Chapter

The Role of Gender in the Onset, Development and Impact of Type 2 Diabetes Mellitus and Its Co-Morbidities

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Abstract

Almost half a billion people worldwide are living with diabetes mellitus (DM). Complications associated with DM are common and approximately half of those people with DM suffer from at least one comorbidity. There is high mortality, morbidity and cost associated with these comorbidities which include cardiovascular disease, retinopathy, nephropathy, neuropathy and osteopathy. Gender influences the relative risk of developing complications from DM via differing mechanisms – both directly and indirectly. Generally, an increased relative risk of cardiovascular disease and kidney disease is noticed in women with DM compared to the non-DM context, where rates of both are much higher in men. Men appear to be at greater risk of diabetic retinopathy and also of insensate diabetic neuropathy, whereas women suffer from an increased rate of painful diabetic neuropathy compared to men. These differences are not clear cut and vary regionally and temporally, indicating that the field would benefit from further research on both the epidemiology and physiological mechanism of the observed patterns. These differences should be taken into account in treatment programmes for DM and its comorbidities.

Keywords: gender, diabetes, diabetic complications, diabetic comorbidities

1. Introduction

Diabetes mellitus (DM) is a metabolic disease characterised by elevated blood glucose levels resultant of insufficient production or action of insulin, resulting in Type 1 (T1DM) and Type 2 (T2DM) respectively. Chronic hyperglycaemia is responsible for an array of severe macro- and micro-vascular complications resulting in numerous health complications. These include cardiovascular disease, retinopathy, nephropathy, neuropathy and osteopathy. Globally, more than 450 million adults are living with DM, while the annual death toll of DM is over 4 million people [1]. 70% of recorded deaths where T2DM is a contributing factor are due to T2DM comorbidities rather than T2DM itself, indicating insufficient or ineffective treatment of comorbidities [1, 2]. This statistic emphasises the importance of treating not only T2DM but also the complications associated with it, which are often present despite seemingly effective T2DM management.

The cost of treating T2DM includes the direct management of the disease with medication and medical visits as well as that of treating the associated complications and comorbidities which account for 53% of the total cost of T2DM patient care [3]. This puts the annual global healthcare expenditure on complications alone at $324 billion as of 2014 [4]. The continued increase in the healthcare budget spending on DM complications tracks the overall increased prevalence of the disease, but is also dependent on the likelihood of those complications within the DM population. Age is positively correlated with both onset of T2DM and its complications [5, 6]. In some middle income countries T2DM per capita is approaching 30% and increasing, these extraordinarily high rates of disease are intersecting with increasing life expectancy, which is also increasing fastest in middle-income countries [7, 8]. This will further compound the prevalence of T2DM complications and the associated morbidity, mortality and financial costs as the duration of disease and the average age of people living with it increases [9].

Despite a slightly increased prevalence of DM in men than women, more women than men die from DM and its associated complications [1]. Here we discuss the contribution of gender as a variable in the development of T2DM, its associated comorbidities and resulting mortality rates.

2. Gender differences in DM prevalence and mortality

The global prevalence of DM in adults aged 20–79 years is 9.3%, with slightly fewer women (9%) than men (9.6%) estimated to be living with the disease [1]. Prevalence of DM is increasing globally and though there is some evidence in high-income countries that incidence level is stabilising, the incidence in low- and middle-income countries continues to increase [1, 10]. The overall global prevalence of DM continues to increase both due to this increased incidence and due to the reduced mortality associated with DM as diagnosis and treatment continue to improve.

The major risk factors for the development of T2DM are obesity and poor diet. The higher prevalence of DM among men is despite generally higher rates of obesity in women globally - 15% of women and 11% of men were estimated to be in the obese category in 2016 [11, 12]. This epidemiological finding has been supported by studies at the individual level, which demonstrate that men have increased insulin resistance and develop T2DM at a younger age and lower BMI than women. This is primarily due to their overall propensity for visceral and hepatic deposition of lipid [11, 13–16]. In contrast, women tend to experience preferential subcutaneous deposition of lipid. These female and male pattern adipose distributions, commonly referred to as pear- and apple-shaped obesity respectively, are regulated by sex hormones and apple/central adiposity is independently correlated with T2DM status irrespective of BMI or gender [16, 17]. Though this bias exists currently and on a global level, there is high geographical and temporal variability [1, 18]. Despite men's physiologically higher propensity toward the development of T2DM, up until recently higher prevalence was recorded in women than men globally, and still is in many regions [1, 18]. This statistic correlates with what is known about obesity, a robust predictor of T2DM [19].

Although obesity has been recognised since ancient times, it effected a very low proportion of the population even up until the 1960s (1–2% in England at the time) and has only been described as posing a serious threat to public health in the last 50 years [20]. This rapid onset of obesity at the population level has correlated with the change in lifestyle and diet associated with development and westernisation, and, has disproportionately affected women [19]. In all countries assessed,

the prevalence of obesity is higher in women during the growth phase of increasing obesity prevalence within that country [19, 21–26]. Only as obesity levels stabilise does the prevalence of obesity in men reach that of women [27, 28]. As would be expected, this generally tracks with what is known regarding the prevalence of T2DM in women and men over time. 100 years ago, rates of T2DM were higher in women in all regions assessed [18, 29]. Now in 2020, Europe, North America, South-East Asia and the Western pacific IDF regions have recorded either higher rates in men or no difference between genders, while the Africa, Middle East and Central America regions record higher rates of T2DM in women [1].

This may in part explain why despite their metabolically preferential adipose expansion, and lower propensity to T2DM itself, women have higher DM-associated mortality, with 2.3 million women and 1.9 million men dying from DM or DM-associated complications in 2019 alone [1, 7, 30, 31]. However, considering the majority of T2DM-associated mortality is due to associated complications rather than T2DM itself, this also indicates a higher risk of either developing complications or to enhanced severity of those complications in women. The IDF also record increased spending on women with T2DM than men, which may reflect higher rates of comorbidity in this group [1]. Whether gender impacts comorbidity outcomes in response to T2DM has been assessed in studies investigating individual complications, these are discussed below.

2.1 Cardiovascular disease

Cardiovascular disease (CVD), including cardiomyopathy, congestive heart failure, stroke and peripheral arterial disease, is the most prevalent cause of both morbidity and mortality in patients with DM [32–35]. The increased risk of death from CVD compared to the general population has been estimated at being between 1.6 and 2.6 times greater in individuals with T2DM depending on the form of CVD [1, 36–38].

The T2DM milieu increases CVD risk via a number of pathways. Atherosclerosis build-up is accelerated by the combination of hyperglycaemia, insulin resistance and increased free fatty acid release. In tandem, blood pressure is increased; hyperglycaemia impedes the production of nitric oxide (NO), while free fatty acid release resultant from insulin resistance reduces the bioavailability of NO (reviewed in [39]). NO has a vasoprotective role through increasing vasodilation, and therefore reducing blood pressure, as well as inhibiting inflammation and platelet activation [40]. The upregulation of inflammatory signalling pathways, including AGEs (advanced glycation end-products) and their receptor; RAGE, further promotes plaque deposition (reviewed in [39, 41]). The culmination of these processes is a patient at high risk of cardiovascular insult. While rates of CVD have decreased in patients with and without T2DM over the past few decades, risk of an event and risk of mortality from CVD remain higher in patients with T2DM [42, 43]. This is at least in part due to high rates of inability to achieve glycaemic control, but even in cases of robust glucose control, there is an increased level of risk that remains, indicating a metabolic memory of the hyperglycaemia present prior to control of T2DM [44]. This is exacerbated the longer the person has been diagnosed with T2DM. The mode of modulation of this metabolic memory is discussed in Cooper et al. [45], where both epigenetic mechanisms and immune memory are put forward. The treatment of patients with T2DM with standard CVD treatment regimens largely ameliorates this risk [46].

In women there is a 44% greater T2DM-associated risk of coronary heart disease (CHD) than in men [47]. The vastly increased risk of CVD in T2DM-diagnosed women is so great that it has been proposed as the primary attribute accounting for

high diabetes-associated mortality in this population [30], see **Table 1**. In the general population men are at greater risk for CVD which is explained by the protective functions of oestrogens [54]. Primarily estradiol, for which there is receptors on cardiomyocytes, acts in a cardioprotective manner with numerous mechanisms for its action described in the literature (by improving mitochondrial function and reducing reactive oxygen species (ROS), via anti-fibrotic action in extracellular matrix remodelling, by stimulation of angiogenesis, via eNOS-dependent vasodilation, or possibly via aromatase action) as reviewed in Iorga et al., 2017 [55]. It is hypothesised that T2DM reverses the protective functions of oestrogens via immune-modulation [48]. As well as this increased disease burden, women with CHD and T2DM are at a nearly three times higher risk of death from CHD than men with CHD and T2DM [52]. A statistic that is likely related to the fact that women are less likely to be prescribed appropriate blood pressure and lipid lowering drugs [56–60].

Androgens, hormones which promote the development of male characteristics in vertebrates, have been shown to up-regulate the expression of known atherosclerosis associated genes in monocyte-derived macrophages from male donors but not from female donors [47]. However, men with hypogonadotropic hypogonadism (decreased androgen levels) have worse cardiovascular health and outcomes and are at increased risk of T2DM [61, 62]. Additionally, testosterone therapy has been shown to increase lean mass and insulin sensitivity in a small study of men with this condition [63].

As is the case with CHD, T2DM has been identified as an independent risk factor for stroke with a relative risk of 2.1 compared to the general population [64]. In the non-diabetic population, women have a higher lifetime risk of stroke despite lower risk in the majority of age categories [65]. Their risk increases over the age of 85 and the higher life time risk is a likely a factor of this combined with women's longer life expectancy [65]. Additionally, that female gender is associated with poorer outcome and increased risk of post-stroke disability is due to both differences in the types of strokes experienced by women and men and the significantly older age at which women experience stroke [65]. Women diagnosed with T2DM are at a 27% greater risk of stroke compared to men with T2DM, an effect which correlates with HbA1c levels [66]. Women are also less likely to achieve target levels for HbA1c [67]. Additionally, each 1% increase from baseline HbA1c is associated with a 5% increase in risk of stroke for women whereas the same increase from baseline in men is only associated with a 1% increase in risk of stroke [66]. This association is stronger in women over 55 years of age than those under 55, supporting a protective role of oestrogens, which are lost following menopause [68].

Study location	Measure	Hazard ratio		Reference
		Women	Men	
Finland	Myocardial infarction	**14.40**	2.90	Juutilainen et al. 2004 [48]
USA	CHD mortality	**3.30**	1.90	Barrett-Connor et al. 1991 [49]
Italy	Stroke	**2.56**	1.89	Policardo et al. 2015 (varied by age) [50]
Asia Pacific	CHD mortality	**2.54**	2.03	Woodward et al. 2003 [51]
Taiwan	CHD mortality	**2.46**	1.83	Lin et al. 2013 [52]
USA	PAD	1.72	**2.12**	Palumbo & Joseph Melton III 1995 [53]

Table 1.
T2DM hazard ratio for CVD events by gender.

While a number of studies have found women with DM at higher risk of stroke, Dhamoon et al. found that this increased risk disappeared when other factors including medication were accounted for [69]. This highlights a trend in the treatment of women in general for CVD, whereby a focus by doctors and the public on men's cardiovascular health has resulted in a greater risk to women who have not received a similar increase in attention to symptoms and biomarkers [70].

2.2 Diabetic retinopathy

Diabetic retinopathy is a leading cause of preventable visual impairment, effecting many in the working age demographic with significant personal and socioeconomic consequences [1]. It presents in approximately one third of patients with DM [71]. There are two main forms of diabetic retinopathy: nonproliferative and proliferative diabetic retinopathy. Nonproliferative retinopathy, also known as background diabetic retinopathy, is the early stages of the disorder in which hyperglycaemia leads to vascular cell apoptosis and neural damage within the retina but without major symptoms or an effect on vision. Proliferative diabetic retinopathy is the advanced form of diabetic retinopathy which is brought on by progressive retinal ischemia and results in vision loss through complications such as retinal detachment, neovascular glaucoma and vitreous haemorrhage [72].

Men appear to be at greater risk than women of developing diabetic retinopathy as well as progressing to proliferative retinopathy [73], see **Table 2**. Interestingly this pattern was not found in a large study in China [78], where there was found to be no effect of gender on the prevalence of diabetic retinopathy in people with DM [78].

While, in general, improvement in diabetic retinopathy status appears to be associated with improved glycaemic control and blood pressure, these factors cannot be attributed to the greater chance of improvement observed in women compared to men. Women in the UKPDS study were found to have a higher incidence of risk factors than the men in that study, including older age, more obesity, higher blood pressure, higher fasting plasma glucose levels, higher glycosylated haemoglobin levels, higher plasma cholesterol levels, higher insulin levels and increased insulin resistance [77].

Study	DR type	Women (%)	Men (%)	P value	Reference
CURES	DR	15	**21**	<0.0001	Rema et al. 2005 [74]
GADPVD	DR	22	**24**	<0.0001	Hammes et al. 2015 [75]
NHANES	DR	26	**32**	<0.05	Zhang et al. 2010 [76]
	V-DR	4	6	>0.05	
UKPDS	DR	35	39	None	Kohner et al. 1998 [77]
	V-DR	5	**8**	<0.001	
CCSS	DR	31	30	ns	Liu et al. 2017 [78]
	V-DR	14	14	ns	
WESDR	DR	Hazard ratio men = 1.3		0.002	Klein et al. 2008 [79]

NHANES = The National Health and Nutrition Examination Survey, USA; UKPDS = The United Kingdom Prospective Diabetes Study; WESDR = Wisconsin Epidemiological Study of Diabetic Retinopathy, Wisconsin, USA; GADPVD = German/Austrian Diabetes-Patienten-Verlaufsdokumentation Database, Germany and Austria; CURES = Chennai Urban Rural Epidemiology Study, Chennai City, India; v-DR = vision-threatening DR. Statistically significant values bolded. ns = not significant; none = no statistical analysis performed.

Table 2.
Prevalence of diabetic retinopathy in women and men with DM.

It has been hypothesised alterations to sex hormone levels may be in part responsible for the increased chance of retinopathy progression in males. Sex hormone-binding globulin (SHBG) levels were found to be reduced in men who progressed to proliferative retinopathy as compared to those whose retinopathy did not progress over a 6 year period [80]. SHBG binds sex hormones, and lower levels allow for increased sex hormone activity, in men this would be associated with increased androgenicity.

2.3 Diabetic kidney disease

Diabetic kidney disease (DKD) is characterised by increased urinary albumin excretion in individuals living with DM who have not been diagnosed with any other renal disease [81]. It affects 20–40% of patients with T2DM and is the primary cause of kidney disease in patients who require renal replacement therapy [82]. Chronic Kidney Disease (CKD) in the absence of DM is more prevalent and more severe in men, but this gender disparity is not as striking in the case of DM-induced CKD (i.e. DKD) [83–85]. While some studies have found that men retain a significantly greater chance of developing DKD with DM [86, 87], others have found a similar prevalence of DKD women and men [88], see **Table 3**.

Study	Measure	Women (%)	Men (%)	P value	Reference
Saudi Arabia	Prevalence	41	**59**	$p < 0.001$	Al-Rubeaan et al. 2014 [86]
Denmark	Cumulative Incidence	18	**35**	0.02	Gall et al. 1997 [87]
NHANES	Prevalence	39	40	None	Wu et al. 2016 [88]
Korea	Odds ratio (OR)	OR for men = 1.31		0.0024	Yang et al. 2011 [89]

Statistically significant values bolded. None = no statistical analysis performed.

Table 3.
Prevalence of diabetic kidney disease in women and men with DM.

This increased relative risk in women mirrors the loss of protection from oestrogens seen in CVD rates in women with DM, and as per CVD, protection from CKD in women has also been recorded to be lost after menopause [90]. This, along with evidence from animal models supports a role for oestrogens and/or androgens in CKD progression that is blunted or lost in a DM setting [91, 92]. Mouse models of both menopause (ovariectomy) and DM demonstrate worsened nephropathy [93, 94]. The mechanism by which estradiol or other sex hormones may impact CKD risk is unknown but both direct action on the kidney (eg. podocyte viability) or indirect action (eg. due to increased blood pressure or via transforming growth factor-β (TGF-β)-induced collagen synthesis) have been posited [84, 95, 96].

2.4 Diabetic neuropathy

Diabetic neuropathy (DN) is one of the most frequently observed complications in diabetic populations, averaging at about 20% of people with T2DM globally – though much higher estimates are observed in older populations and in communities with suboptimal therapeutic adherence (eg. up to 66% in older women in rural South Carolina, USA) [97, 98]. DN is characterised by nerve damage resultant from hyperglycaemia, with a correlation between risk of development and the duration and severity of hyperglycaemia [99, 100]. Symptoms of diabetic neuropathy include pain, idiopathic sensations (paraesthesia), excessive sensitivity to stimulus, loss of

sensitivity, loss of coordination and altered sense of position [101]. These symptoms are associated with considerable morbidity, impacting quality of life [102]. The mechanism for nerve damage is through loss of protection and nutrient-provision from Schwann cells, leading eventually to axonal loss, most likely due to both high blood glucose levels and the absence of insulin, for which there are high affinity receptors throughout the nervous system [103, 104].

DN is the most significant contributor to diabetic foot syndrome (DFS) and results in a high risk of lower extremity amputation (LEA) among individuals living with DM [105]. DFS is characterised by the presence of foot ulcers and is causative of over 130,000 LEAs annually in the USA alone, this is approximately 0.6% of people with DM in the USA [10, 106]. The percentage of people with DM who experience DFS and the percentage of those who go on to have an amputation vary between countries, with higher rates of amputation in Sub-Saharan Africa, the Caribbean and parts of Latin America [107, 108]. The USA also has a high rate when compared to other developed countries [109].

Generally, men have a younger onset of DN and more severe symptoms, including higher rates of foot ulceration [100, 102, 110, 111]. Therefore, men are more likely to undergo a lower-extremity amputation (LEA) than women and at younger ages [102, 112–116], see **Table 4**. Globally, the number of people in 2016 who had amputations which were attributed to DM is 6.8 million people, with 4.1 million (60%) of those being men [107].

Although it has been hypothesised that lower rates of ulceration and/or LEA in women are due to indirect effects such as less physical work, superior preventative foot care and following care instructions [123–127], women and men have the same rate of ulceration when severity of DN is taken into account and equal rates of LEA within a population who have ulcers [111, 128]. Furthermore, though it has been reported that women heal ulcers more effectively than men [126], this study was in

Prevalence of DN in diabetic populations by gender				
Study location	**Women (%)**	**Men (%)**	**Significance**	**Reference**
Qatar	22	24	ns	Ponirakis et al. 2020 [117]
India	8	10	P = 0.001	Sharath Kote et al. 2013 [118]
UK	19	23	P < 0.0001	Abbott et al. 2011 [97]
Bangladesh	19	21	None	Mørkrid, Ali and Hussain 2010 [119]
UK	29	29	None	Young et al. 1993 [120]
Sri Lanka	26	20	p < 0.01	Katulanda et al. 2012 [121]
Incidence of LEA in diabetic populations by gender				
Study Location	**Women (per 100,000)**	**Men (per 100,000)**	**Significance**	**Reference**
USA	28	**55**	p < 0.05	Correa-de-Araujo et al. 2006 [122]
Sweden	192	197	None	Johannesson et al. 2008 [113]
Spain	145	583	None	Almaraz et al. 2012 [116]
USA	300	600	None	Margolis et al. 2011 [112]

Statistically significant values bolded. ns = not significant; none = no statistical analysis performed.

Table 4.
Prevalence of DN and incidence of LEA in women and men.

the context of a therapeutic bioengineered human dermal substitute, while studies of ulcer healing generally demonstrate no effect of gender on ulcer healing [129].

Therefore, the physiological link between DN and gender remains unclear and interestingly height alone, with men being on average taller than women, may be the greatest predictor of the incidence of DN [130]. This may explain the regional variation in DN prevalence differences by gender, as average height also varies geographically. For example average adult male height in the USA (where men experience higher rates of DN) is 175 cm compared to men in Sri Lanka, (where lower rates of DN are recorded in men compared to women) and the average height of men is 166 cm. The absence of a direct effect of gender on DN is corroborated by studies in mice which demonstrate similar nerve tissue dysfunction in female and male mice [131].

DN can be classified as painful or insensate and interestingly, painful DN is more prevalent in women and does not correlate with height [97, 118, 130, 132, 133]. This specific form of DN has independent risk factors from overall DN and seriously impacts on quality of life due to persistent sensation of pain in effected individuals [134, 135]. Why painful DN associates with the female gender is unknown but there is evidence of a genetic predisposition to the disorder based on high heritability [135]. This difference in painful DN between women and men may be attributable to the differences in pain processing, for which many hypotheses have been proposed to explain the differences present between genders, rather than differences related to DM or even DN specifically [136, 137].

2.5 Diabetic osteopathy

Bone health can be measured in a number of ways, including dual-energy x-ray absorptiometry (DXA) scan or measurement of bone turnover markers in the blood, however, the clinical importance of the disease lies in the elevated rate of fracture [138, 139]. In the non-diabetic population, the lifetime prevalence of hip fracture is significantly greater in women than in men [140]. This is driven by the higher rate of bone-turnover in postmenopausal women which results in decreased bone mineral density (BMD) culminating in osteoporosis [141–144]. As diagnosis and treatment for osteoporosis have increased, in conjunction with lower smoking rates and higher average BMI, the rate of hip fracture is decreasing. However, with an ageing population the absolute number of hip fractures is predicted to increase [139, 140]. Compounding this challenge in managing orthopaedic health is the increased fracture risk in people living with T2DM [145–149]. Contrary to the osteoporotic context, this increase in fracture risk is despite generally increased BMD in the T2DM population [148, 150, 151].

T2DM is associated with a relative risk of hip fracture of 1.3 with greater durations of T2DM increasing this risk [152, 153]. The presence of T2DM also increases the odds ratio of poor fracture healing, resulting in a malunion or non-union [154]. Hospital stay length and mortality following orthopaedic procedures are also increased in people with T2DM [149, 155]. The increased risk of fracture is present in both women and men, with contradicting evidence regarding whether women or men are preferentially impacted in terms of fracture risk by T2DM, while worse outcomes post-operatively seem to be more prevalent in men [149, 152, 153, 155, 156], see **Table 5**. Regardless, it is important that the increased risk of osteopathy in men with T2DM leads to appropriate intervention, where currently the emphasis of bone health is on women, in the T2DM context both women and men need to be considered.

Although DM-associated complications such as neuropathy and retinopathy increase the risk of falls which may result in fracture, the increased relative risk in

Study	Measure	Women	Men	Significance	Reference
Korea	HR	1.7	1.8	None	Kim et al. 2017 [156]
USA	HR	1.5	1.5	ns	Melton et al. 2008 [143]
Scotland	IRR	1-	1-	ns	Hothersall et al. 2014 [157]
Meta-Analysis	**RR**	**1.3**	1.1	$p < 0.001$	Vilaca et al. 2020 [153]
	RR	2.1	2.8	ns	Janghorbani et al. 2007 [158]
	RR	1.1	Baseline	ns	Fan et al.2016 [152]

Statistically significant values bolded.HR = hazard ratio; IRR = incidence risk ratio; RR = relative risk; ns = not significant; none = no statistical analysis performed.

Table 5.
Summary of hip fracture risk in women and men living with T2DM.

fracture remains when these variables are taken into account [159]. The reason for the increase in fracture risk in individuals with T2DM is not well characterised, but several hypotheses exist. DM induces systemic changes including inflammation and the generation of ROS which can negatively impact bone remodelling and changes in bone structure and mineral distribution [160–162], reviewed by [163]. People with T2DM have also been recorded as having lower density specifically of cortical bone and a more heterogeneous distribution of mineral, indicating compromising structural alterations that would yield impaired mechanical strength and increase the risk of fracture [160, 162]. Additionally, alterations to the mesenchymal stem cells (MSCs) responsible for maintaining bone homeostasis and for stimulating repair following an injury have also been reported [164–167]. Finally, pharmaceutical choice has also been reported to impact on the future risk of fracture in the DM population - thiazolidinediones have been associated with bone fragility while DPP4i and Metformin may reduce relative fracture risk [168–175].

In order to understand the gender aspect of the role of DM in bone health, recent publications investigated the aetiology of this increased fracture risk in men living with T2DM, identifying correlations with high levels of follicle-stimulating hormone and reduced estradiol with fracture risk [176]. There is also a discrepancy in the prescription of pharmaceuticals aimed at treating DM between women and men. For example, men are prescribed thiazolidinediones more often than women [177]. The disparity within the literature regarding the impact of gender in T2DM-induced fracture risk indicates the complexity of the question, with confounding variables such as the impact of pharmaceuticals, age, BMI, duration of diabetes and the presence of other diabetes-associated comorbidities.

3. Conclusions

DM is a growing global pandemic. DM is associated with several severe complications which have a major impact on patient outcomes and quality of life, and which make up a considerable component of healthcare budgets worldwide. Diabetic complications include cardiovascular disease, retinopathy, nephropathy, neuropathy (including diabetic foot syndrome) and osteopathy. Gender has been proposed across numerous studies as an important variable in the risk of development of these complications. However, teasing apart the role of gender is complex. Both the physiological impact of sex and the psychosocial impact of gender on behaviour and treatment are confounded by numerous factors. These include direct and indirect biological traits that associate with each gender, from hormone levels (which are

vastly different for women post-menopause) to average height, life span and access to appropriate treatment. Many of these biological traits, and also psychosocial and socioeconomic traits that impact risk vary widely geographically. Understanding the epidemiology and physiological mechanisms of DM-associated complications, including the role of gender, allows for the implementation of appropriate treatment and research programmes that ultimately reduce morbidity and mortality.

In the non-DM population, oestrogens such as estradiol are protective against some of these comorbidities but the protective effects are often diminished in a DM context. This pattern is evident in both CVD and CKD where women with DM undergo a much larger relative increase in risk compared to men. Numerous studies have also shown that women are less often prescribed ACE inhibitors and lipid lowering drugs, including statins [56–60]. This prescription bias compounds the higher rates of CVD and CKD in women with T2DM, leading to increased mortality rates, a major factor in the high T2DM-assocaited mortality in women [30]. Therefore, particular awareness needs to be paid to the gender discrepancy in patient care in the context of T2DM in order to address this inequality and improve outcomes for women living with T2DM.

The onset of diabetic retinopathy is also linked to sex hormones - with levels of androgens correlating to likelihood of diagnosis. There is therefore increased incidence of diabetic retinopathy in men compared to women. Contrasting to this, neuropathy incidence, though higher in men, does not correlate directly with gender but instead with height which is a predictor of neuropathy development in both diabetic and non-diabetic populations [111, 118]. Therefore the higher rates in men in many regions are likely due to the greater average height of men with the causality possibly being longer nerve fibres which are more susceptible to injury and take longer to heal [111, 118].

Diabetic osteopathy is one of the less-reported complications of DM. People living with T2DM experience higher fracture rates both due to increased rates of falling and due to poorer bone health, which is present despite increased BMD [159]. In terms of the role of gender in diabetic osteopathy, the disorder follows an opposite pattern to that seen in CVD and DKD. Poor bone health experienced primarily by women in the non-DM population as they age is largely absent in men, but in the context of DM there is an increased relative risk for men to experience, for example, hip fracture [149, 156]. Fractures such as these are associated with high morbidity, especially functional limitations that results in loss of independence – physically and economically [178].

Interestingly, the overall mortality rates and cost of treatment associated with DM are higher in women than in men despite the general preponderance of comorbidity in men. A number of factors may explain this discrepancy. Firstly, women with DM are older, and epidemiologically there is increased cost of treatment and higher mortality with age. Secondly, regions with high DM-associated mortality (low- and middle-income countries) also report higher rates of DM in women [1]. Finally, men are reported to develop DM with a reduced risk-factor burden (eg. lower BMI). Though this indicates a greater risk of DM development for men, it also signifies that women, once they do develop DM, are diagnosed with such along with a greater set of risk factors for DM complications. These risk factors include inadequate blood glucose control, high blood pressure, high BMI and reportedly less frequent exercise [179]. Though not all women will experience pregnancy, for those that do, their glycaemic control during this time is a strong predictor of future development of T2DM [180]. Targeting those women who experience gestational diabetes for education or treatment options for T2DM would be an effective way of reducing diabetic burden in women and therefore reducing associated morbidity and mortality of T2DM globally [181, 182].

With such a large proportion of society effected by DM and the fact that the major risk factors for T2DM comprise a generally unhealthy lifestyle, the lines between complications of the disease itself and disorders that are simply comorbid, but potentially highly important and relevant to the DM population, become blurred. For example, T2DM is a risk factor for vascular dementia, more so in women compared to men [183]. Women with T2DM also have increased depressive symptoms compared to men with T2DM and these symptoms correlate with worsening T2DM biological profiles [179]. Studying the role of gender in this wider range of comorbidities will be important for a greater understanding of the interplay between common modifiable risk factors and those non-communicable diseases that are increasing in prevalence worldwide. This will ultimately benefit the future wellbeing of those that live with DM.

Gender also plays a role in response to and adherence to medication. While it has been demonstrated that there is no overall difference in medication adherence between women and men, Walker et al. demonstrated a significantly reduced adherence to Metformin in women and this was specifically related to women reporting worse adverse effects from the drug [179, 184]. Although advancements in therapies for DM include expensive pharmaceutical agents which are likely to increase the cost of treatment of DM per patient, significant reduction to overall spend may be achieved through effective reduction of complications [185]. Fewer complications and reduced severity of complications are not only beneficial for the overall costs of DM but also due to the obvious significant reduction in morbidity and mortality that would be associated. It is important that current and future medications are assessed for differential effects between women and men. A more recently explored treatment option, which has potential to rescue many of the disorders associated with T2DM is cell therapy. For many DM comorbidities, MSCs, for example, have been proposed as having a mechanistic role in both pathology and/or recovery [165, 186, 187]. There are fewer MSCs in the bone marrow of people with T2DM and considering the role of MSCs in repair and in reduction of inflammation, they are well poised as an effective treatment option [165]. Furthermore, there does not appear to be an impact of gender on the functioning of MSCs in tissue repair indicating they could benefit both women and men with T2DM comorbidity [165].

In conclusion, there are important implications of gender in terms of the risk of DM itself and subsequently the disorders caused by and associated with it. These differences need to be taken into account in research into T2DM and its complications as well as in the treatment of those individuals diagnosed with the disease. The observed interplay between T2DM and gender warrants further epidemiological and molecular analyses in order to achieve a more complete understanding of the role of gender in the onset and prognosis of diabetic complications. This review also demonstrates that in terms of biomedical research it is of crucial importance for studies to include both genders in their research, and for gender to be recorded as a variable. This supports recommendations made by the SAGER (Sex and Gender Equity in Research) guidelines [188]. It will also be important to further study the mechanism by which gender exerts the described effects, which will be different for different comorbidities of DM, and will likely vary by region.

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Conflict of interest

The authors declare no conflict of interest with regard to the content of this chapter.

Note

In writing about the effect of gender on the development of diabetic complications in this review, it should be noted that only two genders are referred to due to the lack of data in the current literature on people who identify otherwise. We have chosen to use the term gender rather than sex, as it encompasses the combined physiological and psychosocial impacts on health discussed.

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