

Interrelationships Between Antioxidant Status and Some Clinical Chemistry Parameters, and an Indicator of Oxidative Damage: A Neural Network Analysis

D. Smart¹, C. McCusker¹, J.V. Lamont¹,
S.P. FitzGerald¹, A. Lapin² and C. Temml³

1. Randox Laboratories Ltd., Diamond Road, Crumlin, Co. Antrim, UK, BT29 4QY
2. Allgemeine Poliklinik der Stadt Wien, A-1090, Vienna, Austria.
3. Municipal Department of Preventative Care (MA15), A-1010, Vienna, Austria.

Introduction

Oxidative damage has been implicated in the aetiology or pathogenesis of over one hundred different diseases, including different types of cancer, heart and vascular disease, diabetes and neurodegenerative disorders⁽¹⁾. Measurement of the function of the antioxidant system may indicate an individual's susceptibility to oxidant-induced disease, the degree of oxidant damage occurring at that time, or the success of any antioxidant treatment being given to a patient. The antioxidant system is composed of a number of components including enzymes, proteins and small molecules. Recent evidence suggests that these act in concert to form an integrated antioxidant system⁽²⁾. It may, therefore, be more worthwhile to measure the overall function of an individual's antioxidant system. Randox Laboratories Ltd. have recently introduced a kit for measurement of Total Antioxidant Status (TAS) and, when this was tested with sera from a number of normal subjects, the results were found to correlate with several known antioxidant components⁽³⁾. Although statistically significant, the correlations obtained were relatively small and it was felt that this might have been due to complex, non-linear interaction between various components. It was, therefore, decided to use neural network analysis (NNA), a non-linear pattern recognition technique previously used to analyse various types of clinical data, to try to discern trends in the data.

Methods

Data were taken from a study of a group of subjects from the Viennese working population⁽³⁾. Only complete data vectors (i.e. those for which all values were available) were used. This resulted in 148 sets of data. Neural network analysis of the data was performed using Brainmaker™ 3.1 software (California Scientific Software) running under Windows™. The software automatically generated a testing file by extracting 10% of the data at random and training the networks with the remaining 90%. Thus, the networks were tested on data not used for training so as to more accurately assess how the network had learnt patterns in the data rather than specific data vectors. Where testing revealed poor network performance, the number of hidden neurones was altered, the connections randomised and the network re-trained. The possible effects of different analytes on TAS were then investigated by systematically varying individual analytes over the range encountered in the study, with other analytes held at their mean values, and using the network to predict the corresponding change in TAS.

Results

Networks correlating the levels of malondialdehyde (MDA), an indicator of oxidative damage, and of TAS with the levels of a number of other analytes were produced. "Internal" error in both networks (i.e. the difference between predicted MDA, or TAS, and the actual value, when all analytes were set to their mean levels) was <5%. Thus, a change in the predicted value of either TAS or MDA >10% was taken as significant.

The MDA network predicted that MDA would vary significantly with age (Figure 1); therefore, analyses using the MDA network were performed with age set to either 30 or 55. No effect of age was predicted for TAS, therefore analyses with the TAS network were performed with age set to 38 (the mean age of the sample). Four distinct types of variation were seen in the predicted values for either TAS or MDA when other analytes were varied. These were linear (eg. TAS vs albumin, Figure 2), sigmoidal (eg. TAS vs uric acid, Figure 3), threshold (eg. MDA vs HDL-cholesterol, Figure 4) and optimum (eg. TAS vs bilirubin, Figure 5). Variation of SOD, GPx, Hb, and TG did not produce significant alterations in predicted TAS or MDA. The results for analytes which caused a significant variation in predicted TAS or MDA are summarised in Tables 1 and 2 respectively.

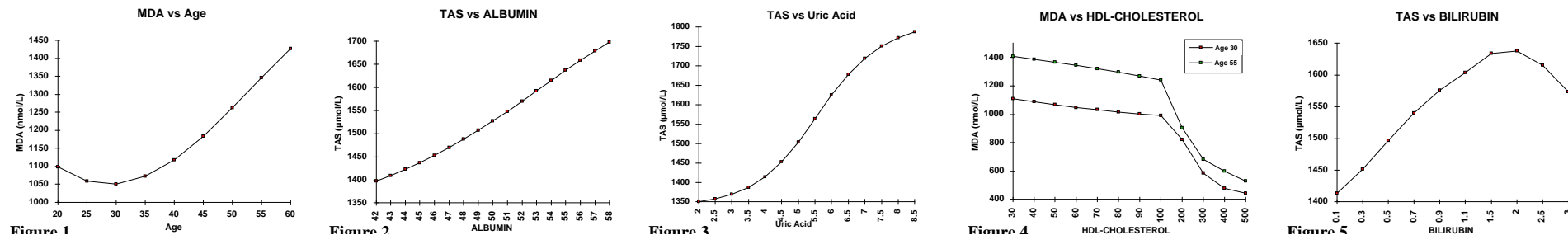


Table 1. Summary of Results for TAS NNA

Analyte	Effect on Predicted TAS of Increasing Analyte Concentration	Type of Variation
MDA	Increase	Sigmoid
ALP	Increase	Linear
Glucose	Increase	Sigmoid
Cholesterol	Increase	Sigmoid
HDL-Cholesterol	Increase	Threshold (above 300 md/dl)
LDL-Cholesterol	Decrease	Linear
Bilirubin	Increase-Decrease	Optimum
Albumin	Increase	Linear
Transferrin	Decrease	Sigmoid
Uric Acid	Increase	Sigmoid
AST	Decrease	Linear
ALT	Decrease	Linear
-GT	Decrease	Sigmoid

Table 2. Summary of MDA NNA

Analyte	Effect on Predicted MDA of Increasing Analyte Concentration at Age 30	Effect on Predicted MDA of Increasing Analyte Concentration at Age 55	Type of Variation
TAS	NS	Decrease	Sigmoid
Glutathione Reductase	Decrease	Increase	Sigmoid
Creatine	Increase	NS	Linear
AST	NS	Decrease	Sigmoid
ALT	Increase	Increase	Linear
-GT	Decrease	Decrease	Sigmoid
HDL-Cholesterol	Decrease	Decrease	Threshold 100 mg/dl
Bilirubin	Increase	Increase	Sigmoid
Albumin	Increase	NS	Linear
Iron	NS	Increase	Sigmoid
Transferrin	Decrease	Decrease	Sigmoid
Uric Acid	NS	Increase	Linear
ALP	Increase	NS	Sigmoid
Glucose	Increase	Increase	Linear

NS - No significant change

Conclusions

1. Modelling of the data obtained from a study of over 100 individuals produced networks which appeared to predict either TAS or MDA with a reasonable degree of accuracy, when various analyte values were used as inputs to the network.
2. Use of these networks for simple analysis of the effects of varying one analyte on either predicted TAS or MDA suggested that a number of different factors can affect both these values.
3. The predictions of the TAS model confirm some of the results of regression analysis of the data⁽³⁾ i.e. there is a relationship between uric acid, albumin, bilirubin, ALP, glucose, and -GT and TAS.
4. However, some of the predictions of the model do not confirm results of regression analysis: glutathione reductase, creatinine and iron all correlated with TAS⁽³⁾, but were not predicted to have an effect on TAS by the model. This suggests that the model may not be a complete description of the various factors affecting the TAS value in serum and that further refinement of the networks are needed.
5. The results of this study indicate that Total Antioxidant Status, and the levels of an indicator of oxidative damage (MDA) are influenced by a number of factors, and that, individually, these factors act in different ways to vary either TAS or MDA levels. This is shown by the different ways in which TAS or MDA varies (linear, sigmoid etc.) as different analytes are varied. The networks produced to model these interactions are currently being used to examine multiple interactions between the various factors influencing TAS and MDA.
6. The complex way in which different factors interact to modulate either the antioxidant system, (TAS) or the rate of oxidant-induced damage, (MDA) indicated by the two data models, suggests that use of a "broad spectrum" assay, like TAS, may be a more appropriate means of assessing antioxidant system function than measurement of individual antioxidant components.

References

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