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ORIGINAL ARTICLE

Gender difference in the risk for cardiovascular events or mortality of patients with diabetic foot syndrome

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Abstract

Aims Diabetic foot syndrome (DFS) increases the risk for atherosclerotic cardiovascular disease (ASCVD), chronic kidney disease (CKD), or mortality. The present study aims at ascertaining whether such DFS-related excess risk differs between genders, retrospectively investigating a population with diabetes from Tuscany, Italy, followed-up for 6 years (2011–2016).

Methods People with diabetes living in Tuscany on January 1st 2011 identified by administrative databases, were divided by baseline history of prior DFS hospitalizations, stratified by presence/absence of peripheral vascular disease and evaluating, by Cox regression analysis, whether adjusted DFS-related excess risk of incident ASCVD, CKD or mortality differed between genders.

Results In an overall population of 165,650 subjects with diabetes (81,829M/83,821F), basal prevalence of DFS was twice higher among males, who were moreover at a significantly greater risk of all considered outcomes along the 6-year period. On the contrary, baseline DFS significantly increased the hospitalization risk for ASCVD, CKD and mortality equally or at a slightly greater extent in females, while the risk for stroke was significantly associated with DFS only among females (HR: 1.622 (1.314–1.980); $p=0.0001$ vs. HR: 1.132 (0.955–1.332); $p=\text{NS}$). This finding was even reinforced in non-vascular DFS, which was associated with a significant raised risk for stroke, heart failure or mortality exclusively in females.

Conclusions In this population, DFS prevalence and overall risk for ASCVD, CKD or mortality were significantly higher among males. Baseline co-presence of DFS, however, conferred a similar adjusted risk for all these outcomes between genders, and in case of non-vascular DFS the risk was significantly increased only among females.

Keywords Diabetic foot syndrome · Gender · Cardiovascular diseases · Chronic kidney disease · Mortality

Introduction

Diabetes is associated with an increased risk for atherosclerotic cardiovascular disease (ASCVD), being also a well-known risk factor for reduction in life expectancy [1, 2]. A fearful and insidious complication of diabetes is diabetic foot syndrome (DFS), especially when associated with peripheral artery disease, representing a further significant multiplier for further risk of atherosclerotic cardiovascular events, chronic kidney disease (CKD) and reduced survival [3–9]. Moreover, while, independently of diabetes, males are at greater risk for ASCVD, CKD, and DFS [10, 11], and diabetes seems to reverse this background males' disadvantage increasing the risk for cardiovascular events mostly in females [12–14], especially when in post-menopausal age [15]. From most of previous published studies, however, the risk of DFS associated or not to peripheral vascular diseases, is significantly higher in diabetic males as compared to females [16–19]. What remains still poorly investigated, however, is whether the excess risk for cardiovascular outcomes, associated with DFS is different between genders, since several studies suggest that DFS, whether associated or not with lower limbs' peripheral vascular disease, has a worse prognosis as well as a reduced survival among females, relative to males [20–26].

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The present study has, therefore, been designed to address the question whether having a DFS history is differentially associated between genders with the risk of hospitalizations for ASCVD (acute myocardial infarction or ischemic stroke or chronic heart failure), CKD, or for mortality in a population with diabetes residents in Tuscany, Italy and retrospectively followed up for 6 years.

Materials and methods

This study concerned patients with diabetes living in Tuscany, Italy on January 1st, 2011, as identified by a validated algorithm from administrative regional datasets [27] and retrospectively followed up until 31st December 2016. This regional database is estimated to cover more than 80% of all diabetic patients living in Tuscany [27].

The population with diabetes, stratified by gender, was then divided into two groups: those with or without previous hospitalizations for DFS as of December 31st, 2010. DFS was identified by any of following ICD-9 CM codes: foot ulcers: 440.23, 707.14-5, Charcot neuroarthropathy: 713.0, 713.5, 713.8, procedures of both major or minor lower extremity amputations: 84.10–84.19, revascularizations (surgical: 39.25, 39.29, endoluminal: 39.50, 39.90), gangrene: 785.4, 040.0, 440.24. Since the term of DFS comprises both vascular and non-vascular foot lesions which, although often each other overlapped in the same subject, may be divided into two groups: those with presence of peripheral vascular disease (procedures of both major or minor lower extremity amputations, revascularizations, gangrene) and those without vascular diseases (foot ulcers or Charcot neuroarthropathy).

Along the whole observation period, the date of first hospitalization for cardiovascular events was identified using ICD9-CM codes for: myocardial infarction (ICD9 410.xx), ischemic stroke (ICD9 430.xx, 431.xx, 432.xx, 434.xx or 436.xx), chronic heart failure (ICD9 401.91, 402.01, 402.11, 402.91, 404.01, 404.3, 404.13, 404.93, 428.0, 428.1, 428.9), after querying the regional dataset of hospitalizations. In addition, the date of first hospitalization for chronic kidney disease (CKD) was identified by ICD9 code 585. xx. At baseline, moreover, each subject was scored by Charlson index regarding previous comorbidities [28], based on all hospitalizations until the end of 2010. This index is coded as 0 in case of no comorbidity or prior hospitalizations, 1, or ≥ 2. From the regional dataset concerning the flux of drug prescriptions, it was moreover possible to obtain data about baseline glucose-lowering therapy, identified as none, oral drugs, insulin alone or insulin + oral drugs. For each subject, the vital status was verified along the entire period by querying the database of the regional registry office.

Whether the risk of first hospitalization for the abovementioned outcomes, was associated with DFS, has been calculated by Cox proportional hazards model identifying the hazard ratios (HR), separately in males and females, after adjusting for age, therapy and Charlson index (model 1). This procedure was then done for each considered outcome with DFS with vascular disease and DFS without vascular disease acting as covariates, in an unique model where the absence of diabetic foot at baseline was the reference group. This same model was then used to assess the effect of gender (as covariate) for each outcome, after adjusting for other covariates including overall DFS (model 2). Observation interval, in both models, was represented by time from baseline to the first considered outcome including death, the date of exit from database, or alternatively, time lag from the onset to the end of study.

The analysis was finally completed by comparing males and females with diabetes, after fully matching for main confounders by means of the coarsened exact matching (CEM) non-parametric approach [29].

All data were anonymized preventing disclosure of patients' identity as well as of any other sensitive information. Because of such formal protection, no informed consent or any approval by an Ethics Committee was required.

All analyses were performed using SAS ver. 9.3, SAS Institute Inc., Cary, NC, USA.

Results

Overall, the diabetic population was composed by 165,650 individuals (81,829 males and 83,121 females). The overall DFS included 4589 (3119 M/1470 F) patients of whom 3933 patients presented with vascular and 656 with non-vascular DFS. The adjusted risks for both vascular and non-vascular DFS were higher among males (OR: 2.088; 95% CI 1.958–2.228; $p < 0.0001$ for the former, and OR: 1.253; 95% CI 1.073–1.465; $p = 0.0045$ for the latter). In addition, females were older, had a significantly lower burden of comorbidities and, additionally, antidiabetic therapy was significantly different between genders, with more females on therapy with insulin or insulin + oral drugs (Table 1). These characteristics remained after stratifying the population by baseline history of previous hospitalizations for DFS (Table 2). The incidence rate of ASCVD outcomes, CKD as well as of mortality, expressed as cases per 1,000 person-years were higher among males and in patients with vascular or non-vascular DFS (Table 3).

After Cox regression, in agreement with this trend, males were at significantly higher risk for all-cause mortality as well as for all considered outcomes, even if at a different extent, ranging from an increase of 20% in the

Table 1 Main characteristics of study population with diabetes, stratified by gender

	Males (81,829)	Females (83,121)	*p*
Age (years)	64.9 ± 12.7	66.1 ± 15.0	0.0001
Charlson index > 2 (%)	22,576 (27.6)	17,840 (21.5)	0.0001
Previous hospitalization for diabetic foot (no. %)	3119 (68.0)	1470 (32.0)	0.0001
No antidiabetic drug therapy (no. %)	13,618 (16.64)	16,172 (19.46)	0.0001
Antidiabetic oral drugs (no. %)	55,173 (67.42)	53,667 (64.56)	0.0001
Only insulin (no. %)	6181 (7.44)	6648 (8.12)	0.0001
Insulin + antidiabetic oral drugs (no. %)	6390 (7.81)	7101 (8.54)	0.0001

Table 2 Main characteristics of population with diabetes, by gender and baseline history of previous hospitalizations for DFS

	DFS +		*p*	DFS −		*p*
	Males (3,119)	Females (1,470)		Males (78,710)	Females (81,651)	
Age (years)	69.7 ± 9.4	72.6 ± 10.9	0.0001	64.7 ± 12.8	66.0 ± 15.1	0.0001
Charlson index > 2 (no. %)	2,272 (72.84)	981 (66.73)	0.0001	20,304 (25.80)	16,859 (20.65)	0.0001
No antidiabetic drug therapy (no. %)	373 (11.96)	198 (13.47)	NS	13,245 (16.83)	15,974 (19.56)	0.0001
Antidiabetic oral drugs (no. %)	1,602 (51.36)	647 (44.01)	0.0001	53,571 (68.06)	53,020 (64.93)	0.0001
Only insulin (no. %)	573 (18.37)	312 (21.22)	0.02	6075 (7.72)	5869 (7.19)	0.0001
Insulin + antidiabetic oral drugs (no. %)	571 (18.31)	313 (21.29)	0.016	5819 (7.39)	6788 (8.31)	0.0001

Table 3 Incidence rate per 1000 person-years for ASCVD, CKD or mortality, by gender and presence of vascular or non-vascular DFS

	Males		Females	
	No. events	Events per 1000 p-year (95% CI)	No. events	Events per 1000 p-year (95% CI)
AMI				
Vascular diabetic foot	268	46.62 (41.36–52.55)	108	43.64 (36.14–52.27)
Non-vascular diabetic foot	19	24.05 (15.33–37.70)	8	12.93 (6.46–25.84)
No diabetic foot	3395	20.10 (19.44–20.79)	2035	11.51 (11.02–12.02)
Total	3682	20.99 (20.33–21.68)	2151	11.95 (11.46–12.47)
Stroke				
Vascular diabetic foot vs	144	24.47 (20.78–28.81)	85	33.79 (27.32–41.79)
Non-vascular diabetic foot	12	15.02 (8.53–26.45)	15	24.30 (14.65–40.31)
No diabetic foot	2445	14.37 (13.81–14.95)	2124	12.01 (11.51–12.53)
Total	2601	14.71 (14.16–15.29)	2224	12.36 (11.85–12.88)
Heart failure				
Vascular diabetic foot	229	37.58 (33.01–42.78)	103	39.19 (32.31–47.55)
Non-vascular diabetic foot	14	17.16 (10.16–28.96)	17	26.95 (16.75–43.36)
No diabetic foot	2217	12.80 (12.27–13.34)	2090	11.63 (11.14–12.14)
Total	2460	13.65 (13.13–14.21)	2210	12.08 (11.58–12.59)
CKD				
Vascular diabetic foot	150	31.86 (27.15–37.39)	57	28.19 (21.75–36.55)
Non-vascular diabetic foot	17	23.79 (14.79–38.27)	9	16.53 (8.59–31.76)
No diabetic foot	945	6.05 (5.67–6.45)	579	3.47 (3.20–3.77)
Total	1112	6.17 (5.82–6.55)	645	3.52 (3.26–3.81)
Mortality (any cause)				
Vascular diabetic foot	402	85.39 (77.44–94.17)	185	91.52 (79.23–105.70)
Non-vascular diabetic foot	31	41.98 (29.35–60.04)	35	62.24 (44.61–87.37)
No diabetic foot	4266	27.33 (26.52–28.16)	4400	26.42 (25.65–27.21)
Total	4699	26.10 (25.35–26.85)	4620	25.25 (24.53–25.98)

risk for heart failure to about 76% in the risk for myocardial infarction (Fig. 1a).

DFS-associated risk for all events, however, was similar or slightly higher among females, except for the risk of ischemic stroke, significantly higher only among females: HR: 1.622 (1.314–1.980); $p = 0.0001$ vs. 1.132 (0.955–1.332) in males; $p = \text{NS}$ (Fig. 1b).

Similarly, after dividing DFS patients by the presence/absence of vascular disease, the DFS-associated risk for all events was similar or slightly higher among females in the group with vascular DFS, also in this case except for the risk of ischemic stroke, significantly higher only in the group of females (Fig. 2a). This trend was even more evident in the much less numerous group of patients with non-vascular DFS, where the adjusted risk for all events associated to DFS was almost exclusively significant only among women (Fig. 2b). Finally, data were substantially confirmed after strictly matching males and females for all covariates, by means of the coarsened exact matching (CEM) non-parametric model (Table S1).

Discussion

DFS, either associated or not with lower limbs' vascular disease, is an ominous complication of diabetes, being associated with the need for therapies potentially impacting the quality of life [30] and with a huge burden of direct and indirect costs for patients as well as for all health service organizations [31, 32]. In addition, apart from the impairment in patients' quality of life and autonomy, DFS is strictly tied with the co-presence or with a significantly increased risk of next cardiovascular events, end-stage renal disease and ultimately of mortality [3–9]. According to this as well of other previous studies, moreover, DFS is a strongly gender-oriented complication being much more prevalent among males [16–19]. Nevertheless, it has repeatedly demonstrated that the presence of diabetes adds a greater risk burden for cardiovascular complications among females especially during the post-menopausal age [12–14, 33].

The mechanisms involved in females' excess risk for vascular complications due to diabetes are a object of discussion and investigation: hormonal factors, genetic

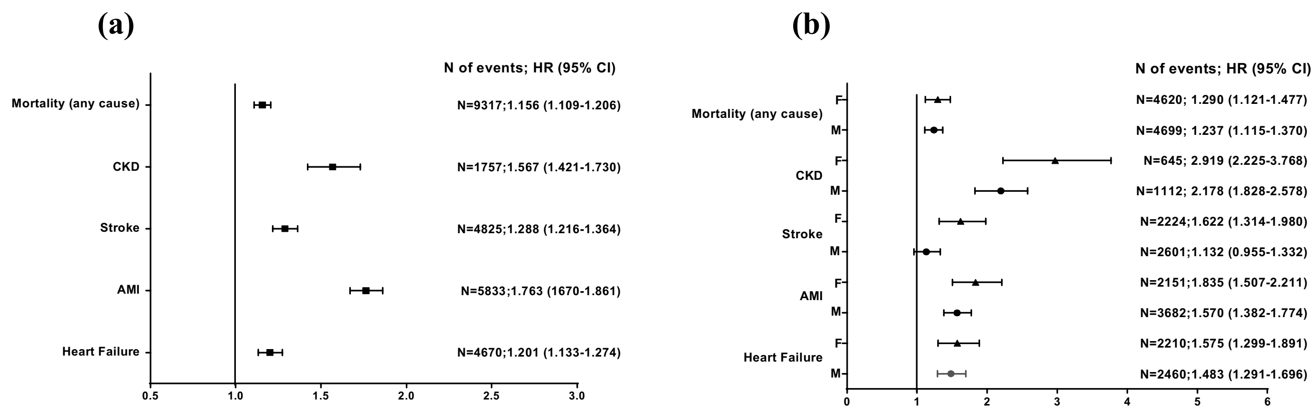

Fig. 1 Adjusted risk, expressed as hazard ratio (HR; 95% CI) for all considered outcomes in males as compared to females (**a**); effect of baseline history of DFS hospitalization on next risk for outcomes in males (filled circle) and in females (filled triangle) (**b**)

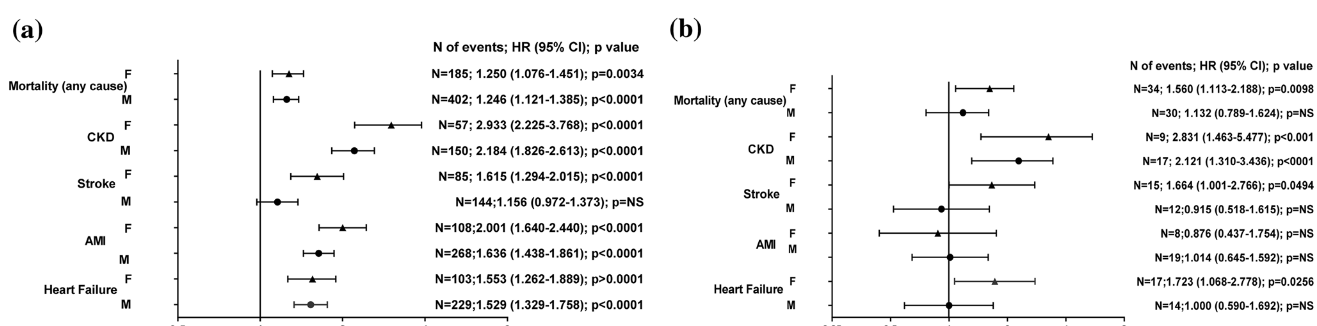

Fig. 2 Adjusted risk, expressed as hazard ratio (HR; 95% CI) of all considered outcomes in males as compared to females, stratified by baseline history of vascular (**a**) or non-vascular (**b**) DFS hospitalization on next risk for outcomes in males (filled circle) and in females (filled triangle)

predisposition linked to sex dimorphism, gender-related inequalities in treatment or in socio-economic status, may individually or all together seem to play a role in disadvantaging females [13, 14]. This analysis, however, mainly refers to comparison between diabetic and non-diabetic status, while, when comparing genders in people with diabetes, according to most epidemiological studies including the present one, diabetic males maintain a greater risk for almost all cardiovascular outcomes, DFS, or CKD [10, 16–19]. It is noteworthy from the present study, however, that the co-presence of DFS seems to revert this trend suggesting that females, relative to males, are presenting a risk equal or slightly higher for cardiovascular events, CKD or mortality, or, in case of ischemic stroke, even significantly greater. This finding seems robust enough, being confirmed after strictly matching populations, thus suggesting that DFS represents a particularly elevated risk for cardiovascular complications especially among females. Moreover, this finding is reinforced and possibly justified by previous observations that women with peripheral artery disease, when compared to men, have more severe symptomatic states, uncontrolled risk factors, as well as a more pronounced pro-inflammatory profile of circulating biomarkers [20, 21, 26]. It has additionally been described that among patients with symptomatic peripheral artery disease, females have a more limited peripheral microcirculation, in association with a more pronounced endothelial oxidative stress and inflammation [22]. Furthermore, in this study females are on average older than males and it should be remembered that aging plays an important role in modifying gender-driven risk of DFS or peripheral vascular disease: before 65 years of age males are at higher risk of foot ulcers and amputations, whereas for females the risk of amputation increases significantly with age [19, 34]. There are, in addition, other factors which may further justify the disadvantage of diabetic females: women may have a history of previous worse treatment of all risk factors for cardiovascular diseases [35, 36], exposure to diabetes may have been longer due to a later diagnosis of diabetes among females [37] and finally, after menopause, the risk of cardiovascular diseases increases steeply in females [15].

A further interesting finding of our data is that this females' disadvantage is evident not only in the group of patients with DFS with peripheral vascular disease, being even more evident in those labelled as without peripheral vascular complications. In this much less numerous patients' subset, in fact, DFS-associated risk of stroke, heart failure or mortality resulted significant only among females. Interestingly, a recent study has demonstrated that the presence of foot ulcers without clinical evidence of peripheral vascular disease has been associated with a greater risk of mortality and of ischemic heart disease, compared to those with ischemic foot lesions in both males and females [38].

Our data support the hypothesis that even if both types of DFS, vascular and non-vascular, have the same impact increasing the risk for mortality, renal, or cardiovascular outcomes, non-vascular DFS seems to be especially detrimental for females significantly augmenting the risk for all outcomes.

Interestingly, our data suggests that DFS-related excess risk for ischemic stroke is significantly higher in females, as compared to males. This finding agrees with recent reports, including a meta-analysis of 64 cohorts and with the guidelines on the prevention of stroke in women released by the American Heart Association, reporting that diabetes is a stronger risk factor for stroke in women compared with men [39]. Possibly, an explanation may be found in the fact that diabetes has more deleterious effects on encephalic vessels in females, as testified by a higher prevalence of preclinical atherosclerosis (carotid plaque presence and burden) in women with new-onset type 2 diabetes [40]. Risk of stroke, moreover, may be higher over time in women with diabetes as suggested by the slower yearly trend in progressive decrease of stroke incidence rate observed in diabetic females of our population especially in age class 55–74 year, as compared with males of the same age group [41]. Finally, females are known to be more disadvantaged than males regarding the control of all known cardiovascular risk factors for ischemic stroke, synergistically acting, in addition to diabetes, to build up overall stroke risk [42].

Previous studies have shown a strong relationship between DFS and CKD which hypothetically interacts in both directions: diabetic individuals with DFS are more at risk of end-stage renal disease, and, in turn, this latter is at the origin of a significantly higher burden of lower limbs' amputations [43, 44]. Again, also in this case, why diabetic females with DFS are losing their expected background advantage may be only speculative: interestingly it has previously been observed that women with type 2 diabetes are more at risk of non-albuminuric renal impairment which seems to be associated with a significantly higher CVD burden [45].

According to this study, DFS, whether vascular or not, significantly increases (even if not significantly) the risk of mortality slightly more in females than in males (HR: 1.290; 1.121–1.477 vs. 1.237; 1.115–1.370), confirmed also after fully matching genders, considering that, also in this case, the overall adjusted risk of any-cause mortality is significantly higher among males [HR: 1.156 (1.109–1.206)]. It is however difficult to draw conclusions about a hard outcome such as mortality notoriously conditioned by a lot of possible confounders, which cannot totally be accounted for by the design of the present study.

Limitations of the study

This study has a main limitation: its cross-sectional retrospective design based on administrative databases, does not allow considering other important points such as anthropometric or clinical variables, details on quality of treatment or of life style profile, etc., all of which are of obvious interest in evaluating any gender effect on the risk for the considered outcomes. Its strength is represented by the large sample of involved population, and by the homogeneity in treatment as provided by a unique regional health system.

Conclusions

The present study suggests that in this population with diabetes the risk burden concerning history of hospitalizations for DFS, as well as incident cardiovascular events, CKD or mortality are significantly greater among males when compared to females. Nevertheless, this male gender-driven excess risk is completely reversed in presence of DFS which yields a significant excess risk for cardiovascular events, CKD or mortality by a similar extent in both genders. In addition, females with previous history of DFS are further disadvantaged, compared to males, with respect to the risk of ischemic stroke. This trend is particularly reinforced in non-vascular DFS, unveiling a further females' frailty in this condition and suggesting that the risk of mortality as well as of renal or cardiovascular outcomes, are in this case even much higher among females, compared to the male counterpart.

Author contributions No potential conflicts of interest relevant to this article were reported. GS researched/analysed data and wrote the manuscript. He is moreover the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis; LP and EG researched data and reviewed the manuscript; PF and RA researched data and reviewed the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Statement of human and animal rights All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Statement of informed consent Each patient was assigned a unique identifier that was the same for all administrative databases. This identifier does not allow to disclose the patient's identity and other sensitive data and therefore no informed consent was required from all patients for being included in the study.

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