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Lower Extremity Amputation-incidence and Review of Diabetic and Non-diabetic Patients in Central Slovenia Population from 2001 to 2019

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Abstract

Introduction: This retrospective study aimed to determine the trends in the incidence of non-traumatic lower extremity amputations in diabetic and non-diabetic patients.

Methods: A retrospective, population-based cohort study was conducted at the University Medical Center Ljubljana which is representative of Slovenia. By defined inclusion criteria, we gathered information on patients treated for lower extremity amputations over 19 years (2001 - 2019). Patients were divided into two groups, diabetics and non-diabetics. Linear regression analysis was used to analyze amputation trends over the studied years.

Results: A total of 2,341 patients were included in our study, the majority were diabetics (1412/2341; 60.32%). Our results revealed an increased incidence of lower extremity amputations in diabetic and non-diabetic patients alike. The age- and gender-adjusted relative increase in amputation rates were 45% in all amputations and 35% in major amputations ($P < 0.001$). Non-diabetics were slightly older (2 years on average; $P < 0.05$), with a higher mortality rate (6.1% vs. 1.8%; $P < 0.05$).

Conclusions: Despite efforts to reduce lower extremity amputations in diabetics, their incidence in Slovenia is increasing. Higher amputation rates can only partially be justified by an aging population and an increasing number of diabetics. Preventive measures for amputation amply described in the literature are available and implemented also in our country, but considering our results, they need to be re-evaluated.

INTRODUCTION

Lower extremity amputation (LEA) is an event that dramatically changes an individual's life, decreases the quality of life (QoL), and presents a financial and social burden [1]. Diabetes mellitus (DM) and peripheral arterial disease (PAD) are the leading causes of non-traumatic LEA in developed countries [2-8]. It is known that patients with DM have a four times higher likelihood of developing PAD and a 10-20 times higher risk of requiring LEA, compared to non-diabetic patients [7-11]. Since DM and its complications present a major world health problem, many initiatives have been made to alleviate the course of the disease. In 1989, European countries signed the St. Vincent declaration which aimed to reduce diabetic complications and LEA rates by half in the following five years after being signed [12]. Although this declaration encouraged researchers and/or clinicians to follow the rates of LEA, many reporting their decline, the goal has still not been reached [12-15].

We collected data on non-traumatic LEA in the population of Central Slovenia from 2001 to 2019. This study aimed to analyze the incidence of LEA in the selected time observation period and to establish the situation in Slovenia. We hypothesized that the incidence of LEA has not declined and that the system needs further improvements in the multidisciplinary management of such patients.

METHODS

STUDY DESIGN

A retrospective, population-based cohort study was performed by collecting patient data (national hospital discharge data) on LEA, performed at the University Medical Center Ljubljana (UMCL) from January 2001 to December 2019. UMCL is a major Slovenian hospital serving the population of Central Slovenia, approximately a quarter of the country's population, and is representative of the entire Slovenian population.

We gathered patients' demographic data, comorbidities,

mobility data, complications, level and cause of amputation, possible revascularization procedures, and their postoperative course and mortality.
Inclusion criteria were amputations of lower extremity performed due to PAD or/and infection in patients with diabetes mellitus (D+) or without diabetes mellitus (D-). Patients were classified as diabetics if DM type 1 or 2 was known before or confirmed during hospitalization. Exclusion criteria were amputations due to trauma, tumors, or frostbite and amputations at the level of the knee, ankle, or hip joint. If patients underwent several amputations on the same leg, we only included the most recent amputation, the most proximal, and marked the patient as having had a previous amputation. We divided amputees into two groups: major LEA (below-knee amputation (BKA) and above-knee amputation (AKA)) and minor LEA (all amputations performed distal to ankle joint level). We compared patients with DM (D+) to those without DM (D-).

Statistical Methods

Linear regression analysis was conducted to establish the trends over the studied years. Before performing the analysis, data were adjusted for differences in age and gender distributions. The standard population age and gender distributions were obtained from the Statistical Office of Slovenia, as of 1st December 2020. Ages were grouped into buckets, each spanning five years. Per 100 000 population rates were computed based on population data from January 1st of each year.
Continuous variables were expressed as mean ± standard deviation (SD). Pearson's Chi-Square test was used for testing the relationships between categorical variables. T-test was used for testing the mean of continuous variables between groups. The level of statistical significance was set at $P < 0.05$. Statistical analysis was performed using IBM SPSS Statistics, v. 24 (IBM Corp, Armonk, NY).

RESULTS

Documentation of more than 3000 patients who underwent LEA over 19 years (2001 - 2019) was reviewed. After exclusion criteria, 2341 patients remained in the study. This study mainly focused on the population of diabetic (D+) versus non-diabetic patients (D); the majority, 1412/2341 (60.32%) of enrolled patients were D+. The male/female ratio of our study group was 1.43 (1378/963) and was comparable in D+ and D- groups (Table 1). The leading indication for LEA was PAD both in D+ and D- groups. Diabetics (D+) were significantly younger compared to non-diabetics (D-) (Table1).
The incidence of LEA was increasing during the observation period. An increase of LEA was observed in D+ and D- groups for major as well as minor amputations (Table 2).
Most of the performed amputations in D+ and D- groups were major, but minor amputations were significantly more common in the D+ group (Table 3).

Table 1: Demographic Data and Indication for Lower Extremity Amputation by Diabetic Status

	All patients (N=2341), No. (%)		P-value
	D+ (N=1412)	D- (N=929)	
Gender			0.658
Male	826 (58.50)	552 (59.42)	
Female	586 (41.50)	377 (40.58)	
Indication			0.003
Infection	322 (22.80)	164 (17.65)	
PAD	1090 (77.20)	765 (82.35)	
Age at amputation, y	72 ± 11	73 ± 12	< 0.05

PAD: peripheral arterial disease; N - the total number in the group.

Table 2: Lower Extremity Amputation Rates at the Beginning of the Study (2001) and the End (2019) per 100.000 Inhabitants of Central Slovenian Population

Year	Total LEA	Major LEA
2001	16.79 (87)	12.15 (63)
2019	23.42 (128)	16.10 (88)
Age- and gender-standardized relative change (%)	+45%	+35%
P-value	<0.001	

*population in 2001: 518,128 citizens; population in 2019: 546,314 citizens.
Relative change was computed based on the age- and gender-standardized data.

Table 3: Level of lower extremity amputation in our study group (N=2341).			
	D+ (N=1412), No. (%)	**D- (N=929) , No. (%)**	P-value
Minor (TMT, SM)	613 (43.40)	149 (16.00)	< 0.005
Major (AKA, BKA)	799 (56.60)	780 (84.00)	

TMT: transmetatarzal amputation, SM: supramelolar, BKA: below-knee amputation, AKA: above-knee amputation

Table 4. Postoperative Complications			
	D+ (N=1412) , No. (%)	**D- (N=929) , No. (%)**	**P-value**
Wound infection	142 (10.06)	90 (9.68)	0.770
Post-operative bleeding	16 (1.13)	8 (0.86)	0.523
Wound dehiscence	31 (2.20)	18 (1.94)	0.670
Cardiovascular disease	68 (4.82)	48 (5.17)	0.702
Cerebrovascular insult	5 (0.35)	4 (0.43)	0.770
Pulmonary embolism	4 (0.28)	2 (0.22)	0.750
Deep vein thrombosis	0	0	-
Delirium	9 (0.64)	6 (0.65)	0.980
Decubitus	12 (0.85)	13 (1.40)	0.206
Death (during the operation)	0	0	-
Death (postop)	25 (1.77)	57 (6.13)	< 0.05

Diabetic patients (D+) had significantly higher previous amputation rates on the same leg (475/1412; 33.6%) compared to non-diabetics (D-) (190/929; 20.5%) (P < 0.00001). The same holds for a previous amputation on the contralateral leg, as the incidence in the D+ group was 396/1412 (28.0%) compared to 118/929 (12.7%) in the D- group (P < 0.00001). The length of hospital stay was comparable between the groups (17.7 days for diabetics and 15.8 days for non-diabetics; P = 0.078).

Postoperative complications were comparable in D+ and D- groups, as shown in Table 4. No difference was established in wound infection, dehiscence, or postoperative bleeding. All the patients survived the operative procedure, but postoperative mortality during hospitalization was significantly higher in the D- group (Table 4).

DISCUSSION

The global number of diabetes mellitus (DM) patients is rising, despite the initiatives (St. Vincent declaration, Diabetes Prevention and Care Development Program 2010-2020 preventative measures) to limit the epidemic [12, 16]. Some countries succeeded to lower the amputation rates; reports from the USA, United Kingdom, Italy, Finland, and Germany have confirmed a decrease of at least major amputations [6, 13-15, 17].

Considering our results, the incidence of major and minor amputations in Slovenia is still increasing in both groups-in diabetic (D+) and non-diabetic (D-) patients alike. Our analyzed data do not provide an insight into preventive measures that were performed to avoid amputation, only demographic and medical patient data. Since the number of amputations is increasing, it seems that the efforts for better control of diabetes aimed at postponing late complications were not effective in Slovenia. It is also true that the population is aging, which contributes to higher morbidity rates and lower limb amputations. During the observation period, the percentage of citizens aged 65 years or more rose from 12 to 17%, and life expectancy has seen an increase from 74 to 80 years [18]. In addition, the prevalence of diabetes rose from 6.0 to 6.9% [18]. Even after adjusting amputation rates to age and gender, the incidence of major and minor amputations still increased. It is true, that our results do not include all amputations in the whole country. But UMCL is a leading hospital in the country and also a referral center for patients with chronic wounds. An increase in amputation rates shows that the preventive measures have not been (successfully) implemented. Our results support extant findings from the literature that LEA is more frequent in men and that diabetics are usually younger compared to non-diabetics and have a higher rate of minor amputations [19, 20]. According to literature, diabetics are younger at the onset of amputation, and amputations are more often performed at a distal level, which was confirmed also in our study [19-21]. Diabetics have a higher rate of reamputations, which raises the question of whether it might not be better to perform a higher amputation in the first place [6, 22]. In some cases, that would undoubtedly be the case, but on the other hand, lower amputation enables the patient to walk easier with a prosthesis for a limited time until the next amputation is unavoidable.

In various countries, diabetes is associated with at least half of all LEA. Diabetics are estimated to be at an 8 to 24 times higher risk of LEA compared to non-diabetics [2-4, 21]. In our study, 1412/2341 (60.32%) of all non-traumatic and non-neoplasm LEA were performed in diabetics, which is comparable to other publications [15].

Although the mortality rate for diabetics with LEA is reported to be high (from 18-55%), none of the patients died during the amputation procedure in the period which our study looked at [4, 6, 23, 24]. The postoperative mortality rate due to complications post LEA was 3.5% (82/2341) and mostly affected non-diabetics: 6.14% (57/929) of non-diabetics died and only 1.77% (25/1412) of diabetics. Most of

them (86%) had an above-knee amputation (AKA) and all had cardiovascular disease, which was a factor contributing to a worse prognosis. Lower amputations were more common in diabetics since this group gets amputated more often due to vascular complications associated with PAD and/or infection. In non-diabetics, AKA was the most common (poor vascular system). Considering these findings, special care should be offered to the group of patients with advanced age and cardiovascular disease that require AKA, despite a negative diabetic status, as well as those with minor amputations and known diabetic foot syndrome, since these factors increase the likelihood of reamputation due to diabetic and/or vascular complications.

The length of hospital stay in our study and extant literature is comparable for diabetics and non-diabetics. The average hospital stays at our clinic was 16 to 17 days, which is comparable to data from the USA (15.9 days), Australia (24.7 days), UK (28 days) and is shorter than in the Netherlands (42 days) and Spain (52 days) [2, 20, 21].

Lower limb amputation rates in the UMCL, the main Slovenian hospital, increased over a 19-year surveillance study. Reports from most countries show a decrease in LEA [13, 14, 17, 25]. An increase in LEA has been reported in a study from Ireland but in a much shorter, 5-year study interval [26]. A diabetic foot ulcer is the most common complication in diabetics that leads to LEA [27]. Prevention and appropriate management of diabetic foot ulcers that can lower LEA rates have been described [27-30]. All mentioned preventive measures, including patient and staff education, preventive foot care, protective or therapeutic shoe availability, multidisciplinary management of the diabetic foot ulcer, and availability of vascular interventions are available in our country. Considering the results of our study, preventive measures for LEA in Slovenia should be re-evaluated.

CONCLUSION

Despite efforts to reduce lower extremity amputations in diabetics, their incidence in Slovenia is increasing. Higher amputation rates can only partially be justified by an aging population and an increasing number of diabetics. Preventive measures for amputation amply described in the literature are available and implemented also in our country, but considering our results, they need to be re-evaluated.

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ETHICAL STATEMENT

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Hospital Ethics Board.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

AUTHORS' CONTRIBUTION

I.F. designed the study, contributed data, critically reviewed the manuscript, and supervised the research. T.N.K. drafted the manuscript, organized data, and performed the statistical analysis, N.A. contributed to the study performance and critically reviewed the manuscript. All authors have read and agreed to the published version of the manuscript.

REFERENCES

1. Lin C, Liu J, Sun H. Risk factors for lower extremity amputation in patients with diabetic foot ulcers: A meta-analysis. PLoS One. 2020;15(9):e0239236. DOI: 10.1371/journal.pone.0239236 PMID: 32936828
2. Preece RA, Dilaver N, Waldron CA, Pallmann P, Thomas-Jones E, Gwilym BL, et al. A Systematic Review and Narrative Synthesis of Risk Prediction Tools Used to Estimate Mortality, Morbidity, and Other Outcomes Following Major Lower Limb Amputation. Eur J Vasc Endovasc Surg. 2021;62(1):127-35. DOI: 10.1016/j.ejvs.2021.02.038 PMID: 33903018
3. Wrobel JS, Mayfield JA, Reiber GE. Geographic variation of lower-extremity major amputation in individuals with and without diabetes in the Medicare population. Diabetes Care. 2001;24(5):860-4. DOI: 10.2337/diacare.24.5.860 PMID: 11347744
4. Resnick HE, Carter EA, Lindsay R, Henly SJ, Ness FK, Welty TK, et al. Relation of lower-extremity amputation to all-cause and cardiovascular disease mortality in American Indians: the Strong Heart Study. Diabetes Care. 2004;27(6):1286-93. DOI: 10.2337/diacare.27.6.1286 PMID: 15161777
5. Teraa M, Conte MS, Moll FL, Verhaar MC. Critical Limb Ischemia: Current Trends and Future Directions. J Am Heart Assoc. 2016;5(2). DOI: 10.1161/JAHA.115.002938 PMID: 26908409
6. Geiss LS, Li Y, Hora I, Albright A, Rolka D, Gregg EW. Resurgence of Diabetes-Related Nontraumatic Lower-Extremity Amputation in the Young and Middle-Aged Adult U.S. Population. Diabetes Care. 2019;42(1):50-4. DOI: 10.2337/dc18-1380 PMID: 30409811
7. Albayati MA, Shearman CP. Peripheral arterial disease and bypass surgery in the diabetic lower limb. Med Clin North Am. 2013;97(5):821-34. DOI: 10.1016/j.mcna.2013.03.009 PMID: 23992894
8. Malyar NM, Freisinger E, Meyborg M, Luders F, Gebauer K, Reinecke H, et al. Amputations and mortality in in-hospital treated patients with peripheral artery disease and diabetic foot syndrome. J Diabetes Complications. 2016;30(6):1117-22. DOI: 10.1016/j.jdiacomp.2016.03.033 PMID: 27118161
9. Gregg EW, Sorlie P, Paulose-Ram R, Gu Q, Eberhardt MS, Wolz M, et al. Prevalence of lower-extremity disease in the US adult population >=40 years of age with and without diabetes: 1999-2000 national health and nutrition examination survey. Diabetes Care. 2004;27(7):1591-7. DOI: 10.2337/diacare.27.7.1591 PMID: 15220233
10. Mills JL. Lower limb ischaemia in patients with diabetic foot ulcers and gangrene: recognition, anatomic patterns and revascularization strategies. Diabetes Metab Res Rev. 2016;32 Suppl 1:239-45. DOI: 10.1002/dmrr.2753 PMID: 26455728
11. The Saint Vincent Declaration on diabetes care and research in Europe. . Acta Diabetologica. 1989;10:143-4.
12. Felton A-M, Hall MS. Diabetes — from St Vincent to Glasgow. Have we progressed in 20 years? The British Journal of Diabetes & Vascular Disease. 2009;9(4):142-4. DOI: 10.1177/1474651409341318
13. Lombardo FL, Maggini M, De Bellis A, Seghieri G, Anichini R. Lower extremity amputations in persons with and without diabetes in Italy: 2001-2010. PLoS One. 2014;9(1):e86405. DOI: 10.1371/journal.pone.0086405 PMID: 24489723
14. Kröger K, Berg C, Santosa F, Malyar N, Reinecke H. Lower Limb Amputation in Germany. Deutsches Aerzteblatt Online. 2017. DOI: 10.3238/arztebl.2017.0130
15. Monteiro-Soares M, Vale-Lima J, Martiniano J, Pinheiro-Torres S, Dias V, Boyko EJ. A systematic review with meta-analysis of the impact of access and quality of diabetic foot care delivery in preventing lower extremity amputation. J Diabetes Complications. 2021;35(4):107837. DOI: 10.1016/j.jdiacomp.2020.107837 PMID: 33423910
16. Diabetes Prevention and Care Development Programme 2010 - 2020

Based on the National Diabetes Prevention and Care Development Programme Development Strategy 2010 - 2020 Ljubljana2010 [cited 2020 December 20th]. Available from: http://www.mz.gov.si/fileadmin/mz.gov.si/pageuploads/mz_dokumenti/delovna_podrocja/javno_zdravje/diabetes/National_Diabetes_Prevention_and_Care_Development_Programme.pdf.
17. Vamos EP, Bottle A, Edmonds ME, Valabhji J, Majeed A, Millett C. Changes in the incidence of lower extremity amputations in individuals with and without diabetes in England between 2004 and 2008. Diabetes Care. 2010;33(12):2592-7. DOI: 10.2337/dc10-0989 PMID: 20833865
18. Diabetes in Slovenia, data from Slovenian National Institute of Public Health. 2020 [cited 2020 December 20th]. Available from: http://www.nijz.si/en/report-on-national-conference-on-diabetes-management-2020.
19. Dangelser G, Besson S, Gatina JH, Blicklé JF. Amputations among diabetics in Reunion Island. Diabetes & Metabolism. 2003;29(6):628-34. DOI: 10.1016/s1262-3636(07)70079-4
20. Long CA, Mulder H, Fowkes FGR, Baumgartner I, Berger JS, Katona BG, et al. Incidence and Factors Associated With Major Amputation in Patients With Peripheral Artery Disease: Insights From the EUCLID Trial. Circ Cardiovasc Qual Outcomes. 2020;13(7):e006399. DOI: 10.1161/CIRCOUTCOMES.119.006399 PMID: 32615798
21. Faglia E, Clerici G, Clerissi J, Gabrielli L, Losa S, Mantero M, et al. Early and five-year amputation and survival rate of diabetic patients with critical limb ischemia: data of a cohort study of 564 patients. Eur J Vasc Endovasc Surg. 2006;32(5):484-90. DOI: 10.1016/j.ejvs.2006.03.006 PMID: 16730466
22. Johannesson A, Larsson GU, Ramstrand N, Turkiewicz A, Wirehn AB, Atroshi I. Incidence of lower-limb amputation in the diabetic and nondiabetic general population: a 10-year population-based cohort study of initial unilateral and contralateral amputations and reamputations. Diabetes Care. 2009;32(2):275-80. DOI: 10.2337/dc08-1639 PMID: 19001192
23. Papazafiropoulou A, Tentolouris N, Soldatos RP, Liapis CD, Dounis E, Kostakis AG, et al. Mortality in diabetic and nondiabetic patients after amputations performed from 1996 to 2005 in a tertiary hospital population: a 3-year follow-up study. J Diabetes Complications. 2009;23(1):7-11. DOI: 10.1016/j.jdiacomp.2007.11.008 PMID: 18413176
24. Malyar NM, Freisinger E, Meyborg M, Luders F, Furstenberg T, Kroger K, et al. Low Rates of Revascularization and High In-Hospital Mortality in Patients With Ischemic Lower Limb Amputation: Morbidity and Mortality of Ischemic Amputation. Angiology. 2016;67(9):860-9. DOI: 10.1177/0003319715626849 PMID: 26764367
25. Lopez-de-Andres A, Jimenez-Garcia R, Aragon-Sanchez J, Jimenez-Trujillo I, Hernandez-Barrera V, Mendez-Bailon M, et al. National trends in incidence and outcomes in lower extremity amputations in people with and without diabetes in Spain, 2001-2012. Diabetes Res Clin Pract. 2015;108(3):499-507. DOI: 10.1016/j.diabres.2015.01.010 PMID: 25866357
26. Buckley CM, O'Farrell A, Canavan RJ, Lynch AD, De La Harpe DV, Bradley CP, et al. Trends in the incidence of lower extremity amputations in people with and without diabetes over a five-year period in the Republic of Ireland. PLoS One. 2012;7(7):e41492. DOI: 10.1371/journal.pone.0041492 PMID: 22859991
27. Schaper NC, Van Netten JJ, Apelqvist J, Lipsky BA, Bakker K, International Working Group on the Diabetic F. Prevention and management of foot problems in diabetes: a Summary Guidance for Daily Practice 2015, based on the IWGDF Guidance Documents. Diabetes Metab Res Rev. 2016;32 Suppl 1:7-15. DOI: 10.1002/dmrr.2695 PMID: 26335366
28. Meza-Torres B, Carinci F, Heiss C, Joy M, de Lusignan S. Health service organisation impact on lower extremity amputations in people with type 2 diabetes with foot ulcers: systematic review and meta-analysis. Acta Diabetol. 2021;58(6):735-47. DOI: 10.1007/s00592-020-01662-x PMID: 33547497
29. Rossboth S, Lechleitner M, Oberaigner W. Risk factors for diabetic foot complications in type 2 diabetes-A systematic review. Endocrinol Diabetes Metab. 2021;4(1):e00175. DOI: 10.1002/edm2.175 PMID: 33532615
30. Alvarsson A, Sandgren B, Wendel C, Alvarsson M, Brismar K. A retrospective analysis of amputation rates in diabetic patients: can lower extremity amputations be further prevented? Cardiovasc Diabetol. 2012;11:18. DOI: 10.1186/1475-2840-11-18 PMID: 22385577