Jun Ren[1] and James R. Sowers[2]

Application of a Novel Curcumin Analog in the Management of Diabetic Cardiomyopathy

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COMMENTARY

Diabetes mellitus is becoming an epidemic health threat and represents one of the most prevalent chronic noncommunicable disorders. Cardiovascular complications are considered the leading cause of death for diabetic patients. Diabetes leads to undesired changes in cardiac structure and function, a condition commonly known as diabetic cardiomyopathy, which occurs independent of macro- and microvascular comorbidities in diabetes (1,2). Both systolic and diastolic dysfunctions have been demonstrated in diabetic hearts including prolonged duration of contraction and relaxation, reduced velocity of contraction and relaxation, and depressed myocardial contractility (1,3). In particular, clinical evaluation using electrocardiogram and echocardiography has revealed substantial functional changes in diabetic hearts, including shorter left ventricular ejection time, prolonged preejection duration, increased wall stiffness, decreased fractional shortening, decreased rate of left ventricular filling, and increased action potential duration (4,5). To date, a plethora of cellular and molecular mechanisms have been postulated for the onset and development of diabetic cardiomyopathy, including reduced energy production due to decreases in mitochondrial respiration and pyruvate dehydrogenase activity, accumulation of reactive oxygen species, oxidative stress, apoptosis, impaired autophagy, and malfunction of cardiac contractile and intracellular Ca^{2+} regulatory proteins such as myosin, sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA), and Na^{+}-Ca^{2+} exchanger (1–3,5,6). The high morbidity and mortality for diabetic cardiomyopathy warrant aggressive clinical management involving lifestyle modification, control of glucose and lipid abnormalities, and treatment of hypertension and coronary artery diseases, if present. The commonly used therapeutic regimes in diabetic patients with heart anomalies encompass ACE inhibitors, digoxin, diuretics, β-blockers, Ca^{2+} antagonists, and spironolactone (7). Nonetheless, the mortality rate for diabetic cardiomyopathy still remains high, warranting novel and effective therapeutic strategies.

In this issue, Pan et al. (8) extended their earlier work revealing that C66 [(2E,6E)-2,6-bis(2-(trifluoromethyl) benzylidene) cyclohexanone], a curcumin analog, reduces streptozotocin-induced hypertriglyceridemia in both serum and hearts, in addition to the significantly reduced plasma and cardiac triglyceride levels. The authors further reported that reduction in hyperlipidemia in response to C66 therapy is accompanied by improved cardiac function, inhibition of Jun NH_2-terminal kinase (JNK) signaling and cardiac inflammation in the type 1 experimental diabetic model. Pretreatment with C66 inhibited a high glucose–induced rise in proinflammatory cytokines via inactivation of nuclear factor κB (NF-κB). Furthermore, they showed that inhibition of JNK phosphorylation may be responsible for the beneficial effect of C66 against inflammation and apoptosis. In diabetic mice, administration of C66 or another JNK inhibitor SP600125 effectively lowered plasma and cardiac levels of tumor necrosis factor (TNF)-α, accompanied by lessened apoptosis and improved histology, including interstitial fibrosis and functional anomalies in the heart. These findings support the notion that the curcumin analog protects against diabetes and hyperglycemia-induced cardiac damage via inhibition of inflammation. More important, these findings depict a critical role for JNK activation in diabetic cardiac injury and suggest that JNK may be considered as a therapeutic target for diabetic cardiomyopathy. A recent report from the same group indicated that C66 is capable of preventing JNK activation in diabetes, leading to protection against diabetes-induced cardiac fibrosis, oxidative stress, endoplasmic reticulum (ER)

[1]Center for Cardiovascular Research and Alternative Medicine, University of Wyoming College of Health Sciences, Laramie, WY
[2]Diabetes and Cardiovascular Center, University of Missouri School of Medicine, and VA Medical Center, Columbia, MO

Corresponding author: Jun Ren, jren@uwyo.edu, or James R. Sowers, sowersj@health.missouri.edu.

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stress, and cell death, along with a preserved level of the heavy metal scavenger metallothionein in the heart (9). The findings from Pan et al. (8) took it to the next level, suggesting a role of antagonism against inflammation and cytokine behind C66-offered benefits in diabetes. Inflammation with increased cytokine levels has been known to contribute to the development of diabetic cardiomyopathy (10). Both diabetes and hyperglycemia are accompanied by elevated cytokine levels, such as TNF-α and interleukin (IL)-1β, in both cardiomyocytes and/or immunocompetent cells recruited to the heart, leading to cardiomyocyte apoptosis and ultimately cardiac dysfunction (11,12). Nonetheless, further scrutiny is needed to determine if the observed suppression of inflammation and cytokine release by C66 serve as a permissive step in the combat against diabetic cardiomyopathy (Fig. 1).

Curcumin, a natural bioactive compound derived from the root of *Curcuma longa*, has been used to treat inflammatory conditions and chronic diseases (13). In addition, curcumin is also commonly used as a coloring and flavoring additive in foods. Recent studies indicate that dietary administration of curcumin may be effective in treating conditions such as cancer, Alzheimer disease, and cystic fibrosis (14,15). With regards to the mode of action, curcumin exerts a rather diverse array of metabolic, cellular, and molecular activities (15). However, certain pharmacokinetic defects, such as low bioavailability and fast metabolism, and poor chemical stability significantly limit the clinical application of curcumin. In the past decade, this group of investigators have designed and synthesized a series of monocarbonyl analogs of curcumin including C66, which exhibit overtly enhanced chemical stability and improved pharmacokinetic profiles in vivo (16). Their earlier work has depicted benefits of C66 in diabetic nephropathy via a mitogen-activated protein kinase (MAPK)-dependent anti-inflammatory or anti-ACE mechanism (17–19). Pan et al. (8) further demonstrated that C66, at a relatively low dosage of 5.0 mg/kg/day, protects against diabetic cardiac injury via JNK inhibition. Thus, discovery and identification of novel derivatives from natural active products may be an effective strategy for drug development in the management of diabetes complications. Although this study has revealed the therapeutic potential of C66 in the management of diabetic cardiomyopathy, more questions remain to be answered. First, can C66 be developed as a potential lipid-lowering agent, and if so, through which mechanism(s) in diabetic hyperlipidemia? Second, although JNK activation is well documented in diabetes and diabetes complications, the precise role for JNK in diabetes-induced hyperlipidemia remains unclear. The lipid uptake or transport proteins involved in JNK activation-induced change in lipid levels in the circulation and heart remain elusive. Last, but not least, diabetic cardiomyopathy was first described in conjunction with diabetic glomerulosclerosis by Rubler et al. in 1972 (20), and it was later recognized as a unique nosologic entity by the World Health Organization in 1995. Despite the large body of literature available on the pathogenesis, diagnostic, and therapeutic approaches for diabetic cardiomyopathy, its existence and etiology as a unique clinical entity continue to be debatable (21). Thus, whether C66

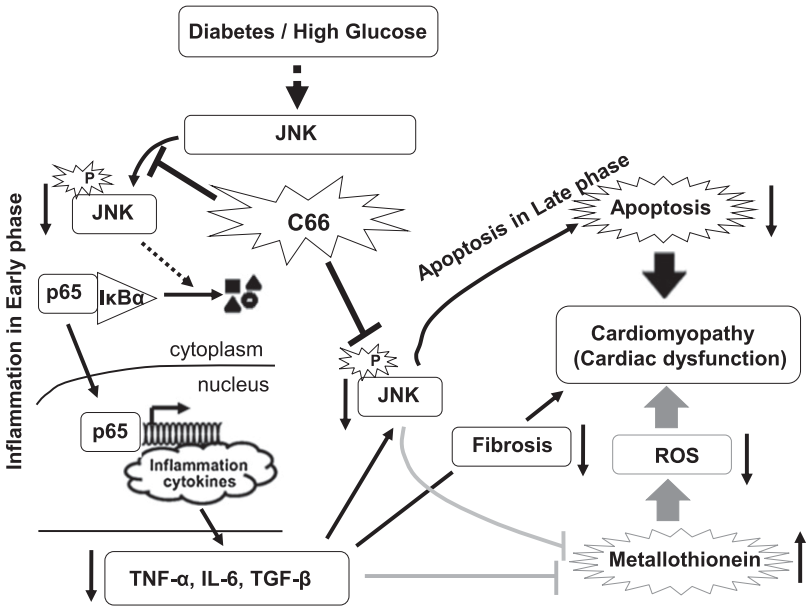

Figure 1—Schematic diagram depicting possible mechanism(s) involved in the beneficial effects offered by the curcumin analog C66 in diabetes/hyperglycemia-induced abnormalities in cardiac function, morphology, and cell survival. C66 inhibits JNK activation to interrupt inflammation and apoptosis during early and late phases of diabetes/hyperglycemia insult, respectively. In addition, C66 preserves levels of heavy metal scavenger metallothionein through JNK inhibition. IκBα, a regulatory protein that inhibits NF-κB by complexing with and trapping it in the cytoplasm; P, phosphorylation; TGF-β, transforming growth factor-β.

offered a beneficial affect specific to diabetic cardiomyopathy remains to be elucidated.

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