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Metal ion dyshomeostasis and coagulatory defects in diabetes

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Diabetes is a term used to describe a group of conditions that impact upon the body's ability to control blood glucose levels. In type-I diabetes (T1DM), the β-cells in the pancreas responsible for producing insulin are lost, typically from an attack from the immune system, causing insulin deficiency. In type-II diabetes (T2DM), cells become resistant to insulin signalling. Both T1DM and T2DM have wide-ranging consequences for the body as glucose levels are associated with many physiological processes. Individuals with diabetes have an increased risk of cardiovascular disease and coagulatory defects are observed in individuals with both T1DM or T2DM. Our work has revealed that metal ion homeostasis is differentially affected in T1DM and T2DM. For example, HbA1c, a marker for elevated blood glucose, correlates with plasma concentrations of magnesium (negatively) in T1DM and copper (positively) in T2DM. Notably, using a validated turbidimetric assay, the decrease in plasma Mg^{2+} in T1DM was found to be associated with abnormal thrombin-stimulated fibrin clotting or with fibrinolysis. In addition, we found that T2DM is associated with defective plasma Zn^{2+} handling, caused by increased non-esterified fatty acid binding to human serum albumin (HSA) – an interaction which allosterically regulates the ability of the protein to bind Zn^{2+}. Using ITC we reveal that 1-5 mol. eq. of myristate, palmitate, stearate, palmitoleate and palmitelaidate reduce Zn^{2+} binding to HSA. Addition of myristate and Zn^{2+} increase thrombin-induced platelet aggregation in platelet-rich plasma and increase fibrin clot density and clot time in a purified protein system. The concentrations of key saturated and monounsaturated NEFAs positively correlated with clot density in subjects with T2DM (and controls). Collectively, this work increases our understanding of the roles metal ions play in T1DM and T2DM pathogenesis and will have future implications for the management of diabetes.

Biography

Dr Alan J. Stewart is a Reader in Molecular Medicine at the University of St Andrews. His research is focused on metal ion handling in the body and the roles they play in regulating medically/physiologically relevant processes. Collectively, his work provides detailed and reliable data relating to the transport and speciation of metal ions (particularly Zn^{2+}) in the circulation and new insights into their cellular functions and role in disease states. He has published >80 peer-reviewed publications, many in world class and field-leading journals. He sits on the Editorial Boards of the journals, Scientific Reports, Frontiers in Endocrinology, Nutrients and BioMetals.

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