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Gender Differences in Diabetes-related Lower Extremity Amputations

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Abstract
Background Diabetes is a major cause of morbidity and mortality in the United States, with much of the economic and social costs related to macrovascular and microvascular complications, such as myocardial infarctions, renal failure, and lower extremity amputations. While racial/ethnic differences in diabetes are well documented, less attention has been given to differences in diabetes outcomes by gender.
Questions/purposes Does gender influence the rate of diabetes-related lower extremity amputations and/or the rate of mortality after amputation?
Methods I reviewed the literature utilizing peer-reviewed publications found through MEDLINE searches.
Where are we now? Major complex gender differences exist in diabetes-related lower extremity amputations: men are more likely to undergo lower extremity amputations, but women apparently have higher mortality related to these procedures. The reasons for such differences are not entirely clear, but it appears biologic factors may play important roles (increased rates of peripheral vascular disease and peripheral neuropathy in men, interaction between gender and cardiac mortality in women).
Where do we need to go? More research is warranted to confirm gender differences in diabetes-related lower extremity amputation mortality and explore underlying mechanisms for the gender differences in lower extremity amputations and its associated mortality.
How do we get there? Exploring gender disparities in diabetes-related outcomes, such as lower extremity amputations, will need to become a national priority from a research (eg, National Institutes of Health) and policy (eg, Centers for Medicare and Medicaid Services) perspective. Only when we have a better understanding of the causes of such differences can we begin to make strides in addressing them.

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Introduction

In the United States, there are approximately 24 million people (7.8% of the population) currently living with diabetes, nearly 6 million of whom are unaware of their diagnosis [4]. There are 12 million men (11.2% of men older than 20 years) and 11.5 million women (10.2% of women older than 20 years) with diabetes [4], and prevalence rates have continued to escalate over the past decade. The financial cost of diabetes is estimated at approximately $132 billion annually; $92 billion is attributed to direct medical care and the remaining $40 billion is due to disability, work loss, and premature mortality [3]. It is estimated annual diabetes-related costs will reach $336 billion by 2034 [19].

Much of the cost related to diabetes results from macrovascular and microvascular complications, such as myocardial infarctions, cerebrovascular events, end-stage renal disease, and lower extremity amputations (LEAs). The highest diabetes-related hospitalization rates are for long-term complications, such as LEAs, rather than uncontrolled hyperglycemia or short-term complications [13]. This underscores the disproportionate expenditure of diabetes-related healthcare costs on complications such as LEAs. Diabetes is an independent predictor of limb amputation (versus revascularization) for the treatment of critical limb ischemia [1]; patients with diabetes are 20 times more likely to undergo a LEA than those without diabetes [39]. Patients with diabetes who have LEAs and other diabetes-related foot disorders have lower quality-of-life measures (health-related quality of life, physical functioning, social functioning, and mental health) than other patients with diabetes [18, 27]. Given the important economic, health, and personal costs, reducing the number of diabetes-related LEAs has become a national healthcare priority [37].

Not all of the contributors to diabetes-related LEAs are known but include poorly controlled diabetes, sensorimotor peripheral neuropathy, peripheral arterial disease (PAD), foot ulceration, increased age, longer duration of diabetes, hypertension, cigarette use, decreased ankle ROM, and hyperlipidemia [5, 8, 14, 28, 36, 38]. For example, patients with PAD have nearly four times the odds of undergoing a LEA than those without PAD [16]. While racial/ethnic differences in diabetes are well documented, it is unclear whether the rates and causes of diabetes-related LEAs are influenced by gender [2, 32].

Therefore, this review explores whether there are gender differences in (1) the incidence of diabetes-related LEAs and (2) mortality associated with diabetes-related LEAs.

Search Strategies and Criteria

A search was conducted using electronic databases Cochrane, CINAHL, ACP Journal Club, Psychinfo, and MEDLINE using prespecified Medical Subject Headings (MeSH) and keywords to identify evaluation studies (evaluation studies, clinical trials, effectiveness, improvement, and performance) among adults with diabetes-related LEAs and risk factors for LEA (diabetes mellitus, Type 2; diabetes mellitus, Type 1; diabetes complications; amputation; peripheral vascular disease; dyslipidemia; hypertension; peripheral neuropathy; tobacco; smoking; diabetic foot; diabetic neuropathies; foot ulcer; lower extremity; risk factors), with a focus on gender differences in outcomes (gender). English-language papers published from 1985 to February 2010 were included in the search. I also searched the web sites of major organizations (ie, the Centers for Disease Control and Prevention) known for tracking diabetes health outcomes. Of the 373 originally identified papers and informational sources, I selected 27 that were relevant to my key areas and included them in my review. Although there is a general paucity in the literature about gender disparities in diabetes-related LEAs, data do exist regarding my two key areas: disparities in LEA incidence and mortality.

Gender Differences in Incidence of LEA Amputation in Diabetes

There is strong, consistent evidence that men are more likely to undergo diabetes-related LEAs [6, 15, 22, 28] and are younger at the time of amputation than women, regardless of the level of amputation (ie, foot, thigh) [6]. National estimates of avoidable hospitalizations for diabetes-related LEAs show consistent patterns of gender differences. Men are more likely to undergo the procedure, despite equal hospitalization rates for uncontrolled diabetes and evidence suggesting equal outpatient control of diabetes [7, 13, 26]. In 2001, men had a rate of 55 LEAs per 100,000 diabetes patients, compared to women with 28 LEAs per 100,000 diabetes patients [13] (Fig. 1). Gender differences persisted across racial/ethnic groups: 45 versus 19 LEAs among non-Hispanic white men and women, respectively; 134 versus 93 LEAs among African Americans; and 84 versus 45 LEAs among Hispanic Americans [13] (Fig. 1). National trends indicate a

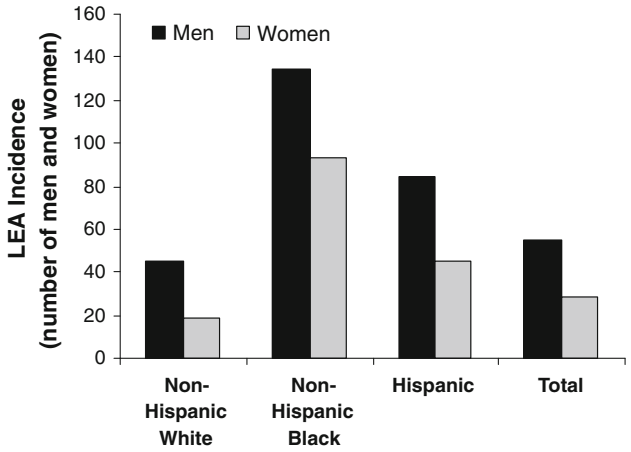

Fig. 1 A graph shows the differences in diabetes-related LEA incidence by race and gender. Men had a higher LEA incidence than women (55 versus 28 LEAs per 100,000 diabetes patients), and the gender differences persisted across racial/ethnic groups: 45 versus 19 LEAs among non-Hispanic white men and women, respectively; 134 versus 93 LEAs among African Americans; and 84 versus 45 LEAs among Hispanic Americans ($p < 0.05$ for all groups).

reduction in diabetes-related LEAs over the past several decades [15, 22] and show the gender gap has narrowed [10] but persists.

Men are more likely to have some of the independent predictors for LEA, such as diabetic foot ulceration [20], PAD [21], cigarette use [29, 35], and peripheral neuropathy [9]. Peripheral neuropathy may be a particularly important factor in gender differences in LEA. Sensory neuropathy is the most common type of neuropathy associated with diabetic foot ulceration, and men have nearly twice the odds of having insensate neuropathy as women and have nerve conduction abnormalities that are more severe [5, 20, 34]. Insensate neuropathy is partially determined by peripheral nerve length (a function of height) because longer fibers are more vulnerable to injury. The increased odds of sensory neuropathy in men are entirely due to the effect of height [34]. Additionally, hormonal factors may play a role since women (particularly of reproductive age) may have additional neural protection afforded to them, due to better endothelial function in both the microvasculature and microvasculature [25].

Gender differences in biomechanics may contribute to the differences between men and women regarding LEA. One recent study suggested decreased joint mobility and higher foot pressures were predictors for the development of diabetic foot ulcers; men had less joint mobility and higher foot pressures than women [14]. However, women with measures of neuropathy, joint mobility, and foot pressures equivalent to those of men also had similar chances of developing diabetes-related foot ulcers.

Healthcare factors do not appear to affect gender differences in LEA. Men receive equal and, in some cases, higher-quality diabetes-related outpatient care, including foot examinations by healthcare providers (63.7% of women versus 69.1% of men, $p = 0.021$), which, when stratified by race/ethnicity, persists among non-Hispanic whites (64.2% of women versus 71.3% of men, $p = 0.026$) [13]. After adjusting for sociodemographic factors (age, race/ethnicity, income, education, place of residence) and insurance status, women had 0.78 times the odds of having had a foot examination in the prior year in comparison to men [13]. This same nationally representative study reported on four other areas of diabetes care and noted equal proportions of men and women received glycosylated hemoglobin (HbA1c) testing, eye examinations, and influenza immunizations, and slightly higher ($p = 0.035$) proportions of men had lipid testing (95.3% of men versus 92.9% of women), although it is unclear whether this is clinically meaningful [13].

There is some (although limited) evidence that prior gender differences in diabetes foot self-care may have resolved [12]. In 2000, men had age-adjusted prevalence rates of foot self-examinations that were 7% lower than that for women (58.5% versus 65.8%, respectively), but by 2007, the rates were 65.8% for both genders, according to national data from the Behavioral Risk Factor Surveillance Study [12].

Gender Differences in Mortality After LEA Amputation in Diabetes

Despite having lower incidence rates of disease, several studies suggest women have higher mortality rates associated with diabetes-related LEAs [23, 24, 31, 33]. In a California study of operative and perioperative mortality associated with diabetes-related LEAs, women had 37.7 deaths per 1000 amputations, compared to 29.7 deaths per 1000 amputations among men [24] (Fig. 2). Gender differences were found among whites (43.0 deaths among women and 31.5 among men per 1000 amputations) and Hispanics (25.9 deaths among women and 19.7 among men per 1000 amputations) but not African Americans (38.5 deaths among women and 41.5 among men per 1000 amputations) [24] (Fig. 2). National US data are currently unavailable, making it difficult to draw any conclusions about the overall patterns of gender differences in the mortality associated with diabetes-related LEAs.

Some research suggests higher rates of cardiovascular deaths among women during the postoperative LEA period may account for the reported gender difference in mortality. Epidemiologic studies indicate the increased risk of atherosclerotic complications among patients with diabetes is particularly pronounced in women [30], and cardiac

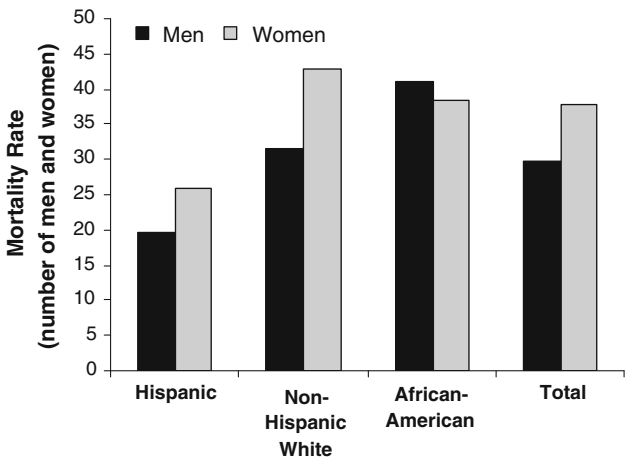

Fig. 2 A graph shows the differences in age-adjusted mortality associated with diabetes-related LEAs by race and gender. Women had a higher mortality rate than men (37.7 versus 29.7 deaths per 1000 amputations), and gender differences were found among whites (43.0 versus 31.5 deaths among women and men, respectively) and Hispanics (25.9 versus 19.7) but not African Americans (38.5 versus 41.5).

disease, including congestive heart failure, is one of the most common causes of inpatient mortality associated with diabetes-related LEAs [17, 23]. One study of diabetes-related LEAs among Native Americans reported interactions between gender and cardiovascular disease mortality, suggesting a higher LEA-associated cardiovascular disease mortality risk among women with LEAs [31]. However, data from the National Hospital Discharge Survey [11] documents higher rates of cardiovascular disease, including ischemic heart disease, among hospitalized men with diabetes when compared to women, although recent trends indicate similar rates of congestive heart failure and stroke between genders.

Discussion

Diabetes is a major cause of morbidity and mortality in the United States, with much of the economic and social costs related to macrovascular and microvascular complications, such as myocardial infarctions, renal failure, and LEAs. While racial/ethnic differences in diabetes are well documented, it is unclear whether the rates and causes of diabetes-related LEAs are influenced by gender [2, 32]. Therefore, this review explores whether there are gender differences in (1) the incidence of diabetes-related LEAs and (2) mortality associated with diabetes-related LEAs.

I identified gaps in the literature. First, there are limited national US data, particularly in the area of LEA-associated mortality, thus making it difficult to draw any conclusions about the overall patterns of gender differences in LEAs. Conclusions must primarily be drawn from relatively small individual studies. Second, there is limited information regarding the causes of gender differences in diabetes-related LEAs. For example, there are relatively few studies examining potential gender differences in diabetes quality of foot care, and more evidence is needed before we can conclude foot care is unrelated to rates of LEA. Fourth, research in the causes of gender differences in mortality is limited and not entirely conclusive.

Where are we now? Current evidence indicates men are more likely to undergo diabetes-related LEAs and suggests women are more likely to die in the perioperative period of such procedures. Men are also younger at the time of amputation than women, regardless of the level of amputation (ie, foot, thigh). National trends suggest the number of diabetes-related LEAs have decreased over the past several decades [15, 22], and the gender gap has narrowed but persists. However, despite having lower incidence rates of disease, several studies suggest women have higher mortality rates associated with diabetes-related LEAs. Women have 37.7 deaths per 1000 amputations compared to 29.7 deaths per 1000 amputations among men (Fig. 2). Further, gender differences in mortality rates vary by race. In summary, men are more likely than women to undergo diabetes-related LEAs, but the underlying reasons have not been fully elucidated. Biologic factors appear to contribute to these gender differences, while healthcare factors do not. More research in this area is warranted.

Where do we need to go? We need more information about the causes of differences in rates of diabetes-related LEAs (both clinical and health system related), although there are more data regarding differences in clinical factors that make men more likely to undergo diabetes-related LEAs. For unknown reasons, women appear more likely to die from diabetes-related LEAs. While cardiovascular disease may play a role, little work has been done in this area. It is possible gender differences in hospital-based quality of care may play a role, although this is speculative at this point. Additional research utilizing national data is needed to confirm the existence of gender differences in mortality associated with diabetes-related LEAs and explore potential biologic, behavioral, and healthcare system causes.

How do we get there? Public health programs that target men at higher risk for diabetes-related LEA may be a feasible strategy for addressing the biologic factors that predispose men to undergo more LEAs than women. For example, interventions that target high-risk diabetic men for smoking cessation may be effective at reducing LEAs in this population. If future research supports the existence of gender disparities in LEA-related mortality that are attributable to health system factors, utilizing quality improvement approaches to make health system changes is a potential strategy for addressing the problem. For example, hospital-based quality improvement teams could utilize Plan-Do-Study-Act cycles to identify and address health system barriers to the delivery of gender-equitable cardiovascular care among patients with diabetes undergoing LEA procedures. Exploring gender disparities in diabetes-related outcomes, such as LEAs, will need to become a national priority from a research (the National Institutes of Health) and policy (the Centers for Medicare and Medicaid Services) perspective. Only when we have a better understanding of the causes of such differences can we begin to make strides in addressing them.

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