The Impact of Statin Therapy on the Healing of Diabetic Foot Ulcers: A Retrospective Chart Review.

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Abstract

Background

Diabetic foot ulcers (DFU) are a costly complication of diabetes mellitus (DM), with significant implications for the patient and the healthcare professionals that treat them. The primary objective of this study was to evaluate if there were improved healing rates in patients with DFU that were taking a statin medication compared to those patients with a DFU who were not taking a statin medication. Secondary outcomes assessed were associations with wound healing or statin use on data obtained from retrospective chart review.

Methods

A retrospective chart review was performed to obtain appropriate demographic information, comorbid conditions, laboratory values, and physical examination findings. From the time of presentation with DFU, these patients were followed for 12 weeks to evaluate for healing. Healing was defined as full epithelialization of the DFU with no further drainage. Wound healing and statin use association testing was then done for collected variables and each cohort. A univariate analysis was then performed with a linear regression calculator to identify any significant associations.

Results

Our study identified 109 patients, 75 patients with DFU on statin medication and 34 patients with DFU not on statin medication. The statin cohort was more likely to be older, less than 5-year duration of diabetes, have more comorbidities, decreased low-density lipoprotein (LDL) cholesterol, and decreased total cholesterol (p < 0.05). 48.0% (36/75) of patients taking a statin medication healed their DFU within 12 weeks. Among those patients not taking a statin medication, 44.1% (15/34) healed their DFU within 12 weeks. No association was noted between wound healing and statin use (p = 0.71). For wound healing, associations were noted for prior minor amputations (p < 0.05). For statin use, associations were noted between age, duration of DM, LDL cholesterol level, total cholesterol level, HTN, CAD, and HLD (p < 0.05).

Conclusions

Statin medication did not influence DFU healing rates between cohorts. There was an association noted between wound healing and prior minor amputations and between statin use and age, duration of DM, LDL cholesterol, total cholesterol, HTN, CAD, and HLD. Additionally, we observed no association between DFU healing rates and use of a statin medication.

1. Background
In 2018, 34.2 million Americans were living with diabetes mellitus (DM) (1). A patient with a new diabetic foot ulcer (DFU) has a 5% mortality rate within the first year after receiving treatment (2). At 5 years, that mortality rate increases to approximately 42% (2). Approximately 16% of newly diagnosed DFU will progress to major lower extremity amputation (3). Those persons who progress to amputations often have a high metabolic comorbid burden, including dyslipidemia (1).

Approximately 43.5% of DM patients have a non-high-density lipoprotein (HDL) cholesterol level of 130 mg/dL or higher (1). Hyperlipidemia occurs with total cholesterol in the blood greater than 200 mg/dL (4). In 2006, 51.3% of adults with DM were also taking a statin medication to control cholesterol levels (4). Statins are the guideline-preferred first-line medication for reducing low-density lipoprotein (LDL) cholesterol (5). Lifestyle modifications are recommended and consist of improving diet and nutritional intake, weight loss, and physical activity. Lifestyle modifications are recommended in conjunction with primary preventative methods. This is often accomplished by adding a moderate or high-intensity statin medication. Moderate-intensity statin therapy is recommended in those 40–75 years old, whereas high-intensity may be necessary if a patient has a greater risk of atherosclerotic cardiovascular disease. Secondary prevention with the addition of other non-statin cholesterol medications may be considered if there is not adequate control with statin therapy and lifestyle modifications alone (5), with a goal of achieving LDL cholesterol ≤ 55 mg/dL, > 50% reduction in LDL cholesterol, or non-HDL cholesterol ≥ 85 mg/dL (6).

Statin medications work by acting as competitive inhibitors of Hydroxymethylglutaryl (HMG) CoA reductase in the biosynthesis of cholesterol. Statin medications do have pleiotropic effects that could potentially influence DFU healing (7–9). By selectively competing and interfering with cholesterol biosynthesis, a subsequent decrease in LDL cholesterol, increase in HDL cholesterol, and a decrease in total cholesterol and triglycerides are seen (10). The mechanism of statin therapy on DFU healing is unclear, but Gulcan et al. proposed that it causes increased vasodilation by increasing nitric oxide synthesis, decreasing endothelin-1 synthesis, and a decrease in vasoconstriction in the lower extremity by reducing available angiotensin-2 (7). Goggi et al. proposed that neovascularization is promoted by increasing endothelial progenitor cells by increasing vascular endothelial growth factor and capillary density (8). Another theory put forth by Spampinato et al. asserts there is the possibility that statins inhibit farnesyl pyrophosphate and cortisol, which act to inhibit keratinocyte migration and epithelialization (9). Despite these proposed mechanisms, the relationship between statin use and DFU healing remains unclear.

Multiple studies have evaluated the effects of statin medications on DFU healing (7–9, 11–16). Fox et al. compared several medication classes and reported an association between DFU wound reduction and intervention for hyperlipidemia via statin therapy. However, this did not reach statistical significance (p = 0.057) (11). Johansen et al. compared dosage of atorvastatin and reported a protective effect from the higher dosage as it related to recurrence of a DFU (12).
Given these potential mechanisms and prior studies examining the relationship between statin use and aspects of DFU healing, we sought to determine if there was an association between DFU healing rates and concomitant statin use. We hypothesized statin therapy promotes DFU healing. Thus, the primary objective of this study was to investigate if there was improved DFU healing among patients on a statin medication compared to those with a DFU who were not taking a statin medication. Secondary outcomes assessed were associations with wound healing or statin use on data obtained from the retrospective chart review.

2. Methods

A retrospective chart review was performed to obtain patient information through University of Michigan Health, a large tertiary care academic health system. A software medical record extraction tool (Data-Direct) was used to identify the study cohorts. Data-Direct is a tool developed by the University of Michigan to assist with data extraction from the unified electronic medical record (EMR). Institutional Review Board approval was obtained (IRB no. HUM-0020797).

We included adult DM patients with active DFU who were administered a statin medication of either atorvastatin, simvastatin, rosuvastatin, fluvastatin, pravastatin, lovastatin, and pitavastatin between January 2015 and December 2019. Patient encounters were limited to the outpatient setting. Data Direct was used to obtain International Classification of Disease (ICD) versions 9 and 10 diagnostic codes relating to DM, foot ulcer, skin breakdown, infection, and foot and lower extremity. A full list of the included codes can be seen in Appendix A. Common Procedural Terminology (CPT) codes for wound debridement (11042–11047) for DFU patients were used to assist in evaluating wound progression during usual DFU care.

2.1 Outcome Measures

Demographic and comorbid conditions were obtained from the EMR. Information collected included age, sex, race, body-mass index (BMI), type and duration of DM, duration of smoking in pack-years, history of DFU, history of minor lower extremity amputation (e.g., distal to the ankle). Comorbid conditions included hypertension (HTN), coronary artery disease (CAD), hyperlipidemia (HLD), chronic kidney disease (CKD) and stage based on race-based estimated glomerular filtration rate (eGFR) (17), congestive heart failure (CHF), and diabetic retinopathy (DR). Lab values were reviewed and included if they were obtained within 6 months of the onset of the DFU. These included HDL cholesterol, LDL cholesterol, non-HDL cholesterol, total cholesterol, triglyceride, blood glucose levels, hemoglobin A1c, eGFR, creatinine, and urine microalbumin. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) starting values were included if obtained at time of onset of DFU and at time of healing of DFU or after 12 weeks of failed healing. Healing was defined as full epithelialization of the DFU with no further drainage as seen at follow-up visits.
Physical examination characteristics at time of DFU onset were reviewed and included palpable pedal pulses, ankle-brachial index (ABI) and toe-brachial index (TBI) values (included if within 6-months of DFU onset), most distal level of intact sensation as tested via 5.07-10g Semmes Weinstein monofilament (18), location of DFU, local signs of infection on presentation, and surface area/volume of DFU. Offloading status was recorded to ensure appropriate DFU treatment. Appropriate DFU treatment included regular wound debridement, assessing and addressing vascular status if indicated, infection control, and offloading. The type of statin medication was recorded and included atorvastatin, simvastatin, rosuvastatin, fluvastatin, pravastatin, lovastatin, and pitavastatin (Supplementary Table 7). All patients were then followed for 12 weeks to evaluate for healing.

2.2 Data Analysis

Demographic and comorbid data was analyzed using chi square (X2). Pearson correlation coefficients were obtained for (dichotomous) categorical variables including wound healing and statin use. Strength of association was defined as weak for an r-value < 0.3, mild for r-values between 0.3–0.6, and strong above 0.6. Statistical analysis was assisted by GraphPad by Dotmatics (19). All p-values were two-sided, and findings were considered statistically significant at p < 0.05.

3. Results

109 patients were identified and included in the study. 75 patients with a DFU were statin users (statin cohort) and 34 patients with a DFU were not administered a statin medication (non-statin cohort).

3.1 Demographics

Statin users were older, with the average age being 59.8 years versus 52.6 years in the non-statin cohort (p < 0.05). Statin users were likely to have had DM for less than 5 years (p < 0.05). Table 1 demonstrates patient demographic data. Both cohorts were similar in terms of sex, race, BMI, type of DM, smoking history, personal history of DFU, and personal history of lower extremity amputation.

3.2 Comorbidities and Physical Exam

Statin users had a higher prevalence of HTN (92.0% vs. 67.6%), CAD (36.0% vs. 8.8%), HLD (86.7% vs. 20.6%), CKD status overall (41.3% vs. 17.6%), and CHF (18.7% vs. 2.9%) as compared to non-statin users (all p < 0.05). See Table 2 for comorbid conditions of both cohorts. Additionally, CKD stage 3b (20.0% vs. 0%) was higher in statin users (p < 0.05). Both cohorts had similar rates of DR.

Patient physical examination findings to assess peripheral vascular status, including rates of palpable pulses, ABI, and TBI, along with DFU location, were similar amongst groups. Patient physical examination data for both cohorts is included in Table 3.

3.3 Laboratory Values
Mean LDL cholesterol was 74.8 mg/dL and 101.5 mg/dL for statin users and non-statin users, respectively (p < 0.05). Mean total cholesterol was 151.0 mg/dL and 180.2 mg/dL for statin users and non-statin users, respectively (p < 0.05). The mean eGFR was 54.0 ml/min/1.73m2 among statin users and 59.0 ml/min among non-statin users (p < 0.05). Statin users had a mean creatinine of 1.2 mg/dL and a mean of 0.9 mg/dL in non-statin users (p < 0.05). Patient laboratory value data for both cohorts can be found in Table 4.

3.4 Statin Medication

68% (51/75) of patients were taking atorvastatin, 14.7% (11/75) of patients were taking simvastatin, 12% (9/75) of patients were taking rosuvastatin, 2.7% (2/75) of patients were taking pravastatin, and 2.7% (2/75) of patients were taking lovastatin, as shown in Supplement Table 7. No patients were taking ertavastatin or pitavastatin.

3.5 Clinical Outcomes

48.0% (36/75) of patients in statin users healed the DFU within 12 weeks. Among non-statin users, 44.1% (15/34) healed the DFU within 12 weeks and showed no association (p = 0.71).

A significant association was noted for wound healing and prior minor amputation status with a r-value of -0.34 (p < 0.001).

Separately, significant associations were noted between statin use and age, duration of DM, LDL cholesterol level, total cholesterol level, HTN, CAD, and HLD with r-values of -0.25 (p < 0.01), -0.31 (p = 0.001), 0.33 (p = 0.01), 0.28 (p = 0.03), 0.31 (p = 0.001), 0.28 (p = 0.003), and 0.65 (p < 0.0001), respectively. There was no association between wound healing and statin use (r = 0.036, p = 0.71).

4. Discussion

The primary objective of this study was to investigate if there were improved healing rates of DFU among those patients on a statin medication compared to those with DFU who were not taking a statin medication at 12 weeks. Margolis et al. found that approximately 24% of patients receiving standard DFU treatment are expected to heal at 12 weeks (20). Among statin users in our study, there was a 48.0% DFU healing rate and 44.1% DFU healing rate for non-statin users (p = 0.71) at 12 weeks. There were improved healing rates for both cohorts in our study compared to 24% receiving standard treatment at the 12-week mark. Association testing was performed for wound healing and statin use and no association was found, with an r-value of 0.036 (p = 0.71). These findings did not support our hypothesis that statin use would lead to increased healing rates of DFU.

Johansen et al. studied two groups taking atorvastatin, with group 1 using the dose of 10 mg and group 2 of 80 mg. In group 1, there was a 100% DFU healing rate and group 2 had a 66% DFU healing rate (12). Our study did not consider the dosages of statin medications or monitor for recurrence and was retrospective in nature, which could have contributed to the difference in findings.
Among those patients that were statin users, they were likely to have more comorbidities. Statin users were older with a higher comorbid burden at baseline, including higher prevalence of HTN, CAD, HLD, CKD, and CHF. Not unsurprisingly, statin users had improved LDL (74.8 mg/dL vs. 101.5 mg/dL, p < 0.05) and total cholesterol levels (151.0 mg/dL vs. 180.2 mg/dL, p < 0.05). Non-statin users were more likely to have better baseline renal function as noted in eGFR and creatinine levels.

There was a significant association between prior minor amputations as it relates to DFU healing. As minor amputations are often precipitated by DFU, this finding can be unfortunately common given DFU recurrence rates can be up to 40% after 1 year (21).

There were limitations to this study. First, the study was retrospective, which inherently raises concern for selection bias. We attempted to mitigate this limitation by selecting patients consecutively who met all eligibility requirements. Second, multiple providers with different backgrounds provided DFU care at our institution. This does introduce treatment heterogeneity that would not have occurred with fewer providers. We feel this reflects a real-world scenario as patients are frequently evaluated and treated in this manner. Third, there was variation in the types of DFU that were included, as some were first-time DFU or recurrences. On DFU that healed, there was no follow-up period to ensure they remained healed. With the high DFU recurrence rate after a healing event, this is not unexpected (21). We attempted to address this by selecting a DFU at random during the study period but did not differentiate between first-time or recurrent DFU. Fourth, there was no distinction on low, moderate, or high-intensity statin therapy as dosages were not recorded. Our study did not find a difference in healing rates between our evaluated cohorts. One of the main studies which evaluated the healing effect of statin medications and DFU healing specifically questioned if statin dose affected DFU healing and recurrence rates (12). The intensity of statin therapy could be an avenue for further research.

In conclusion, there was not an association between DFU healing and statin therapy. Future studies should include multiple institutions to prospectively study various dosages of statin medication and pre-specify if the DFU in question is new or recurrent.

Declarations

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.
Competing Interests

The authors declare that they have no competing interests.

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Author's Contributions

All authors contributed to the findings discussed in this paper. All information is the original work of the authors who approve of this submission.

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References


Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarymaterial.docx