly involved in the pathophysiology of CVD in diabetic women than in men. Again, CRP-lowering agents might be of particular interest in women with DM.
- **Metabolic syndrome** and CRP levels have a stronger correlation in women than in men, with a worse cardiovascular outcome. Women with DM and the metabolic syndrome should be carefully monitored for ischaemic heart disease as they are at increased risk of ischaemic cardiovascular events and mortality.
- Prothrombotic status is worse in women than in men. Low-dose aspirin primary prevention is recommended to both men and women with DM, although it appears that aspirin in men and women has different effects.
- Men and women with DM should stop smoking: alcohol consumption should be limited to one daily drink in women and two in men.

Aspirin is a standard pharmacological agent for prevention of CVD by the inhibition of platelet aggregation. DM is a particular prothrombotic status, which indicates the use of aspirin. Ulcerative coronary plaques, for example,
are more frequently observed in patients with DM than in individuals without DM, probably because of a procoagulation status, which is in part because of inflammation-related endothelial dysfunction and haematological changes associated with high coagulable status and a lower platelet threshold activation, especially in women [155]. Aspirin has gender-specific effects; in primary prevention [156,157], it reduces the incidence of stroke in women and MI in men. Effects of aspirin as secondary cardiovascular prevention are well known in both men and women [158]. The American Diabetes Association (ADA) recommends starting low-dose aspirin in both male and female patients with either type 1 or type 2 DM over the age of 40 years with additional risk factors (family history of CVD, HTN, smoking, dyslipidaemia or albuminuria). Consideration of low-dose aspirin as primary prevention should be made in patients with DM aged 30–40 years with added risk factors but not in patients younger than 21 years [29,159]. Women seem to be more resistant to the actions of aspirin than men [160], and this could be an added cardiovascular risk factor to consider when evaluating women with DM.

The ADA recommends different therapeutic HDL levels according to gender (50 mg/dl in women and 40 mg/dl in men) but recommends the same target LDL levels less than 100 mg/dl in both sexes [29]. Therapies for hyperlipidaemia differ between men and women. First, a low-fat diet benefits more men than women in improving dyslipidaemia and CVD [161]. Second, the use of HDL-elevating drugs might better benefit women than men, and this topic should be studied in randomized controlled trials. Third, statins do not have identical effects in men and women [162,163]. In women, the use of statins was not shown to be beneficial in primary prevention [58], except maybe in the Heart Protection Study, which specifically included women with DM [164]. Statins reduced cardiovascular events in secondary prevention in women although without reducing mortality contrary to men [163]. It is of particular interest to note that in regard to the specific role of inflammation as a cardiovascular risk factor in women, the use of statins might be a means to lowering CRP levels and thus to be of marked importance as a pharmacological agent in women with DM [165]. However, to date, there are no data supporting this approach and the indication as well as the dose of statins remains to be titrated according to observed LDL levels in patients.

As stated above, increased BP has a significantly worse impact on cardiovascular outcomes in women than in men. However, the ADA recommends [29] the same BP levels of less than 130/80 mmHg in both men and women with DM. This recommendation should be challenged, and it is possible that women with DM would benefit from more aggressive treatment and lower targets for BP. There are insufficient data to recommend these changes, but we recommend that these issues are investigated in prospective clinical studies. In light of the particular role of inflammation in cardiovascular pathophysiology in women, it might be interesting to consider favouring the antihypertensive drugs such as RAAS blockers and beta-blockers, which lower CRP levels [154].

The combination of DM with obesity, HTN and dyslipidaemia defines the metabolic syndrome [166–168]. In most countries, there is a higher increase in the prevalence of the metabolic syndrome in women than in men [60,127]. Individuals with the metabolic syndrome are at risk of developing type 2 DM [169,170] and have an increased cardiovascular morbidity and mortality [167,171–173]. Women with DM and the metabolic syndrome should be considered as very high-risk patients for CVD, and screening as well as prevention or therapeutic considerations should be an area for future research in this population.

Finally, lifestyle modifications in the form of exercise and diet to lose weight are important issues for women with diabetes, even slim women [10]. Indeed, elevated BMI is more strongly correlated to impaired cardiovascular risk factors (low HDL, high LDL, apolipoprotein A1 and CRP) and adverse cardiovascular outcomes than inactivity in women [174]. Also, aiming to reduce the cardiovascular mortality and morbidity in patients with DM, the ADA annually publishes mandatory recommendations to stop smoking for any individual with DM and to limit the alcohol consumption to one drink in women and two in men [29].

Conclusions

The available data suggest that there are gender-specific differences in the care of DM. The large, prospective trials made in the past 20 years have assumed that efficiency of glucose-lowering therapies as well as management of hyperglycaemic-related complications could be attributable without distinction to men and women, whereas a much higher number of men than women were included in these trials and no gender-specific analysis of the results was made. There is a growing awareness that gender influences aetiology, ways of diagnosis, prognosis and therapeutic efficiency in many clinical conditions. We have exposed in this review the critical points, which are apparent regarding the specific management of women with diabetes, and have underlined the areas that require further research in the future. Gender-specific
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