Anti-Inflammatory Effects of Insulin and Pro-Inflammatory Effects of Glucose: Relevance to the Management of Acute Myocardial Infarction and Other Acute Coronary Syndromes

Paresh Dandona, MD, PhD, Ajay Chaudhuri, MD, Husam Ghanim, PhD, Priya Mohanty, MD

Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, School of Medicine and Biomedical Sciences, State University of New York at Buffalo, and Kaleida Health, Buffalo, NY

Hyperglycemia worsens morbidity and mortality for patients in intensive care or with acute myocardial infarction, stroke, or coronary artery bypass grafts. The control of hyperglycemia with insulin improves clinical outcomes for patients with these conditions. This article reviews the anti-inflammatory effects of insulin and pro-inflammatory effects of glucose and free fatty acids, and provides a mechanistic justification for maintaining euglycemia with insulin infusions. Hyperglycemia induced by infusions of a fixed dose of insulin with high rates of glucose may neutralize the benefit of insulin, and such regimens should be replaced by infusion of insulin to restore and maintain euglycemia.
[Rev Cardiovasc Med. *2006;7(suppl 2):S25-S34*]

Key words: Hyperglycemia • Insulin • Glucose

Since its discovery in 1921, insulin has been considered a key metabolic hormone with profound effects on glucose and lipid metabolism. However, over the past decade, studies have shown that insulin exerts several unexpected biological effects, especially in relation to the endothelial cell, the platelet, and leukocyte function. Most recently, insulin has been found to affect

the heart. These effects are important in understanding some recent uses of insulin in clinical situations. This is particularly relevant because insulin is anti-inflammatory, glucose is pro-inflammatory, and atherogenesis is a chronic inflammation of the arterial wall. In addition, coronary syndromes are associated with marked inflammation that may be further exacerbated by hyperglycemia.

Insulin has been shown to suppress 3 important inflammatory mediators in vitro: intercellular adhesion molecule-1 (ICAM-1), macrophage chemoattractant protein-1 (MCP-1) expression, and nuclear factor kappa B (NF-κB) binding in human aortic endothelial cells.

Reactive Oxygen Species–Suppressive and Anti-Inflammatory Effects of Insulin

Insulin is known to be a vasodilator and to increase blood flow at the arterial, venous, and microcirculatory levels.[1,2] This vasodilatory effect has been shown, in vitro, to be due to the rapid release of nitric oxide (NO) by the endothelium.[2,3] Insulin also induces an increase in the rapid release of NO and the expression of endothelial NO synthase (eNOS).[4] The eNOS generates NO through activation of PI 3-kinase (phosphatidylinositol 3-kinase) and Akt kinase (protein kinase B) and thus by an insulin signaling mechanism similar to the mechanism that mediates the uptake of glucose through the glucose transporter. In the mid-1990s, insulin was also shown to be inhibitory to platelet aggregation through the activation of platelet NOS and generation of NO following release of cGMP (cyclic guanosine monophosphate).[5,6]

Because NO is a vasodilator, reduces leukocyte adhesion to the endothelium, and is anti-inflammatory, and because insulin causes the release of NO, we investigated whether insulin has an anti-inflammatory effect. Indeed, insulin has been shown to suppress 3 important inflammatory mediators in vitro: intercellular adhesion molecule-1 (ICAM-1), macrophage chemoattractant protein-1 (MCP-1) expression, and nuclear factor kappa B (NF-κB) binding in human aortic endothelial cells.[7] NF-κB is an important transcription factor that induces the transcription of > 200 pro-inflammatory genes. Therefore, our data pointed strongly to an anti-inflammatory effect of insulin.

Experiments were undertaken to establish whether insulin exerted an anti-inflammatory effect in vivo. Insulin infusion (2 U/h) in obese subjects who are insulin resistant and have chronic inflammation was shown to suppress the generation of reactive oxygen species (ROS) and $p47^{phox}$ expression in mononuclear cells (MNCs), along with suppression of 2 major pro-inflammatory transcription factors: NF-κB and early growth response-1 (Egr-1).[8,9] Both the binding of Egr-1 and its expression as a protein were also suppressed. The intracellular inhibitor of NF-κB, IκBα, was increased. Plasma concentrations of ICAM-1, MCP-1, matrix metalloproteinases (MMP-2, MMP-9), tissue factor (TF), and plasminogen activator inhibitor-1 (PAI-1), and expression of genes regulated by these transcription factors also decreased following insulin infusion during which plasma glucose concentrations were maintained at a constant, normoglycemic level.[8,9] Insulin also suppressed the concentration of vascular endothelial growth factor (VEGF), the cytokine thought to contribute to neovascularization of the retina in the pathogenesis of diabetic retinopathy and to cause expansion of an experimental myocardial infarction in the rat through microcirculatory changes.[10,11]

These properties of insulin comprise a potent and comprehensive anti-inflammatory and antioxidant effect. This action is rapid: it is observed within 2 hours, and the magnitude of the effect with 2 U/h of insulin is similar to that of 100 mg of hydrocortisone given intravenously.[12]

Anti-Inflammatory Effects of Insulin in Acute Myocardial Infarction and Coronary Artery Bypass Surgery

The anti-inflammatory, antioxidant (ROS-suppressive), antithrombotic, and pro-fibrinolytic effects of insulin have also been found in patients with acute myocardial infarction (AMI) when treated with low-dose infusions of insulin, independent of a decrease in glucose concentrations. In these patients, there was an impressive 40% reduction in plasma C-reactive protein (CRP) and serum amyloid A (SAA) concentrations at 24 hours. This reduction was maintained at 48 hours of insulin infusion (Figure 1).[13] In addition, insulin prevented the increase in PAI-1 concentrations induced by the thrombolytic agent reteplase. Similarly, insulin infusion prevented the marked increase in $p47^{phox}$ expression in MNCs that is observed in patients receiving thrombolytic treatment alone. Insulin infusion also reduced pro-MMP-1 concentrations.[13,14]

Low-dose insulin infusion in patients with AMI prevented a heparin-induced increase in plasma free fatty

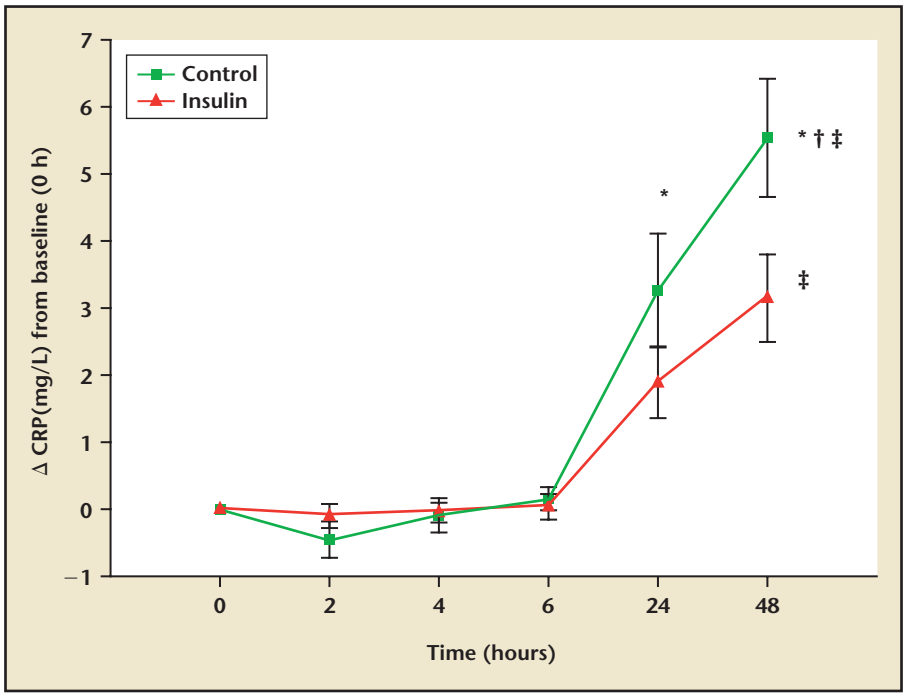


Figure 1. *Time course of the absolute difference in mean (± standard error) concentration of C-reactive protein (CRP) from baseline (0 hour) over 48 hours. *P < .05 between groups at 24 and 48 hours (by two-way analysis of variance); †P < .05 between groups at 48 hours (t-test); ‡ P < .01 within group (by 1-way RMANOVA). Adapted with permission from Chaudhuri A et al.*[13]

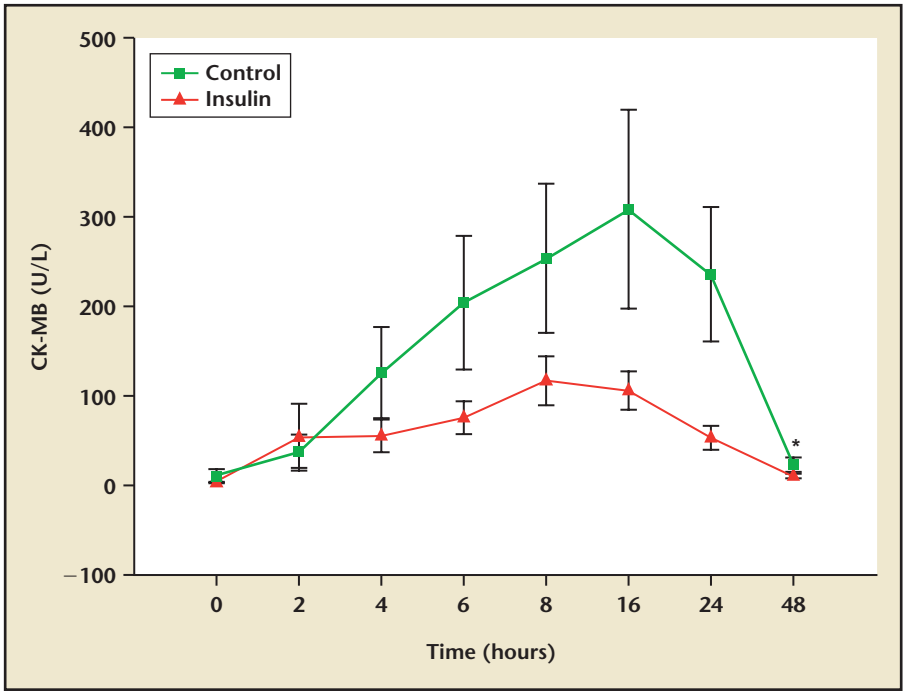
changes in mitochondrial inner membrane and cristae induced by oxidative stress were also inhibited by insulin infusion that maintained euglycemia.[16]

Anti-inflammatory effects of insulin have recently been shown in patients undergoing coronary artery bypass grafts (CABG) in association with extracorporeal circulation.[17] The increase in plasma CRP concentrations occurring within 16 hours of surgery is 30 times greater than that in patients with ST-elevation MI (STEMI). Reduction in the magnitude of the increase in CRP and SAA with insulin infusion is 40%, very similar to that observed following insulin infusion in patients with STEMI. In this study of patients undergoing CABG, cessation of insulin infusion with the resultant increase in glucose concentration led to increased CRP and SAA levels within

acid (FFA) concentrations, which probably is secondary to heparin-induced lipolysis.[14] Low-dose insulin did not, however, lower the basally elevated concentrations of FFAs in these patients. The profound suppressive effect of insulin on CRP concentrations in patients with AMI has been confirmed by another recent study.[15] As the increase in CRP concentrations is known to be related to the size of the infarct in patients with AMI, the effect on CRP may be indicative of cardioprotection. In our study,[13] insulin infusion reduced creatinine kinase-MB (CK-MB) in patients with inferior wall AMI (Figure 2).

The anti-inflammatory effects of insulin have also been shown in patients in intensive care, with demonstrated suppression of plasma ICAM-1, E-selectin, hepatic iNOS (inducible NOS) expression, and plasma NO metabolites.[16] In these patients, the

Figure 2. *Creatinine kinase-MB (CK-MB) in inferior wall myocardial infarction. Absolute values are presented as mean ± standard error. *P < .01 between groups (by two-way analysis of variance after logarithmic transformation). Adapted with permission from Chaudhuri A et al.*[13]



hours. Clearly, there is a very close relationship between glycemia, insulin, and CRP and SAA concentrations. Such a close association between CRP and SAA concentrations and any pharmacologic agent has not been shown before, nor is any other agent known to reduce plasma CRP and SAA concentrations by 40% within hours. An anti-inflammatory effect of insulin has also been demonstrated in patients with burn injuries.[18]

Anti-Inflammatory Effect of Insulin in Experimental Animals

In addition to the human data, some recent experimental data from animal studies are also important. For example, in the isolated rat heart preparation, addition of insulin, even without glucose and potassium, at the time of reperfusion following ligation of the anterior descending coronary artery reduces the size of the infarct by 45%.[19,20] This has been attributed to an anti-apoptotic action of insulin mediated by a PI 3-kinase, Akt, BAD, and NOS phosphorylation.[21]

More recently, insulin was shown to be the essential component of the glucose-insulin-potassium (GIK) infusion in reducing infarct size by 45% in an in vivo rat heart model of myocardial infarction. Insulin exerted an anti-apoptotic effect, which was found to be dependent on PI 3-kinase–dependent Akt and eNOS phosphorylation and the subsequent increase in NO production.[21] In a canine model of low-flow ischemia, insulin was shown to improve contractile function and myocardial metabolic efficiency without alteration of ATP (adenosine triphosphate), phosphocreatine, and phosphate levels.[22,23]

An anti-inflammatory effect of insulin has also been demonstrated in animal studies. Insulin suppresses endotoxin-induced pro-inflammatory transcription factors and the genes regulated by them.[24,25] These effects in endotoxin-treated rats and pigs were shown during euglycemic conditions. A suppressive effect of insulin on pro-inflammatory factors has also been found in rats exposed to thermal injury.[26]

Anti-Atherogenic Effect of Insulin

A ROS-suppressive and antioxidant effect of insulin has been found in apolipoprotein E (ApoE)-deficient mice, which develop atherosclerosis spontaneously.[27] In these animals, insulin suppressed $O_2^{\bullet}$ production, lipid peroxide content, and cholesterol synthesis by macrophages. In addition, atherogenesis—total atherosclerotic area and number of atherosclerotic lesions in the aorta—was diminished. This constitutes the first evidence that insulin is anti-atherogenic. In addition, interference with insulin signal transduction following deletion of the IRS-2 (insulin receptor substrate-2) gene in mice leads to accelerated atherogenesis, with changes in the intima starting at 8 weeks of age and becoming fully developed by 20 weeks.[28] As atherosclerosis is a chronic inflammation of the arterial wall, the evidence that insulin suppresses atherogenesis is consistent with its antioxidant and anti-inflammatory effects.[29]

It is interesting that the pro-atherogenic effects of insulin proposed primarily on the basis of in vitro studies are being challenged by evidence generated in the past 6 years.

It is interesting that the pro-atherogenic effects of insulin proposed primarily on the basis of in vitro studies are being challenged by evidence generated in the past 6 years.[30] The debate has been further fueled by 2 recent articles showing that knocking out the insulin receptor in myelogenic cells, the precursors of MNCs (which play a crucial role in the pathogenesis of atherosclerosis), is anti-atherogenic in animals with low-density lipoprotein (LDL) receptor deficiency and is pro-atherogenic in the ApoE-deficient animal.[31,32]

Effect of GIK Infusion–Induced Hyperglycemia in Clinical Trials of AMI

As discussed by Nesto in this supplement, hyperglycemia worsens the prognosis of patients with AMI[33] and stroke.[34] Several studies of patients with AMI show that insulin infusion followed by a reduction in hyperglycemia improves clinical outcomes.[35-37] These studies were carried out before the pro- and anti-inflammatory effects of glucose and insulin, respectively, were known, and were based on the hypothesis that GIK infusions may help repolarize the myocardium[38] and reduce plasma FFA concentrations by suppressing lipolysis,[39] thus eliminating the detrimental effects of high FFA levels on myocardial metabolism, necrosis, and function.

However, these GIK regimens induce a significant increase in blood glucose concentrations due to the infusion of large amounts of glucose (25-30 g/h) with a fixed dose of insulin, with no attempt to titrate insulin to maintain euglycemia. It is

therefore possible that the absence of improvement in the GIK group in recent trials of such regimens in patients with AMI may be due to the induction of hyperglycemia despite the infusion of insulin.

We have attempted to calculate the enhanced risk of mortality in patients in the CREATE-ECLA (Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment and Evaluation–Estudios Cardiologicos Latinoamerica) study,[40] based on the relation between hyperglycemia and mortality shown in this study. The projected mortality rates at 0, 6, and 24 hours obtained from the authors' data on the relation between administered glucose and mortality yield trapezoids, and the areas were calculated (Table 1). After dividing by 24 hours, we obtained a weighted average formula for mortality (mort.):

average % mort.
= 0.125 (% mort. at 0 hours)
+ 0.5 (% mort. at 6 hours)
+ 0.375 (% mort. at 24 hours)

This leads to an average 30-day mortality for the control group of approximately 9.9%, which compares favorably with the observed mortality of 9.7% for the control group as reported by Mehta and colleagues.[40] However, the calculated average mortality for the GIK group is 12.2%, which is 2.2% higher than the observed mortality of 9.7% in this group. This would suggest that patients in the GIK group were protected from the excess (2.5%) expected mortality induced by their hyperglycemia. We could conclude, therefore, that the 2.5% reduction in mortality in the GIK group was probably due to the "protective effect of insulin."

Pro-Inflammatory Effect of Glucose, Free Fatty Acids, and Macronutrients

We have recently shown that glucose (75 g) intake leads to oxidative stress as reflected in an increase in generation of the free radical $O_2^{\bullet}$ by leukocytes (both polymorphonuclear leukocytes and MNCs) and the expression of $p47^{phox}$, an essential component of the enzyme NADPH (reduced nicotinamide adenine dinucleotide phosphate) oxidase, which converts O_2 to $O_2^{\bullet}$.[41] In addition to oxidative stress, there is also inflammatory stress, because $O_2^{\bullet}$ activates redox-sensitive pro-inflammatory transcription factors such as NF-κB, activator protein-1 (AP-1), Egr-1, and hypoxia-inducible factor alpha (HIFα). Our work has shown that the intake of 75 g of glucose induces an increase in inhibitor kappa B (IκB) kinases alpha and beta (IKKα and IKKβ), a fall in IκBα, and an increase in intranuclear NF-κB binding.[42] Glucose also causes an increase in AP-1 and Egr-1, and the genes regulated by these transcription factors are induced, as reflected by the increase in MMP-2, MMP-9, and TF in mononuclear cells and plasma.[43] In addition, there is an increased expression of a large number of genes at the mRNA level, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and MCP-1.

In addition to our studies on the effect of orally administered glucose on oxidative stress and inflammation, we have also demonstrated that an intravenous infusion of triglycerides and heparin in normal (non-obese) subjects, which leads to increased plasma concentrations of FFAs to levels comparable to those observed in obesity, induces increased ROS generation, increased NF-κB binding and p65 expression in the nucleus, and increased plasma macrophage migration inhibitory factor (MIF) concentrations.[44] This was associated with a decrease in post-ischemic endothelium-dependent vasodilation. Similarly, a study involving the induction of a steady state of hyperglycemia by intravenous glucose infusion, with the concomitant inhibition of endogenous insulin secretion by somatostatin, led to increased plasma TNF-α and IL-6 concentrations.[45] Clearly, glucose is pro-inflammatory even when given intravenously, especially when endogenous insulin secretion is suppressed.

Table 1
Glucose Levels and Projected Mortality Rate in CREATE-ECLA Study

	Control		GIK	
Time (h)	Blood glucose (mmol/L)	% mortality	Blood glucose (mmol/L)	% mortality
0	9	11.4	9	11.4
6	8.2	10.2	10.4	13.4
24	7.5	9.1	8.6	10.8

The projected mortality rates at 0, 6, and 24 hours, obtained from the authors' data,[40] yielded trapezoids, and the areas were calculated. After dividing by 24 hours, the following weighted average formula for mortality (mort.) was obtained: average % mort. = 0.125 (% mort. at 0 hours) + 0.5 (% mort. at 6 hours) + 0.375 (% mort. at 24 hours). CREATE-ECLA, Clinical Trial of Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation-Estudios Cardiologicos Latinoamerica. GIK, glucose-insulin-potassium.

Glucose intake and triglyceride infusion induce oxidative stress with generation of $O_2^{\bullet}$, as mentioned above. This can reduce the bioavailability of NO, as superoxide combines with NO to form peroxynitrite. Hyperglycemia-induced reduction in NO bioavailability may have a pro-constrictor effect on blood vessels, along with a platelet pro-aggregatory effect, because NO exerts a vasodilatory effect on blood vessels and an anti-aggregatory effect on platelets.[46] In addition, glucose induces an increase in TF, which is an activator of the extrinsic pathway of coagulation through activation of factor VII and conversion of prothrombin to thrombin. Thus, increased glucose concentrations induce a prothrombotic state. These effects would explain the adverse outcomes associated with hyperglycemia.[33,47-49] In addition, hyperglycemia induces inflammation, which would result in increased plasma CRP concentrations; increased CRP is associated with a higher incidence of arrhythmias.[50,51] Thus, hyperglycemia may also predispose to arrhythmias through inflammatory mechanisms.

Hyperglycemia induces inflammation, which would result in increased plasma C-reactive protein concentrations; increased CRP is associated with a higher incidence of arrhythmias.

Pro-Inflammatory State of Obesity

Given that obesity is a state of chronic overnutrition, one can expect it to be associated with chronic oxidative and inflammatory stress, and, indeed, we produced the first data confirming that obesity is associated with an increase in plasma levels of several products of oxidative stress: increased TBARS (thiobarbituric acid–reactive substances) and 9-HODE and 13-HODE (9- and 13-hydroxyoctadecadienoic acid) concentrations, and increased carbonylated protein, orthotyrosine, and metatyrosine concentrations.[52,53] TBARS and HODEs are products of lipid and linoleic acid peroxidation. Carbonylated proteins are products of diabetic oxidative damage to proteins. Orthotyrosine and metatyrosine are formed by free radical ($OH^{\bullet}$) attack on the phenylalanine molecule. It is also of interest that if obese patients are subjected to dietary restriction (1000 calories/day for 4 weeks), ROS generation by leukocytes and the concentrations of TBARS, 9-HODE, 13-HODE, carbonylated proteins, orthotyrosine, and metatyrosine all fall dramatically.[52] This happens in association with loss of a mere 6 to 7 kg of weight while the patient is still obese. The effects are observed as early as 1 week after the start of caloric restriction. Clearly, excessive macronutrient intake maintains oxidative stress levels even in obesity. This was examined further. When normal (non-obese) subjects fasted for 48 hours, $O_2^{\bullet}$ generation by leukocytes fell by 35% at 24 hours and $>$ 50% at 48 hours.[52] The dramatic reduction in $O_2^{\bullet}$ generation following a fast in normal subjects and caloric restriction in obese subjects suggests that macronutrient intake is probably the major contributor to $O_2^{\bullet}$ generation in both non-obese and obese individuals.

In addition to the enhanced oxidative stress, obese subjects are known to have increased chronic inflammatory stress. The expression of TNF-α and other pro-inflammatory cytokines/mediators such as IL-6, MCP-1, and PAI-1 has been shown to be enhanced in circulating MNCs, and the plasma concentrations of these mediators are increased in human obesity.[54] Furthermore, CRP and SAA, 2 accepted markers of systemic inflammation, are also increased in obesity.[55] Interestingly, elevated CRP concentrations predict the development of type 2 diabetes mellitus and atherosclerotic complications.[56]

The observations reported above may also be relevant when considering regimens for total parenteral nutrition and hyperalimentation. Excessive administration of calories may result in high glucose and lipid concentrations, which may be pro-inflammatory.

Because ROS, especially $O_2^{\bullet}$, activate the redox-sensitive major transcription factors such as NF-κB, AP-1, and HIF-1α, an excess of ROS and $O_2^{\bullet}$ is likely to lead to increased transcription of the pro-inflammatory genes regulated by these transcription factors. The pro-inflammatory genes are increased in obesity and in type 2 diabetes.[54,57] Because atherosclerosis is the result of chronic inflammation of the arterial wall, and inflammatory mediators are considered important in the interference of insulin signal transduction, the state of chronic low-grade inflammation and oxidative stress may mediate both atherosclerosis and insulin resistance in obesity and type 2 diabetes.[29,58,59]

Given that most deaths of patients with diabetes and obesity are secondary to cardiovascular disease related to atherosclerosis, it follows

that an understanding of diet-induced oxidative and inflammatory stress is important for preventing and suppressing the processes that lead to atherosclerosis and cardiovascular complications. Another important aspect of our work on the effect of macronutrient intake on indices of oxidative and inflammatory stress is that the cellular target of our investigation is mononuclear cells. This cellular fraction contains the monocyte/macrophage and B and T cells, all of which are involved in atherogenesis. The monocyte/macrophage takes up lipid (oxidatively damaged LDL) and forms the foam cell. Foam cells populate the fatty streak, the initial lesion of atherosclerosis.[29,59] Indeed, our data show not only an increase in NF-κB binding and decrease in IκBα following intake of glucose, fat, and fast food meals, but also an increase in mRNA expression of a whole family of pro-inflammatory genes. Consistent with this, we have demonstrated an increase in NF-κB binding and a decrease in IκBβ expression, along with an increase in IL-6, TNF-α, MMP-9, and MIF expression, in the MNCs of obese patients.[54]

Our data show not only an increase in NF-κB binding and decrease in IκBα following intake of glucose, fat, and fast food meals, but also an increase in mRNA expression of a whole family of pro-inflammatory genes.

The state of chronic oxidative and inflammatory stress observed in obese individuals also affects their ability to handle a macronutrient load. Thus, the increase in ROS generation and NF-κB binding caused by intake of a large (1800 calorie) fast food meal by obese individuals lasted significantly longer than that in normal subjects.[60]

Conclusion

In view of the rapidly accumulating data demonstrating an anti-inflammatory effect of insulin and a pro-inflammatory effect of glucose and FFAs, and the relationship of clinical outcomes to indices of inflammation, it is clear that an important strategy in the care of patients with acute cardiac syndromes (including AMI and CABG surgery) is the maintenance of euglycemia with the help of insulin infusions. This would potentially be of great benefit (Figure 3). This area clearly needs further definitive investigation.

The published data clearly show that hyperglycemia worsens prognosis, including mortality, in intensive care (surgical and medical) patients. It also causes a marked dose-dependent deterioration of morbidity and mortality in patients with AMI and stroke and in all hospitalized patients. For patients with burns and those in intensive care units, the control of hyperglycemia with insulin infusion improves clinical outcomes. The pro-inflammatory and pro-oxidant action of glucose and the ROS-suppressive and anti-inflammatory action of insulin are likely to play an important role in the pathogenesis and the treatment of these complications (Figure 4).[61] Regimens that infuse fixed doses of insulin with high rates of glucose are usually associated with hyperglycemia, as observed in several studies of patients with AMI. The induction of hyperglycemia may potentially neutralize the benefits of insulin, and these regimens should therefore be avoided. We are currently conducting a study to test whether a low-dose insulin infusion that restores normoglycemia in patients with AMI will improve clinical outcomes. ■

Figure 3. *Current view of the action of insulin. The anti-inflammatory, anti-apoptotic, cardioprotective, and neuroprotective effects of insulin have been demonstrated in both humans and animal models. The vasodilatory, reactive oxygen species (ROS)–suppressive, antiplatelet, antithrombotic, and pro-fibrinolytic effects have been demonstrated in humans. NF-κB, nuclear factor kappa B; IκB, inhibitor kappa B; MCP-1, macrophage chemoattractant protein-1; ICAM-1, intercellular adhesion molecule-1; CRP, C-reactive protein; TF, tissue factor; PAI-1, plasminogen activator inhibitor-1; NO, nitric oxide; cAMP, cyclic adenosine monophosphate; eNOS, endothelial NO synthase.*

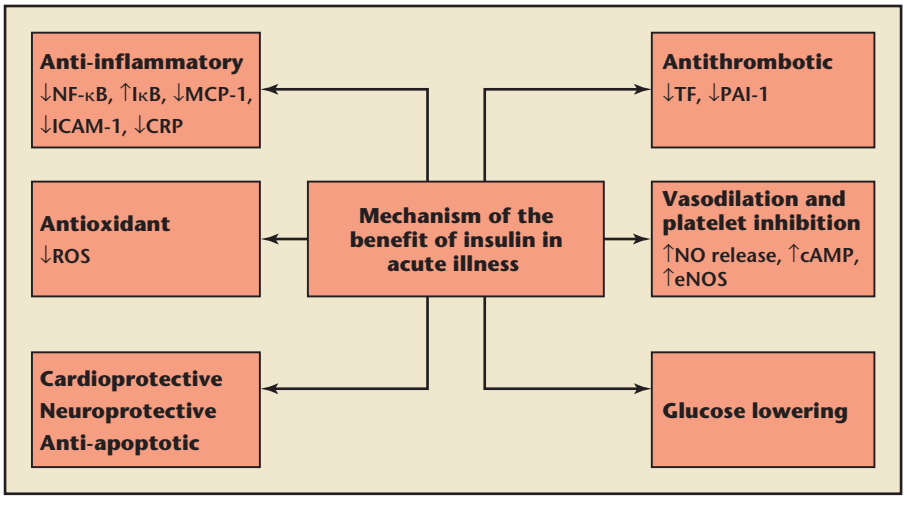
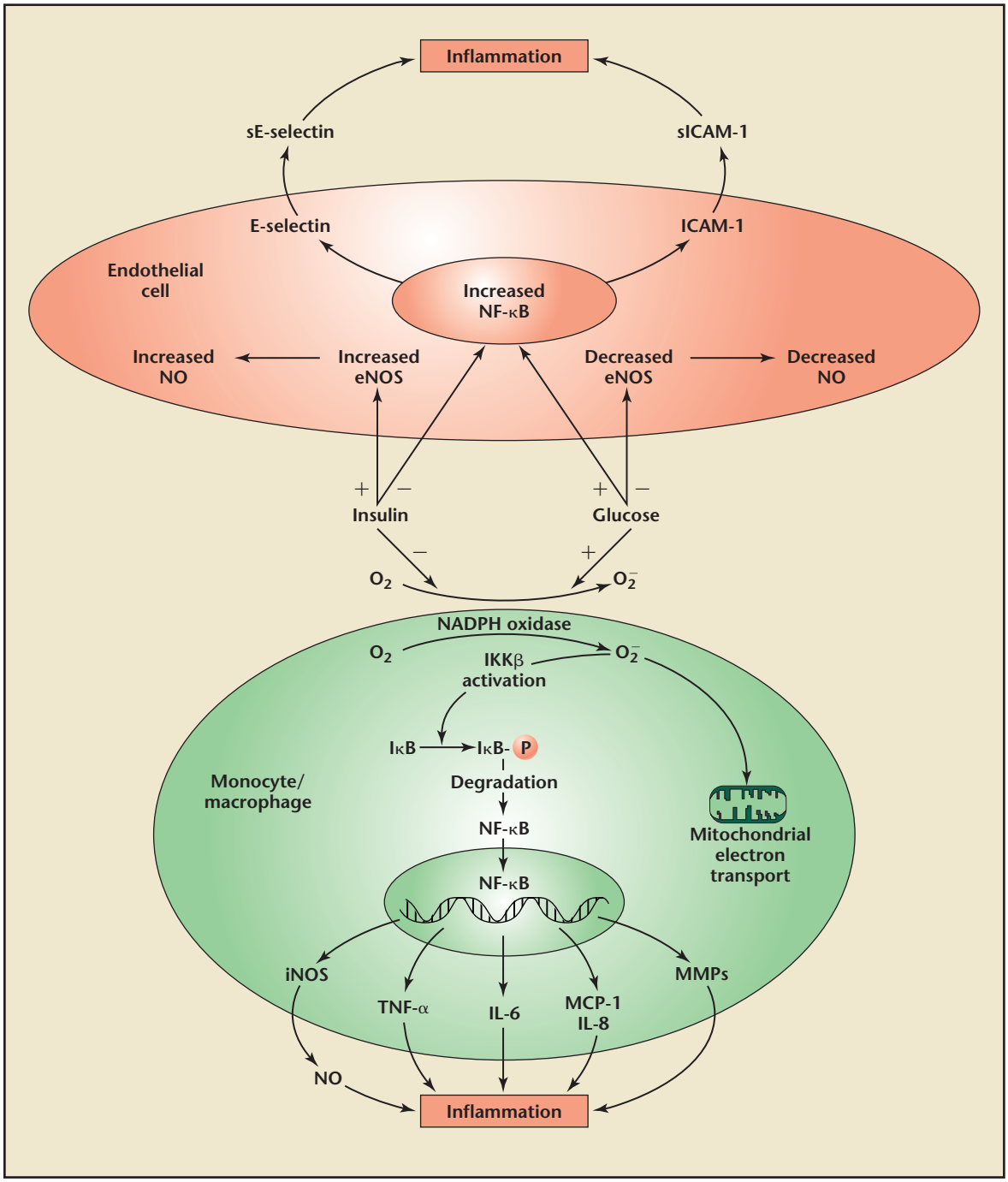


Figure 4. *The anti-inflammatory effect of insulin and pro-inflammatory effect of glucose. Insulin suppresses reactive oxygen species and generation of $O_2^{\bullet}$ and expression of NADPH oxidase; glucose stimulates both. In the macrophage, $O_2^{\bullet}$ activates inhibitor kappa B kinase beta (IKKβ) to enhance phosphorylation of inhibitor kappa B (IκB), such that it undergoes proteosomal degradation, releasing nuclear factor kappa B (NF-κB) to translocate into the nucleus. NF-κB stimulates the transcription of genes encoding pro-inflammatory proteins, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), macrophage chemoattractant protein-1 (MCP-1), and matrix metalloproteinases (MMPs). In the endothelial cell, insulin also induces endothelial nitric oxide synthase (eNOS) expression, which leads to controlled nitric oxide (NO) release and vasodilation; glucose has the opposite effect. Glucose induces the expression of the adhesion molecules intercellular adhesion molecule-1 (ICAM-1) and E-selectin, whereas insulin suppresses their expression in the endothelial cell. iNOS, inducible nitric oxide synthase. Adapted with permission from Dandona P et al.*[61]



References

1. Grover A, Padginton C, Wilson MF, et al. Insulin attenuates norepinephrine-induced venoconstriction: an ultrasonographic study. *Hypertension*. 1995;25:779-784.
2. Steinberg HO, Brechtel G, Johnson A, et al. Insulin-mediated skeletal muscle vasodilation is nitric oxide dependent: a novel action of insulin to increase nitric oxide release. *J Clin Invest*. 1994;94:1172-1179.
3. Zeng G, Quon MJ. Insulin-stimulated production of nitric oxide is inhibited by wortmannin: direct measurement in vascular endothelial cells. *J Clin Invest*. 1996;98:894-898.
4. Aljada A, Dandona P. Effect of insulin on human aortic endothelial nitric oxide synthase. *Metabolism*. 2000;49:147-150.
5. Trovati M, Anfossi G, Massucco P, et al. Insulin stimulates nitric oxide synthesis in human platelets and, through nitric oxide, increases platelet concentrations of both guanosine-3′,5′-cyclic monophosphate and adenosine-3′,5′-cyclic monophosphate. *Diabetes*. 1997;46:742-749.
6. Trovati M, Massucco P, Mattiello L, et al. Insulin increases guanosine-3′,5′-cyclic monophosphate in human platelets: a mechanism involved in the insulin anti-aggregating effect. *Diabetes*. 1994;43:1015-1019.
7. Aljada A, Ghanim H, Saadeh R, Dandona P. Insulin inhibits NFkappaB and MCP-1 expression in human aortic endothelial cells. *J Clin Endocrinol Metab*. 2001;86:450-453.
8. Aljada A, Ghanim H, Mohanty P, et al. Insulin inhibits the pro-inflammatory transcription factor early growth response gene-1 (Egr-1) expression in mononuclear cells (MNC) and reduces plasma tissue factor (TF) and plasminogen activator inhibitor-1 (PAI-1) concentrations. *J Clin Endocrinol Metab*. 2002;87:1419-1422.
9. Dandona P, Aljada A, Mohanty P, et al. Insulin inhibits intranuclear nuclear factor kappaB and stimulates IkappaB in mononuclear cells in obese subjects: evidence for an anti-inflammatory effect? *J Clin Endocrinol Metab*. 2001;86:3257-3265.
10. Dandona P, Aljada A, Mohanty P, et al. Insulin suppresses plasma concentration of vascular endothelial growth factor and matrix metalloproteinase-9. *Diabetes Care*. 2003;26:3310-3314.
11. Weis S, Shintani S, Weber A, et al. Src blockade stabilizes a Flk/cadherin complex, reducing edema and tissue injury following myocardial infarction. *J Clin Invest*. 2004;113:885-894.
12. Dandona P, Thusu K, Hafeez R, et al. Effect of hydrocortisone on oxygen free radical generation by mononuclear cells. *Metabolism*. 1998;47:788-791.
13. Chaudhuri A, Janicke D, Wilson MF, et al. Anti-inflammatory and pro-fibrinolytic effect of insulin in acute ST-elevation myocardial infarction. *Circulation*. 2004;109:849-854.
14. Chaudhuri A, Janicke D, Wilson MF, et al. Free fatty acid suppressive, pro-MMP-1 lowering and cardioprotective effect of insulin in STEMI. Presented at: 87th Annual Meeting of the Endocrine Society, Scientific Session; June 4-7, 2005; San Diego, CA.
15. Wong VW, McLean M, Boyages SC, Cheung NW. C-reactive protein levels following acute myocardial infarction: effect of insulin infusion and tight glycemic control. *Diabetes Care*. 2004;27:2971-2973.
16. Langouche L, Vanhorebeek I, Vlasselaers D, et al. Intensive insulin therapy protects the endothelium of critically ill patients. *J Clin Invest*. 2005;115:2277-2286.
17. Visser L, Zuurbier CJ, Hoek FJ, et al. Glucose, insulin and potassium applied as perioperative hyperinsulinaemic normoglycaemic clamp: effects on inflammatory response during coronary artery surgery. *Br J Anaesth*. 2005;95:448-457.
18. Herndon DN, Tompkins RG. Support of the metabolic response to burn injury. *Lancet*. 2004;363:1895-1902.
19. Jonassen AK, Brar BK, Mjos OD, et al. Insulin administered at reoxygenation exerts a cardioprotective effect in myocytes by a possible anti-apoptotic mechanism. *J Mol Cell Cardiol*. 2000;32:757-764.
20. Jonassen AK, Sack MN, Mjos OD, Yellon DM. Myocardial protection by insulin at reperfusion requires early administration and is mediated via Akt and p70s6 kinase cell-survival signaling. *Circ Res*. 2001;89:1191-1198.
21. Gao F, Gao E, Yue TL, et al. Nitric oxide mediates the antiapoptotic effect of insulin in myocardial ischemia-reperfusion: the roles of PI3-kinase, Akt, and endothelial nitric oxide synthase phosphorylation. *Circulation*. 2002;105:1497-1502.
22. Tune JD, Mallet RT, Downey HF. Insulin improves contractile function during moderate ischemia in canine left ventricle. *Am J Physiol*. 1998;274:H1574-H1581.
23. Tune JD, Mallet RT, Downey HF. Insulin improves cardiac contractile function and oxygen utilization efficiency during moderate ischemia without compromising myocardial energetics. *J Mol Cell Cardiol*. 1998;30:2025-2035.

Main Points

- Rapidly accumulating data demonstrate the anti-inflammatory and antioxidant (reactive oxygen species–suppressive) effects of insulin and the pro-inflammatory effects of glucose (hyperglycemia) and free fatty acids.
- Treatment regimens that infuse fixed doses of insulin with high rates of glucose are usually associated with hyperglycemia, as observed in studies of patients with acute myocardial infarction (AMI).
- The anti-inflammatory, antioxidant, and pro-fibrinolytic effects of insulin have been demonstrated in patients with AMI when treated with low-dose infusions of insulin independent of a decrease in glucose concentrations.
- The anti-inflammatory effects of insulin have also been shown in patients in intensive care and in patients undergoing coronary artery bypass grafts.
- Evidence that insulin suppresses atherogenesis is consistent with its antioxidant and anti-inflammatory effects.
- The absence of improvement in the glucose-insulin-potassium (GIK) infusion group in recent trials of such regimens in patients with AMI may be due to the induction of hyperglycemia despite the infusion of insulin.
- Analyses show that patients in a GIK group were protected from a 2.5% excess expected mortality induced by hyperglycemia, probably due to the protective effect of insulin.
- Glucose is pro-inflammatory even when given intravenously, especially when endogenous insulin secretion is suppressed.
- Obesity is associated with chronic oxidative and inflammatory stress.
- The state of chronic low-grade inflammation and oxidative stress may mediate both atherosclerosis and insulin resistance in obesity and type 2 diabetes.

24. Jeschke MG, Klein D, Bolder U, Einspanier R. Insulin attenuates the systemic inflammatory response in endotoxemic rats. *Endocrinology*. 2004;145:4084-4093.
25. Brix-Christensen V, Andersen SK, Andersen R, et al. Acute hyperinsulinemia restrains endotoxin-induced systemic inflammatory response: an experimental study in a porcine model. *Anesthesiology*. 2004;100:861-870.
26. Jeschke MG, Einspanier R, Klein D, Jauch KW. Insulin attenuates the systemic inflammatory response to thermal trauma. *Mol Med*. 2002; 8:443-450.
27. Shamir R, Shehadeh N, Rosenblat M, et al. Oral insulin supplementation attenuates atherosclerosis progression in apolipoprotein E-deficient mice. *Arterioscler Thromb Vasc Biol*. 2003;23: 104-110.
28. Kubota T, Kubota N, Moroi M, et al. Lack of insulin receptor substrate-2 causes progressive neointima formation in response to vessel injury. *Circulation*. 2003;107:3073-3080.
29. Ross R. Atherosclerosis: an inflammatory disease. *N Engl J Med*. 1999;340:115-126.
30. Dandona P, Aljada A, Mohanty P. The anti-inflammatory and potential anti-atherogenic effect of insulin: a new paradigm. *Diabetologia*. 2002;45:924-930.
31. Han S, Liang CP, DeVries-Seimon T, et al. Macrophage insulin receptor deficiency increases ER stress-induced apoptosis and necrotic core formation in advanced atherosclerotic lesions. *Cell Metab*. 2006;3:257-266.
32. Baumgartl J, Baudler S, Scherner M, et al. Myeloid lineage cell-restricted insulin resistance protects apolipoprotein E-deficient mice against atherosclerosis. *Cell Metab*. 2006;3:247-256.
33. Wahab NN, Cowden EA, Pearce NJ, et al. Is blood glucose an independent predictor of mortality in acute myocardial infarction in the thrombolytic era? *J Am Coll Cardiol*. 2002;40: 1748-1754.
34. Williams LS, Rotich J, Qi R, et al. Effects of admission hyperglycemia on mortality and costs in acute ischemic stroke. *Neurology*. 2002;59:67-71.
35. Diaz R, Paolasso EA, Piegas LS, et al. Metabolic modulation of acute myocardial infarction. The ECLA (Estudios Cardiologicos Latinoamerica) Collaborative Group. *Circulation*. 1998;98: 2227-2234.
36. Malmberg K, Ryden L, Efendic S, et al. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. *J Am Coll Cardiol*. 1995;26:57-65.
37. van der Horst I, Zijlstra F, van't Hof A, et al. Glucose-insulin-potassium infusion in patients treated with primary angioplasty for acute myocardial infarction. *J Am Coll Cardiol*. 2003; 42:784-791.
38. Sodi-Pallares D, Testelli MR, Fishleder BL, et al. Effects of an intravenous infusion of a potassium-glucose-insulin solution on the electrocardiographic signs of myocardial infarction: a preliminary clinical report. *Am J Cardiol*. 1962;9: 166-181.
39. Rogers WJ, Stanley AW Jr, Breinig JB, et al. Reduction of hospital mortality rate of acute myocardial infarction with glucose-insulin-potassium infusion. *Am Heart J*. 1976;92:441-454.
40. Mehta SR, Yusuf S, Diaz R, et al. Effect of glucose-insulin-potassium infusion on mortality in patients with acute ST-segment elevation myocardial infarction. The CREATE-ECLA randomized controlled trial. *JAMA*. 2005;293:437-446.
41. Mohanty P, Hamouda W, Garg R, et al. Glucose challenge stimulates reactive oxygen species (ROS) generation by leucocytes. *J Clin Endocrinol Metab*. 2000;85:2970-2973.
42. Dhindsa S, Tripathy D, Mohanty P, et al. Differential effects of glucose and alcohol on reactive oxygen species generation and intranuclear nuclear factor-kappaB in mononuclear cells. *Metabolism*. 2004;53:330-334.
43. Aljada A, Ghanim H, Mohanty P, et al. Glucose intake induces an increase in activator protein 1 and early growth response 1 binding activities, in the expression of tissue factor and matrix metalloproteinase in mononuclear cells, and in plasma tissue factor and matrix metalloproteinase concentrations. *Am J Clin Nutr*. 2004;80:51-57.
44. Tripathy D, Mohanty P, Dhindsa S, et al. Elevation of free fatty acids induces inflammation and impairs vascular reactivity in healthy subjects. *Diabetes*. 2003;52:2882-2887.
45. Esposito K, Nappo F, Marfella R, et al. Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans: role of oxidative stress. *Circulation*. 2002;106:2067-2072.
46. Dandona P. Endothelium, inflammation, and diabetes. *Curr Diab Rep*. 2002;2:311-315.
47. Umpierrez GE, Isaacs SD, Bazargan N, et al. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J Clin Endocrinol Metab*. 2002;87:978-982.
48. Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *Lancet*. 2000;355:773-778.
49. Capes SE, Hunt D, Malmberg K, et al. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. *Stroke*. 2001;32:2426-2432.
50. Malouf JF, Kanagala R, Al Atawi FO, et al. High sensitivity C-reactive protein: a novel predictor for recurrence of atrial fibrillation after successful cardioversion. *J Am Coll Cardiol*. 2005;46: 1284-1287.
51. Ishida K, Kimura F, Imamaki M, et al. Relation of inflammatory cytokines to atrial fibrillation after off-pump coronary artery bypass grafting. *Eur J Cardiothorac Surg*. 2006;29:501-505.
52. Dandona P, Mohanty P, Ghanim H, et al. The suppressive effect of dietary restriction and weight loss in the obese on the generation of reactive oxygen species by leukocytes, lipid peroxidation, and protein carbonylation. *J Clin Endocrinol Metab*. 2001;86:355-362.
53. Dandona P, Weinstock R, Thusu K, et al. Tumor necrosis factor-alpha in sera of obese patients: fall with weight loss. *J Clin Endocrinol Metab*. 1998;83:2907-2910.
54. Ghanim H, Aljada A, Hofmeyer D, et al. Circulating mononuclear cells in the obese are in a proinflammatory state. *Circulation*. 2004;110: 1564-1571.
55. Mohamed-Ali V, Goodrick S, Rawesh A, et al. Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-alpha, in vivo. *J Clin Endocrinol Metab*. 1997;82:4196-4200.
56. Duncan BB, Schmidt MI, Pankow JS, et al. Low-grade systemic inflammation and the development of type 2 diabetes. The Atherosclerosis Risk in Communities study. *Diabetes*. 2003;52: 1799-1805.
57. Dandona P, Aljada A, Chaudhuri A, et al. Metabolic syndrome: a comprehensive perspective based on interactions between obesity, diabetes, and inflammation. *Circulation*. 2005;111: 1448-1454.
58. Dandona P, Aljada A, Bandyopadhyay A. Inflammation: the link between insulin resistance, obesity and diabetes. *Trends Immunol*. 2004;25:4-7.
59. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation*. 2002;105:1135-1143.
60. Dandona P, Chaudhuri A, Ghanim H, Mohanty P. Data presented at the 65th Scientific Sessions of the American Diabetes Association; June 10-14, 2005; San Diego, CA.
61. Dandona P, Mohanty P, Chaudhuri A, et al. Insulin infusion in acute illness. *J Clin Invest*. 2005;115:2069-2072.