COMMENTARY

Upstream Comprehensive Management of Individuals with Diabetes with Multimorbidity and Frailty to Act Against Amputation

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Introduction

Vuorlaakso *et al.*.[1] evaluated the 5-year overall survival (OS) and major lower extremity amputation (LEA) free survival in a retrospective cohort. This cohort of 1081 individuals that had LEAs performed at a university hospital serving a population of 0.5 million in Finland over nearly 14 years. The authors found that peripheral arterial disease (PAD), nephropathy and major LEA decreased OS, whereas minor LEA, reamputation, hypertension and dyslipidaemia increased it. In addition to PAD and nephropathy, older age was a significant factor for major LEA-free survival.[1] We agree with the authors that this study makes a valuable contribution to the clinical and scientific communities. They have delineated the limitation of their data and have made a fair discussion with previous body of knowledge. Nevertheless, we wish to contribute to the reflection of their results to reiterate the importance of comprehensive upstream management of individuals with diabetes-related foot complications (DRFC). In addition, we wanted to raise the potential effect modification between the interconnected concepts of frailty and multimorbidity on mortality that are difficult to capture in survival studies using administrative databases.

Timely and Comprehensive Team Approach, Upstream

It is well known that an integrated interdisciplinary approach is essential in patients with advanced DRFC and makes it easier to achieve therapeutic targets and more favourable outcomes.[2,3] Indeed, these teams, particularly in the context of integrated limb preservation programs, have demonstrated the benefits of timely and comprehensive management including prevention.[4,5] This is compatible with the findings of Vuorlaakso *et al*.[1] although their lack of specific data on patient management, including medication. We can do upstream cardio-renal-metabolic prevention by using innovative antidiabetic drugs that have shown proven cardio-renal benefit in individuals with type 2 diabetes in recent years, such as sodium

glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide 1 receptor agonists (GLP1 RAs).[6]

Although the use of these molecules has been controversial regarding LEAs – higher LEA rate in the presence of PAD reported with GLP-1-RAs and increased LEA risk with SGLT2i especially with long-term use – recent data have demonstrated reduced risk with GLP-1-RAs and only a hypothetical risk. [7,8] Their protective effects therefore tip the risk-benefit ratio in their favour, especially considering the poor OS with chronic kidney disease (CKD) in this population.[9] Their actions on obesity, hypertension, dyslipidaemia, etc. are consistent with optimal risk factors management and improved survival.[9] Hyperglycemia, hypertension, and dyslipidaemia are metabolic parameters that best meets therapeutic targets in settings with no specialized team approach to foot ulcers during hospitalization.[10] Therefore, we enrich, beyond the diagnosis, that the quality of team care has also beneficial effects.

Although survival data are disconcerting, particularly in the presence of PAD and CKD and end-stage renal disease (ESRD), amputations are an essential upstream treatment for limb- and life-threatening conditions. Re-amputations are high in this population, but subsequent amputations could be confounded by the progression of other underlying health conditions and thereby contribute to an overestimation of the re-amputation rate.[11] These distinctions are difficult with clinical-administrative data as there is a clinical challenge to select the most distal optimal level after the index amputation and therefore some LEA may not be appropriately captured.[11] This is an hypothesis related to the association between OS and re-amputation. In addition, the trend of increased minor LEAs with time may explain by the team-based approach and its continuous improvement over the years.[1] Previous studies have demonstrated similar trends.[4,12]

Effect of Frailty and Multimorbidity in People With Diabetes

Although the authors[1] used multivariate model, it is still unclear how to integrate multimorbidity and its interactions – additive, synergistic, or otherwise – with the concept of frailty. Multimorbidity is defined as the co-occurrence of ≥ 2 chronic conditions such as diabetes, hypertension, depression, anxiety, cancer, etc.[13] In this population, multimorbidity is the norm, occurring in approximately 85% of individuals.[13] Frailty is a syndrome defined as an increase vulnerability in older adults due to lack of physiologic reserve following a stressful situation such as LEA, and by chronic diseases.[14] Frailty is a multidimensional syndrome that takes into account physical, psychological, and social dimensions to health. The presence of frailty is associated with the severity of the diabetic foot disease and poorer outcomes including LEA and mortality.[14] Moreover, systematic reviews have demonstrated that PAD is associated with frailty and this is even increased in the population with CKD and ESRD.[15,16] We don't know the exact amount of multimorbidity in the population studied by Vuorlaakso *et al*[1] given the absence of some data such as depression which is particularly high in this population.[17] However, this is undoubtedly a population with frail individuals.

Because diabetes increases the risk of multimorbidity and frailty, the latter two factors are associated with an increased risk of adverse outcomes in older individuals with diabetes and this exacerbating the effect of age on survival.[18] This may suggest that both have an additive effect on diabetes-related outcomes.[19] Frailty was even found to be associated with an increased risk of mortality at each level of multimorbidity, and frail individuals with multimorbidity had a higher risk of mortality than those with frailty or multimorbidity alone.[19] However, the relationship between frailty and major LEAs remains unclear.[20] Even if the differential contribution of frailty and multimorbidity to DRFC is still not defined, frailty may be an unmeasured confounder for outcomes associated with multimorbidity in this type of study.[19]

Thus, other risk factors (e.g., PAD, sex, and CKD) may influence the clinical course of DRFC, treatment efficacy and ultimately impacting survival. This could explain the heterogeneity of evidence on this topic. As an example, frailty is generally greater in females,[21] whereas males are generally at greater risk for LEAs.[22] Recall that *Vuorlaakso et al.*[1] found an inverse influence of sex on survival, which was cancelled with the multivariable model. Other factors can also influence the clinical course of DRFC and therefore impacting survival, such as the concomitant presence of oxidative stress, inflammation as well as atherosclerotic and vascular complications.[23,24]

Finally, the interaction between CKD, aging, and frailty has been termed “senescent nephropathy” a condition characterized by a synergistic decline of functions.[25] Can we therefore hypothesize a condition termed "senescent diabetic foot disease" that includes a relationship between frailty (especially advanced age), CKD and other multimorbidities such as PAD? This condition could be illustrated by the synergy of the additive effects of the DRFC triads leading to reduced OS (Figure 1).

Conclusion

In conclusion, studies evaluating the team and holistic approach to this population considering all cofounders of complex interventions for DRFC are real research challenges. Unfortunately, such studies are difficult to conduct and costly. Large, prospective cohorts with high internal/external validity and a focus on the quintuple aim of health care quality (i.e., patient and provider experiences, health outcomes, equity, and sustainability) are essential for limb preservation. Meanwhile, upstream prevention is better than cure.

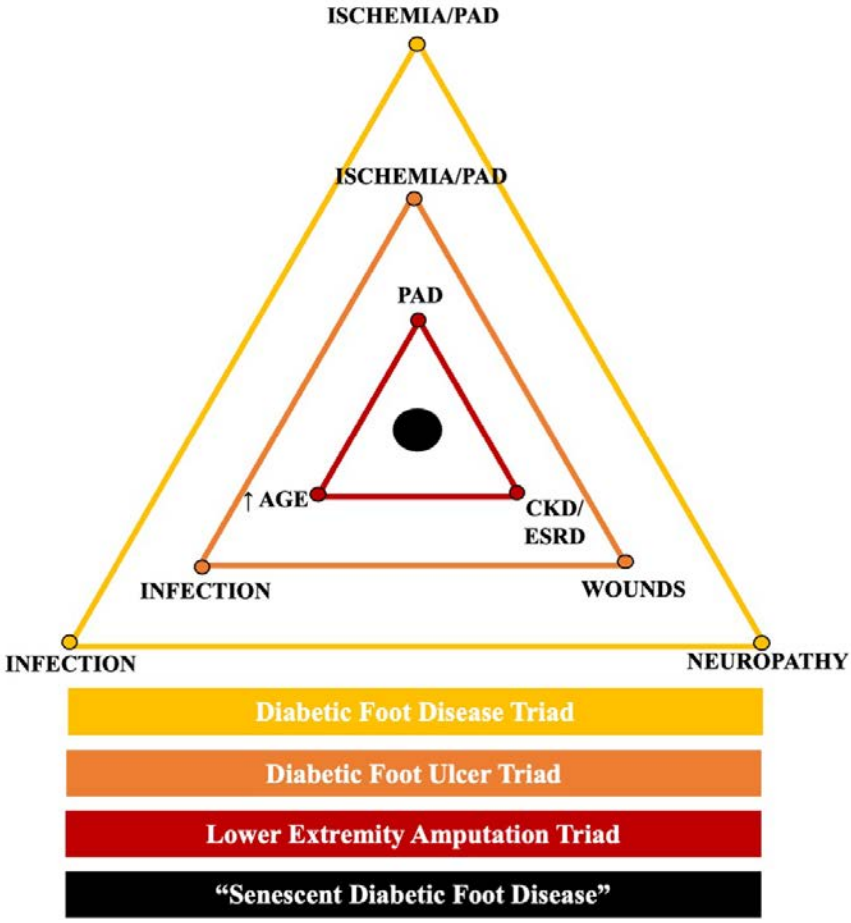

FIGURE LEGEND

Figure 1. Potential schematization of "senescent diabetic foot disease" the fruit of interaction of the recognized triads of diabetes-related foot complications (PAD: Peripheral Arterial Disease; CKD/ESRD: Chronic Kidney Disease/End-Stage Renal Disease)

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