count the potential for Mg^{2+} deficiency now known to be common in Type II diabetes). Further, this could explain the likewise variable results of studies evaluating the effects of Mg^{2+} treatment in myocardial infarction, which could have provided a beneficial effect only to those with Mg^{2+} deficiency.

Yours faithfully,
R. Matz

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Possible beneficial action(s) of glucose-insulin-potassium regimen in acute myocardial infarction and inflammatory conditions: a hypothesis

Dear Sir,
Diabetic ketoacidosis (DKA) is a common acute metabolic complication of diabetes mellitus which is managed by using insulin, intravenous fluids and potassium. Because the plasma glucose concentration invariably falls more rapidly than that of plasma ketone, insulin is given continuously and glucose and potassium are also infused at the same time to prevent the occurrence of hypoglycaemia and hypokalaemia. This forms the glucose-insulin-potassium (GIK) regimen, which can also be used to manage patients with a moderate degree of hyperglycaemia, even in the absence of ketoacidosis.

Recently, The American College of Cardiology (ACC) and the American Heart Association (AHA) have recommended [1] the option of giving intravenous glucose, insulin and potassium (GIK) to patients with acute myocardial infarction (AMI), especially for those who are poor candidates for thrombolytic therapy and in whom the risk of bleeding is high. This recommendation is based on the results of a study done in South America which found that the GIK regimen was remarkably beneficial for treating AMI [1]. It has been suggested that GIK treatment helps save the integrity and function of cells once glucose and potassium are transported in by insulin. The exact mechanism(s) of its beneficial action is, however, not known. I suggest it acts through the suppression of tumour necrosis factor-α (TNF-α) and the production of macrophage migration inhibitory factor (MMIF).

Tumour necrosis factor-α is released early in the course of AMI, and it can decrease myocardial contractility in a dose-dependent fashion. Myocardial injury and dysfunction induced by TNF-α can be reduced by treatment with specific monoclonal antibodies against TNF-α [2]. Providing adequate amounts of glucose and insulin has been shown to antagonize the harmful actions of TNF-α [3]. Studies have shown that treatment with insulin can, almost completely, reverse the nutritional and histopathological toxicity of sublethal doses of TNF in rats [3]. This suggests that the GIK regimen is able to bring about its beneficial action in AMI by antagonizing the harmful effects of TNF. This could explain why n-3 fatty acids are useful in AMI because they also inhibit the production of interleukin-1 and TNF-α [4]. Insulin and n-3 fatty acids might both regulate superoxide generation and TNF-α release [4, 5] which could be another potential mechanism of their beneficial action in AMI.

If it is true that insulin and GIK regimen can suppress TNF-α and superoxide anion release and actions, this suggests that the GIK regimen would be useful in the management of several inflammatory conditions such as ulcerative colitis, Crohn's disease, rheumatoid arthritis, systemic lupus erythematosus and cancer, conditions in which excess production of TNF-α seem to play an important part [4]. Because the majority of patients with ulcerative colitis and Crohn's disease need fluids in the management of their condition, it might be worth a try. The observation that in female NMRI mice, weight loss induced by TNF-α can be reversed by treatment with glucose and water [6] supports the suggestion that the GIK regimen could be beneficial in the treatment of inflammatory bowel diseases. The macrophage migration inhibitory factor, secreted by antigen-sensitized lymphocytes, macrophages, pituitary gland, brain, kidney, lung, prostate and testis, is believed to play an important part in several inflammatory conditions and in septicaemia and septic shock [7]. It is known that TNF-α up-regulates MMIF secretion [8]. Expression of MMIF has been shown to be increased in experimental animals exposed to gram-negative and gram-positive bacterial toxins and neutralization of MMIF or deletion of the MMIF gene to protect mice from lethal endotoxaemia or staphylococcal toxic shock [7]. Further high concentrations of MMIF were found in the peritoneal exudates fluid and in the systemic circulation of mice with bacterial peritonitis and anti-MMIF antibody shown to protect mice from lethal peritonitis, an animal model of human form of sepsis and septic shock [7]. The improved survival secured with anti-MMIF antibody was associated with a reduction in the plasma concentrations of TNF [7]. Even MMIF-knockout mice showed reduced circulation concentrations of TNF-α, suggesting that MMIF augments the synthesis and release of TNF-α and when this stimulus is removed the plasma

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levels of TNF-α would fall [7]. It has also been shown that high concentrations of MMIF are present in the plasma of patients with septicemia and septic shock indicating that this molecule may have a role even in humans [7]. Further, the expression of MMIF in adipocytes can be modulated by insulin and glucose [8]. It has also been found that MMIF is secreted together with insulin from beta cells and to act as an autocrine factor to stimulate insulin release [8]. Based on these studies, I suggest that during stress or the systemic inflammatory process, MMIF is secreted from the pituitary gland accompanied by an increase in glucocorticoid secretion (and macrophages will also produce MMIF and TNF). The increase in plasma glucose concentration that occurs as a result of this glucorticoid production is, probably, controlled by MMIF which has a positive effect on insulin secretion. Thus, glucose homeostasis during stress and inflammation is maintained by glucocorticoids, MMIF and insulin (and TNF by inducing insulin resistance). I suggest that as there is a feedback control between MMIF, glucose and insulin [8], infusion of glucose and insulin can inhibit MMIF production and release, similar to their action on TNF as described above. If this is so, it suggests the GIK regimen can also be used in the management of septicaemia and septic shock in which excess production of TNF-α and MMIF seem to play an important part. It is important to measure plasma TNF and MMIF concentrations both before and after the GIK regimen in patients with septicaemia and septic shock, ulcerative colitis, Crohn's disease, rheumatoid arthritis, systemic lupus erythematosus and cancer, and see whether there is any correlation between the progress of these clinical conditions and the concentrations of TNF and MMIF. Both the frequency and duration of a GIK regimen in the treatment of these inflammatory conditions and cancer needs to be formulated. Thus, it is suggested that GIK regimen might be useful not only in the management of diabetes with or without ketosis but also in the treatment of inflammatory conditions, AMI and cancer in which TNF and MMIF have a critical role.

Yours faithfully,
U.N. Das, MD

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