Combining Elemental Analysis of Toenails and Machine Learning Techniques as a Non-invasive Diagnostic Tool for the Robust Classification of Type 2 Diabetes

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Statement of Purpose

The purpose of this study is to describe the use of elemental analysis of diabetic toenails and machine learning techniques for robust classification of Type 2 Diabetes. To the authors' knowledge, this is the first time the outlined method has been described and may be used for future, non-invasive diagnosis, monitoring, and treatment of Type 2 Diabetes.

Level of Evidence: Level II

Literature Review

Diabetes is a worldwide epidemic and has become a burden with great economic impact. In 2012, Type 2 Diabetes was reported as the 8th leading cause of death with 1.5 million deaths.[1] In 2015, 415 million people were estimated to have diabetes with 5 millions deaths reported and the epidemic is on the rise.[2] Diabetes is currently diagnosed with labs that include invasive blood draws, which measure glucose or glycated hemoglobin A1c.[1] Non-invasive glucose monitoring technology has now become a field of research.[3] Saliva, sweat, and urine have all been studied for glucose monitoring.[4] In previous studies, samples of hair, saliva, and blood have shown differences in concentrations of copper (Cu), magnesium (Mg), manganese (Mn), iron (Fe), vanadium (V), selenium (Se), chromium (Cr), and zinc (Zn) between Type 2 Diabetic patients and healthy individuals.[5] Studies have also shown that fingernails and toenails have differing concentrations of certain elements such as aluminum (Al), Cu, Fe, Mn, and Zn among healthy individuals and those with systemic diseases.[6] These elements previously studied were among the elements chosen to analyze for this study.

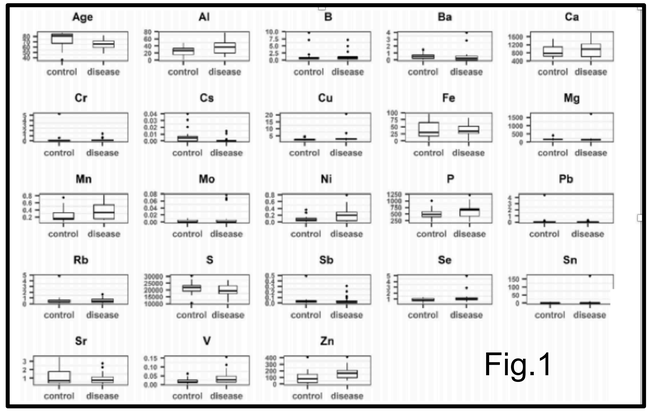

Fig.1

Literature Review (cont.)

In order to make sense of the role these elements play in the pathogenesis of diabetes, advanced computational techniques are needed, such as machine learning. Machine learning is a statistical process that allows for insight into complex problems by applying statistical models to large amounts of data. [7] By applying machine learning techniques to the vast data found in the Type 2 Diabetic toenails, novel methods for diagnoses of the disease can be achieved.

Methods

Toenail samples from 40 patients were collected: 21 diabetic patients and 19 healthy volunteers. Samples were digested with nitric acid (HNO_3) and peroxide (H_2O_2). Microwave-induced plasma omission spectroscopy (MIP OES) and inductively coupled plasma mass spectroscopy (ICP-MS) were used to determine the elemental concentrations in the digested toenails. Seven machine learning algorithms were then employed in order to analyze the concentration of elements, age, smoking history, and gender in order to determine the presence or absence of Type 2 Diabetes

Methods (cont.)

Elements that were measured include Al, cesium (Cs), nickel (Ni), V, Zn, boron (B),barium (Ba), calcium (Ca), Cr, Cu, Fe, Mg, Mn, molybdenum (Mo), phosphorus (P), lead (Pb), rubidium (Rb), sulfur (S), antimony (Sb), Se, tin (Sn), and strontium (Sr). Various models were run in order to determine which factors could be used to determine Type 2 Diabetes reliably.

Results

Forty-six distinct machine learning models were compared and a random forest model was found to correctly predict 7 out of 9 test samples including control and disease (Type 2 Diabetes). Al, Ca, Ni, V and Zn concentrations in toenails were found to be significantly different between healthy volunteers and Type 2 Diabetics (**Fig 1**). Age, Al, Cs, Ni, V and Zn showed a variance that was statistically significant ($p \leq 0.05$) between control and diseased nails and were shown to have the highest feature importance among all factors analyzed (**Fig.2**)

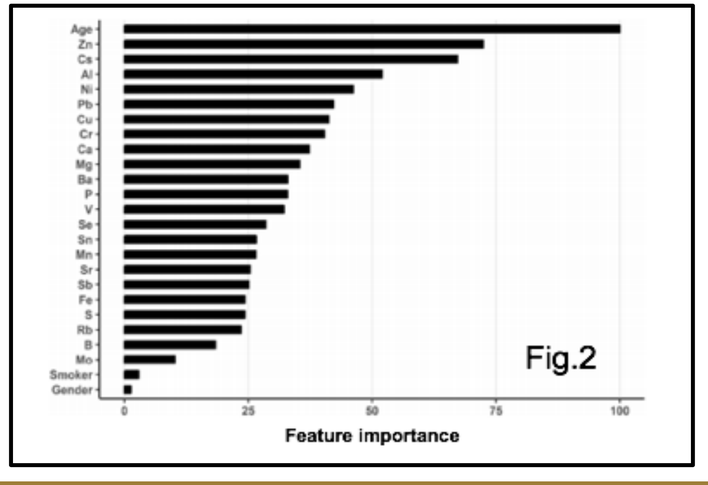

Fig.2

Results (cont.)

Al, Ni, V and Zn were higher, whereas Cs and age were lower in toenail samples from the patient sample.

Analysis and Discussion

The results at this stage of research prove the concept of combining elemental analysis of toenails and machine learning techniques for noninvasive diagnosis Type 2 Diabetes. These results suggest elements in toenails undergo similar biological processes to those in urine of Type 2 Diabetic patients. With proper sample collection and shipping, mobility-limited patients may be able to mail toenail samples for analysis and monitor their Type 2 Diabetes over time. Future work is geared toward also determining severity of Type 2 Diabetes based on elemental concentrations in patient toenails.

References

1 World Heath Organization. (2016) Global Report on Diabetes Geneva, Switzerland.
2 Orgurtsova K, da Rocha Fernandes, J.D., Huang Y. Linnenkamp, U. Guariguata, L. Cho, N. H et al. (2017), IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 20140. Diabetes Research and Clinical Practice, 128, 40-50.
3 Malik S., Khadgawat R., Anand S., & Gupta S., (2016) Non-invasive detection of fasting blood glucose level via electrochemical measurement of saliva. Springer-Plus, 5(1), 701
4 Makaram P., Owens D., & Acaroe J., (2014). Trends in Nanomaterial-Based Non-Invasive Diabetes Sensing Technologies. Diagnostics, 4(2), 27-46.
5 Kazi, T. G., Afridi, H. I., Kazi, N., Jamali, M. K., Arain, M. B., Jalbani, N., et al. (2008). Copper, Chromium, Manganese, Iron, Nickel, and Zinc Levels in Biological Samples of Diabetes Mellitus Patients. Biol Trace Elem Res, 122(1), 1–18
6 Ahmed, S. S., & Santosh, W. (2010). Metallomic profiling and linkage map analysis of early Parkinson's disease: a new insight to aluminum marker for the possible diagnosis. PLoS ONE, 5(6), e11252