pro-inflammatory cytokines is suppressed and synthesis and release of anti-inflammatory cytokines is enhanced, and failure to do so would give negative results. Since, there could be individual variations in response to the anti-inflammatory actions of insulin in response to GIK regimen this has to be given due weightage. I suggest that the CREATE-ECLA trial results would have been positive, provided the investigators infused adequate amounts of insulin to keep plasma glucose levels \(\leq 110\, \text{mg/dL}\). This is supported by the observation that intensive insulin treatment improved survival of the critically ill surgical patients and those without diabetes mellitus who had blood glucose concentrations \(\sim 110-144\, \text{mg/dL}\) (6.1–8.0 mmol/L) had a 3.9-fold higher risk of death than patients without diabetes who had lower glucose concentrations.\(^7\)

Pyruvate, the intermediate product of glucose metabolism, protects myocardium, intestines, hepatic, and renal tissues from reactive oxygen species and cytokines, and ischemia/reperfusion-induced injury. Pyruvate-inhibited TNF-\(\alpha\) production, reduced circulating HMGB1 (high-mobility group B1) levels and NF-\(\kappa\)B signalling pathways, decreased COX-2 (cyclo-oxygenase-2), iNOS (inducible nitric oxide synthase), and IL-6 (interleukin-6) mRNA expression in animal models with shock, and quenched free radicals.\(^7\) Hence, I suggest that plasma levels of TNF-\(\alpha\), MIF, HMGB1, IL-6, IL-4, IL-10, pyruvate, and various free radicals need to be measured in addition to plasma glucose concentrations to ensure that GIK regimen adopted is adequate to ensure its beneficial actions. In the absence of such a comprehensive assessment, it is not prudent to discard GIK regimen in the treatment of AMI as being not beneficial.

References


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Glucose, insulin, and acute myocardial infarction: reply

Dr Das comments that the association between the failure of glucose levels to drop during hospitalization and higher mortality following acute myocardial infarction (AMI) in the CARDINAL study\(^3\) is consistent with basic and translational work demonstrating the pro-inflammatory effects of glucose. In addition to its pro-inflammatory effects, glucose may also directly contribute to the pathogenesis of AMI by promoting thrombosis\(^2\) and impairing vasoreactivity.\(^5\)

We and others\(^6,5\) concur that the maximal benefit of insulin therapy in AMI may be realized only when normalization of glucose levels has been achieved and maintained. This hypothesis is also supported by a meta-analysis of previous trials of insulin therapy in critically ill patients that demonstrated a benefit among trials in which insulin was dosed to achieve a glucose target, but not among trials in which a glucose target was not specified.\(^6\) Although it would be interesting to measure inflammatory markers during insulin infusion in AMI, it is currently impractical to dose insulin based on these markers, as they are markedly elevated in the setting of AMI, few assays are available at the point of care, and the dose of insulin would be necessarily limited by the occurrence of hypoglycaemia. It is our understanding that investigators are already planning a large, simple trial of intensive insulin therapy targeting normoglycaemia in AMI to determine whether this strategy improves clinical outcomes.

References


