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Abstract

Objectives: To assess the trends of peripheral arterial disease associated major lower limb amputations in Hungary over a nine year period (2004-2012) in the whole population.

Design: Retrospective cohort study employing administrative health care data.

Materials and Methods: Major amputations were identified in the entire Hungarian population during a nine-year period (2004-2012) using health care administrative data. Direct standardization was used to eliminate the potential bias induced by the different age and sex structure of the compared populations. For external direct standardization, the European Standard Population 2013 was chosen as reference.

Results: 76 798 lower limb amputations were performed over the observational period. The number of major amputations was 38 200; these procedures affected 32 084 amputees. According to our case detection, 50.4% of the amputees were affected by diabetes. The overall primary amputation rate was 71.5%. The annual crude and age-adjusted major amputation rates exhibited no significant long-term pattern over the observational period. Major lower limb amputations incidence for the overall period were 42.3/10⁵ in the total population, 317.9/10⁵ in diabetic populations, respectively. Incidence data are provided for other subpopulations at risk too.

Conclusions: According to this whole population based study from Hungary, the incidence of lower limb major amputation is high with no change in the past nine years. An explanation for this phenomenon remains to be clarified, as the traditional risk factors in Hungary do not provide an account. The characteristics of major amputations (the rate of primary amputations, the ratio of below/above knee amputations, the age of the affected population) underlines the importance of screening, early detection, improved vascular care and optimal
revascularization policy. Standardization and validation of amputation detection methods and reporting would be essential.

Keywords: Peripheral arterial disease, Lower limb amputation, Critical limb ischemia
Introduction

Amputation of the lower extremities is one of the most devastating consequences of peripheral arterial disease (PAD). Morbidity and mortality data related to this procedure show exceptionally poor result (1, 2). Besides the loss of quality of life in many domains, lower limb amputation as a potential outcome of critical limb ischemia has a complex and immense impact on health expenditures (3, 4). All these aspects underline the importance of the assessment of PAD related lower limb amputation occurrence.

Methodologically, the prospective observational studies have limited value in the determination of amputation incidence. Insufficient patient enrolment due to expenses, insufficient observation time that allows for the assessment of short-term effects only, selection bias in a volunteer sample, and low external validity are the main shortcomings of this design (5, 6). Analysis of electronic records of health care administrative data (codes for diseases, medical procedures, prescription refills) are used prevalingly on the amputation field. It surpasses the clinical cohorts in volume, and the reuse of these data diminish the cost and inefficiencies associated with clinical research. The available amount of data allows for examining more potential confounding variables, exploring rare occurrences, studying long-term consequences, applying more advanced statistical methods, and developing data mining techniques (5). The potential of this method enables the analysis to assess regional (7), nationwide (8, 9, 10, 11, 12), or international trends (13, 14) in amputations.

The published data of PAD related lower extremity amputations incidence show wide variability (14). Trends in amputation are also different showing decline in the USA (15), Italy (10), Sweden (16), Germany (17), Finland (18) steadiness in the Republic of Ireland (8) and increase (for type 2 diabetes related) in Spain (9) and England (11).
Comparing these is difficult not only due to the heterogeneity in the studied populations, but also because of variations in the reporting methods. In interpreting the amputation incidence figures, many potential pitfalls are to be taken into account (19).

The aim of the present study was to determine the temporal trend of major lower limb amputations associated with peripheral arterial disease in the entire Hungarian population over a nine-year period.

**Materials and Methods**

**Database**

The HUNgarian VASCular DATA (HUNVASCDATA) project is based on the analysis of the health care administrative data pertaining to the whole Hungarian population. The raw data for analysis originated from every outpatient and inpatient medical encounters and pharmacy refills in the observational period. The expense claims related to these events are electronically collected for the single health care financer (National Health Insurance Fund) in a data warehouse architecture. The claim data are transferred and converted for analytic purpose to a governmental organization that is responsible for the dissemination and analysis of health care related data supporting governmental health care decision makers. The data are stored in form of a relational database structure (ORACLE) with the potential of performing different query algorithms. The HUNVASCDATA project used this database in close cooperation with before-mentioned governmental organization by developing disease and procedure specific data extraction algorithms resulting in the analytical file. Data extraction was based on the International Classification of Diseases, tenth revision (ICD-10) and International Classification of Procedures in Medicine (ICPM) codes.
In contrast to the insurance claim file, in our database, no patients’ identity was disclosed due to the application of an insurance number encryption algorithm. This process ensures anonymous handling of the patients’ data and simultaneously, a unique record for each health care beneficiary. In the lack of identifiable individual data, Institutional Review Board (IRB) approval to conduct this study was not required. The research was conducted according to the Act XLVII of 1997 on the Management and Protection of Healthcare and Related Personal Data in Hungary.

**Patient data**

Predefined health care administrative data were used in a patient population with a history of major lower extremity amputation over the observational period of 2004-2012. Cases were defined as events with any lower extremity amputation above the ankle (ICPM 58470-crural, 58480- femoral). To exclude amputation events due to causes other than PAD, amputations associated with trauma or bone/skin malignancy were omitted. Aiming at presenting the total burden of major amputations, repeated amputations were also included in the analysis, but stump revisions (ICPM 58500) were excluded. Presence of comorbidity, vascular events and amputation-history were also identified by ICD-10 and ICPM codes. Primary amputation was defined as major amputation event without any lower limb revascularization (bypass surgery, endovascular) procedure done in the preceding one year. To be able to evaluate the preceding history (comorbidity and vascular events) of major amputations, the amputations in the first year of the study period were excluded, so that at least one year history is available before any major amputation. Several populations at risk for major amputations were defined, including patients affected by diabetes, older patients (age above 65 years), previous minor and major amputees, and patients with lower limb revascularization history prior to major amputation. There are different algorithms for the detection of diabetes cases from health care
administrative data, depending on the availability of information (20, 21). In our investigation, subjects were considered diabetic in case of two ambulatory care claims in a two-year period, or one hospital discharge claim using diabetes mellitus specific ICD-10 codes (E10.*-E14.*). This algorithm was complemented with the antidiabetic drug prescription refill data available for a limited period (2010-2012). Diabetes case detection was performed at the time of major amputation event and the preceding observational period. For the reference diabetic population, we used the average of diabetes prevalence data biannually reported by the Hungarian Central Statistics Office (22).

Statistical methodology

Demographic characteristics, comorbidities and vascular history of the amputees are presented as proportions. Age- and sex-specific major amputations incidences were calculated using population counts on 1st January of each year obtained from the Hungarian Central Statistics Office (23). Crude incidences were calculated yearly and for the whole period, with 95% confidence interval for the latter case.

To account both for the changing age- and sex-structure and to make valid international and inter-year comparisons possible, epidemiological standardization (24) was needed. Direct standardization was chosen using different reference populations: (i) population structure of the first investigated year, and (ii) external standard population. The first approach is more straightforward to compare different years within the same country; the second is preferable for international comparisons. As an external reference, the European Standard Population 2013 (ESP 2013) (25) was chosen. The age composition of the Hungarian population, together with these reference populations were scaled to match the Hungarian population in 2004.
Calculations were performed under R software package version 3.0.2 (R Core Team, 2014) and STATA software package version 12.0 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP) using a custom script that is available from the corresponding author on request.

**Results**

We identified 76,798 lower limb amputations performed over the observational period of nine years (2004-2012). In the analysis, we focused on the cases of major amputations (38,200 procedures). The affected population consisted of 32,084 amputees. The demographic and clinical characteristics of the population that underwent a major amputation are shown in Table 1. Major amputations as repeated events occurred in 15%, resulting in both lower extremities loss in 13.9%. The proportion of below knee amputations (leg) was 27%. The primary amputation rate was 71.5%. Age and sex showed a profound influence on major amputations incidences in every year (Figure 1).

After external direct standardization to ESP 2013, the annual sex-specific and total incidences are shown in Table 2. Annual incidences of lower limb major amputations were more than twofold higher in males compared to females.

The annual crude and age adjusted values of lower limb major amputations incidences (2004-2012) are shown in the whole population and in the sex disaggregated populations in Figure 2. While the adjusted incidences do exhibit year-to-year fluctuations, their erratic nature and the largely overlapping confidence intervals (26) indicate that there is no secular trend present.

No trend was seen in case of major amputations incidences in the elderly; after a minor or major amputation; or after a previous lower limb revascularization, therefore major
amputations incidences are shown for the whole exposure period as a single aggregated value (on person-time basis) (Table 3). The diabetes-related major amputations incidence was seven times higher compared to the general population and fifteen times higher in contrast to non-diabetic subjects. If diabetes status was only checked at the major amputation event, it resulted in a 5% decrease in diabetes related amputation incidence in contrast to diabetes case detection in the whole period preceding amputation. In elderly patients, the incidence was four times higher compared to the general population. Any antecedent lower limb procedure (minor or major amputation, revascularization) was associated with markedly increased risk for a subsequent major amputation. In these cases, the incidence was higher by two orders of magnitude (100-180 fold) compared to the general population.

**Discussion**

Our study, in the frame of HUNVASCDATA project, provided the first whole population based data of the PAD associated major lower limb amputations in Hungary.

Before drawing any inference from our data, the accuracy of the health care administrative databases, as the prevailing source of information in amputation research has to be addressed. There are more dimensions of validity of health care administrative data like completeness, correctness, concordance, plausibility, currency (27). We consider our database as acceptably complete, in a sense that it covers almost the whole population in Hungary, where the National Health Insurance Fund is the single financial source of health care service, covering all beneficiaries. Private sector can be neglected, especially on the amputation field. The health care data primarily serve as the base of covering all expenditures for medical service in Hungary. The data record, transfer and analysis are performed according to legal regulations
and as a consequence they are subject of close data quality control by cross-tabulation, regular claim supervision and local inspection. Amputation as a procedure is easily defined, we assess that the error of commission (surplus coding) is low. Error of omission (lack of coding) was not assessed, but underestimating is conceivable. Health care administrative data, using critical limb ischemia (CLI) specific diagnoses showed 75% sensitivity for CLI identification. If CLI specific procedures codes (amputation, revascularization) were added, the sensitivity was even higher (92%) (28). For amputation detection, another publication reported a sensitivity value of 94.4% (29), which is similar or superior compared to other disease conditions (28). As for the comorbid conditions, in case of application of disease classification codes (ICD) alone, the uncertainty is relevantly higher (30), therefore more complex algorithm of ICD codes for case detection, like diabetes definition was applied. This kind of approach is considered to be valid (31).

In sum we believe that the validity of the HUNVASCADATA is similar to other reports on amputation trends, but international harmonization of methods would be highly needed on this evolving field.

The internationally reported amputation incidence data show wide variability. In order to define the basis for comparison to our results, we considered the individual reports in the metaanalysis of Moxey et al. (14), who collected all publications focusing on lower limb amputation in UK and worldwide between 1989-2010. We added six more recent European reports to the national estimates of major amputations incidences (9, 10, 17, 18, 32, 33). According to these sources, the incidence data ranged from 3.6-58.7/10^5 (average 13.07/10^5 of 19 reports) in total population. Although this wide range is partly due to different calculation methods, there is no doubt in our view, that the Hungarian amputations incidence statistics (42.3/10^5, as a single aggregated value) is especially high, being more than threefold compared to the average of published incidences.
The population who underwent major amputation was somewhat younger in contrast to other European reports. The degree of the difference is similar to the difference in life expectancy (34) reflecting general health conditions.

We detected a striking difference between man and women regarding amputation incidence in any age groups. The observed male dominance in major amputation incidence is in accord with the result of a recent meta-analysis showing that the diabetes related amputation risk is 50% higher in males (35). No clear explanation is known on this matter. The role of different barrier to health care access, reluctance to seek medical consultation and more social expectation at job may account for this gender difference (35).

High incidence rate was noticeable in other predefined subgroups, such as in diabetics and in elderly patients too. The diabetes related major amputations showed fifteen fold value compared to non-diabetic subjects. The value of $318/10^5$ can be considered as high compared to other countries (14). However, we see a methodological issue in reporting diabetes related amputations. In the calculation of incidence (as a fraction), both the definition of the numerator (diabetes-related amputation) and the denominator (diabetes prevalence) show uncertainty.

In some publications (8, 11) amputation was considered to be diabetes related if at the amputation event diabetes specific codes were also used. However, underreporting diabetes at the hospital discharge with amputation may result in a decrease in diabetes related amputation incidence. In an Italian report, it reached 10% (10), in our data this effect was less influential (5%). To avoid this in our calculation, we used a complex definition for diabetes case detection fulfilled over the whole period preceding amputation.

As for the denominator, although there are several reports about the increase of diabetes prevalence, using these data without estimating their robustness and scientific merit, it can
result in a potential bias by decreasing the amputation incidence fraction. For this reason, we used an average (constant number) of the diabetes prevalence data reported in primary care in Hungary (22). The amputation literature is not uniform regarding this issue.

We could not detect any change in the trend of amputations over the observational period (2004-2012) which was shown in the whole population and the several predefined risk populations too. The constantly high incidence of major amputations is in contrast with other national reports (10, 15, 16, 17).

Searching for potential explanations, the pattern of traditional risk factors for PAD (smoking, age, sex, diabetes) and the role of vascular care are to be considered.

The Hungarian population shows aging similar to other European countries. The increase in representation of the older population (age above 65 years) was 10% between 2004 and 2012, ranging between 15.5%-17.5% (36) which is similar to European trends (37). Based on this fact, our crude amputation incidence data are also comparable to other published results from this respect. Nevertheless, the distracting effect of age and sex distribution on lower limb amputations incidence can be eliminated by direct standardization to a reference population, as was done in our study with European standard population – ESP-2013. The use of this technique is not prevalent in the amputation literature; however, the mass migration (38) and aging may profoundly influence the incidence data by changing the demographic composition of the societies. The recognition of the importance of the changing composition of European populations lead to the revision of the previous version of ESP data in 2013 (39). The geographical coverage of ESP-2013 was agreed to be the EU-27 and EFTA countries. The Eurostat’s task force determined that it was unnecessary to separate the new ESP by sex in order to avoid a more complex system that is unrequired for most foreseeable comparative uses (39). Nevertheless, in case of lower limb amputations incidence, gender is a very
influential factor. Therefore, disaggregation by sex can lead to greater accuracy and a better reflection of reality. In order to meet these two expectations and to show internationally comparable data, we provided the overall and the sex-specific standardized major amputations incidence rates (Table 2). These data are suitable for international comparison to other cohorts with the same sets of definitions.

According to OECD data (40), Hungarian smoking data are not essentially different in comparison to EU27 (daily smoking rate: 26.5% vs 23%, decline in smoking in the past ten years 12.4% vs 16.3%). Based on these data, smoking is likely not a dominant factor explaining the high value of amputation incidence data in Hungary in our view. However, according to WHO data, the prevalence of smoking is higher in men compared to woman in Hungary (35% vs 27%) that can contribute to the gender differences in amputation rate (41).

Diabetes is certainly one of the most influential factors regarding amputation incidence. In our amputee population diabetes was detectable in 50.4% which is in accord with the results other amputation reports (18). According to the OECD statistical data the Hungarian diabetes prevalence data (6.2%) are close to the European 22 average (6.4%) (42). Based on these comparisons, we assume that diabetes prevalence alone does not account for high major amputations rates in our country.

Summing up the data about the pattern of the traditional PAD risk factors in Hungary, they do not give a clear account for the high and constant major amputation rate. The high primary amputation rate (71.5%), the low below/above knee major amputation ratio (0.3), the younger age of the affected population may indicate that the vascular health care service may have explanatory power.

The most apparent indicator, the primary amputation rate seems to be exceptionally high. A US Medicare based study found that the rate was 33% for the critical limb ischemia affected
population (43). In another publication studying critical limb ischemia, the overall rate of primary amputation was 54%, ranging from 42-68% (44). However, the interpretation of the Hungarian data on primary amputation is problematic. Firstly, in-depth comparison is not possible due to lack of available published data in amputation reports. Secondly, we could not assess, in what extent the indication for primary amputation in our population had met the criteria for unreconstructable arterial diseases. A Medicare claims based report showed that the rate of any preamputation arterial testing (Doppler measurement, vascular imaging) was 68.4% (45). Although no Hungarian or European data are available for comparison, this single observation cautions against far-fetched interpretation of primary amputation rate.

All these points may lead to the assumption that major amputation incidence is closely related to the complexity of vascular care service. The question cannot be reduced to one factor, like access to vascular surgery as a high proportion of patients with vascular disease in Hungary have access to open or endovascular surgery. According to the rough estimate of the Hungarian Society of Angiology and Vascular Surgery, the vascular surgeons to capita population is 1/110.000, which is in the range (1/107.000-1/147.000) of other reports from USA, France and UK (46). The amputation rate is probably related to the failure of many steps of patients’ pathway including the late recognition of PAD, the lack of PAD-specific screening programs, delayed admission for vascular care, the existence of medically underserved regions, and the suboptimal rate of revascularization (surgical or endovascular). The potential impact of these factors should be analyzed in the future.
Conclusions

The HUNVASCDATA study is the first to present a detailed, whole-population based analysis of national lower limb major amputations trends in Hungary. High and constant incidence data were detected; that is presumably related to the capacity and organization of health care service. An improvement in screening and access for revascularization is highly needed. Comparing this data against other national amputations incidence data is problematic because of different reporting methods. Using the European Standard Population-2013 as a tool for external standardization of incidence data is recommended in order to ensure international comparability. Analysis of the whole population health care administrative data increases the breadth into PAD epidemiology; however, the accuracy of algorithms and classifications entails uncertainty and validation studies are needed.

What does this study add to the existing literature and how will it influence future clinical practice?

The study is the first nationwide report on PAD associated lower limb major amputation trends from Hungary showing alarming high level of amputations and no relevant change over a nine year period (2004-2012). It provides amputation incidence data with external standardization to European Standard Population (2013) to ensure international comparability. The different age and sex composition of the countries can be controlled this way that is inevitable in order to avoid a demographics related bias in comparisons. This method was not widely used in amputation literature so far. The high and constant level of our amputation incidence data, based on an international comparison of cardiovascular risk profile, is
presumably related to the shortage of vascular service. The characteristics of this relation are to be clarified in future analysis.

References


5. Patricia Cerrito: Data mining healthcare and clinical databases, Data services online, 2010


22. Hungarian Central Statistics Office, Main diseases tables, Diabetes prevalence by primary care reports (1999-2011)


41. Tobacco control country profiles (WHO)  


Tables

**Table 1:** Demographics and clinical characteristics of major amputees.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>number of major amputations</td>
<td>38,200</td>
</tr>
<tr>
<td>number of subjects</td>
<td>32,084</td>
</tr>
<tr>
<td>male/female (%)</td>
<td>65/35</td>
</tr>
<tr>
<td>age (Mean year±SD)</td>
<td>63.9±11.5</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>50.4</td>
</tr>
<tr>
<td>Renal replacement therapy (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3</td>
</tr>
<tr>
<td>Carotid revascularization in history (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.5</td>
</tr>
<tr>
<td>Stroke in history (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>11.7</td>
</tr>
<tr>
<td>Coronary revascularization in history (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.7</td>
</tr>
<tr>
<td>Myocardial infarction in history (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.5</td>
</tr>
<tr>
<td>Previous lower limb revascularization (%)&lt;sup&gt;a, b&lt;/sup&gt;</td>
<td>36.5</td>
</tr>
<tr>
<td>Primary amputation (%)&lt;sup&gt;a, c&lt;/sup&gt;</td>
<td>71.5</td>
</tr>
<tr>
<td>Minor amputation in history (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>29</td>
</tr>
</tbody>
</table>

<sup>a</sup> in order to ensure at least one year previous history for analysis, major amputations performed in 2004 were excluded from calculation (number of remaining cases is 33,989)

<sup>b</sup> detected in any time in the whole observational period prior to major amputation

<sup>c</sup> defined as major amputation without any detected lower limb revascularization procedure in the preceding one year prior to major amputation
**Table 2:** Lower limb major amputations incidences (rates per $10^5$ persons) after direct standardization to ESP 2013.

<table>
<thead>
<tr>
<th>Year</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>107,3</td>
<td>47,8</td>
<td>69,3</td>
</tr>
<tr>
<td>2005</td>
<td>93,6</td>
<td>46,2</td>
<td>64,1</td>
</tr>
<tr>
<td>2006</td>
<td>112,3</td>
<td>43,9</td>
<td>68,2</td>
</tr>
<tr>
<td>2007</td>
<td>101,6</td>
<td>41,1</td>
<td>63,2</td>
</tr>
<tr>
<td>2008</td>
<td>104,3</td>
<td>42,2</td>
<td>64,8</td>
</tr>
<tr>
<td>2009</td>
<td>101,8</td>
<td>41,2</td>
<td>63,6</td>
</tr>
<tr>
<td>2010</td>
<td>112,4</td>
<td>45,3</td>
<td>69,8</td>
</tr>
<tr>
<td>2011</td>
<td>103,1</td>
<td>41,9</td>
<td>64,5</td>
</tr>
<tr>
<td>2012</td>
<td>106,1</td>
<td>41,3</td>
<td>64,7</td>
</tr>
</tbody>
</table>
Table 3: Crude lower limb major amputations incidences (rates per $10^5$ persons) in different patients groups, calculated for the whole observational period.

<table>
<thead>
<tr>
<th>Group</th>
<th>Exposure [person-years]</th>
<th>Events</th>
<th>Incidence (crude), with 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population</td>
<td>90274308</td>
<td>38200</td>
<td>42.29 [41.87 - 42.7]</td>
</tr>
<tr>
<td>&gt; 65 yr</td>
<td>13727535</td>
<td>22218</td>
<td>161.85 [159.73 - 163.99]</td>
</tr>
<tr>
<td>Diabetic</td>
<td>6559808</td>
<td>20855</td>
<td>317.92 [313.63 - 322.27]</td>
</tr>
<tr>
<td>No Diabetic</td>
<td>83714500</td>
<td>17345</td>
<td>20.72 [20.41 - 21.03]</td>
</tr>
<tr>
<td>Prior major amputation</td>
<td>144114,19</td>
<td>5773</td>
<td>4005.9 [3905.5 - 4108.7]</td>
</tr>
<tr>
<td>Prior minor amputation</td>
<td>125846,46</td>
<td>9859</td>
<td>7843.4 [7686.6 - 7984.3]</td>
</tr>
<tr>
<td>Prior lower limb revascularization</td>
<td>241945,07</td>
<td>9673</td>
<td>3998 [3920.4 - 4077.0]</td>
</tr>
</tbody>
</table>
**Figures**

**Figure 1:** Age- and sex-specific incidences of major lower limb amputations in Hungary (2004-2012). Thin blue lines show the incidences individually for each investigated year (2004-2012). Thick red line is the overall incidence calculated from the whole 2004e2012 period. Pink shading depicts the 95% confidence interval for these latter age- and sex-specific incidence curves.
Figure 2: Crude and age-adjusted incidences of lower limb major amputations by year, 2004-2012.