REVIEW

Understanding One Half of the Sex Difference Equation

The Modulatory Effects of Testosterone on Diabetic Cardiomyopathy

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Diabetes is a prevalent disease, primarily characterized by high blood sugar (hyperglycemia). Significantly higher rates of myocardial dysfunction have been noted in individuals with diabetes, even in those without coronary artery disease or high blood pressure (hypertension). Numerous molecular mechanisms have been identified through which diabetes contributes to the pathology of diabetic cardiomyopathy, which presents as cardiac hypertrophy and fibrosis. At the cellular level, oxidative stress and inflammation in cardiomyocytes are triggered by hyperglycemia. Although males are generally more likely to develop cardiovascular disease than females, diabetic males are less likely to develop diabetic cardiomyopathy than are diabetic females. One reason for these differences may be the higher levels of serum testosterone in males compared with females. Additional preclinical and clinical studies will be required to delineate testosterone’s effect on the diabetic heart. (Am J Pathol 2024, 194: 551–561; https://doi.org/10.1016/j.ajpath.2023.11.009)

Diabetes is a prevalent disease, affecting 8.8% of the world’s population.1 Patients with diabetes have an increased risk of cardiovascular diseases, including atherosclerotic cardiovascular disease and heart failure.2,3 The greater incidence of myocardial dysfunction in diabetic patients, even in those free from coronary artery disease or hypertension, indicates that diabetes negatively affects the heart independent of these pathologies.4–7 Diabetic cardiomyopathy (DbCM) is defined as a disease of the myocardium independent from hypertension or coronary artery disease.4,7,8

DbCM is characterized by left ventricular hypertrophy, diastolic dysfunction, and myocardial fibrosis, which may progress to heart failure.4,7,9,10 A study of patients from the UK Biobank Cardiovascular Magnetic Resonance Substudy found significant remodeling in all four chambers of the heart. Reduced LV and RV volumes were noted, even at an early stage of disease.11 Similarly, myocardial capillary basement membrane thickening and accumulation of lipid droplets were apparent in hearts of diabetic patients.12 Many of these effects are caused by the impact of hyperglycemia and hyperlipidemia on cardiomyocytes.4,13 The cellular mechanisms underlying DbCM are multifactorial and include oxidative stress, fibrosis, hypertrophy, and inflammation.4,13

Testosterone is a steroid hormone and the major sex hormone in males.14,15 It is produced in Leydig cells in the

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testicles, and synthesis is stimulated through the hypothalamic-pituitary-gonadal axis. The normal serum testosterone level for males ranges from 1.86 to 11.18 μg/L. Circulating testosterone diffuses through the cell membrane and binds the androgen receptor (AR) in the cytoplasm of most cells (Figure 1B). The testosterone-AR complex then translocates into the nucleus and binds androgen-response elements within the promoter regions of target genes, leading to the recruitment of coregulatory proteins and the enhanced transcription of these target genes. Impacts of testosterone include male sexual development, erythropoiesis, muscle growth, and increased bone density.

Although it has been established that estrogens play a protective role in heart function, the effect(s) of testosterone is less well-defined. A recent trial found that testosterone replacement therapy in men with hypogonadism and cardiovascular risk factors did not increase the incidence of major adverse cardiac events. However, because all patients in this study were over age 45 years, there is yet to be an adequately powered randomized control trial evaluating the use of this therapy in younger men. Additionally, males are more likely to develop cardiovascular disease than females and levels of testosterone are positively correlated with the development of heart failure in males.

There exist notable sex differences in the development and progression of DbCM. Interestingly, although males are more likely to develop diabetes than females, data pooled from 64 cohorts, including over 800,000 individuals, found that diabetic females have a greater risk of developing coronary heart disease than diabetic males. In addition, the risk of cardiomyopathy is higher in diabetic females than in diabetic males. Unfortunately, limited evidence exists from human subjects to define the impact of sex hormones on cellular processes responsible for DbCM (Figure 1A). Therefore, further research into the impact of diabetes and testosterone on cardiomyocytes is required to direct the development of more effective therapeutic strategies.

The objective of this review is to identify potential interactions between the actions of testosterone and hyperglycemia in cardiomyocytes (Figure 1A). This review focuses on four mechanisms associated with DbCM: hypertrophy, oxidative stress, inflammation, and fibrosis. Particular attention is placed on studies attempting to delineate the influence of hyperglycemia/hyperlipidemia on cardiomyocytes.

**Oxidative Stress**

Diabetes is associated with oxidative stress throughout the body, including the heart. Oxidative stress is hypothesized to contribute to cardiomyocyte apoptosis and the development of heart failure. Oxidative stress is caused by reactive oxygen species (ROS), including free radicals and hydrogen peroxide, which can react with, and damage, DNA, proteins, and lipids in cardiomyocytes. In vitro, elevated concentrations of glucose are associated with the development of ROS and apoptosis of cardiomyocytes in a concentration- and time-dependent manner. Similarly, STZ-injected animals have higher levels of ROS in the heart.

Testosterone exerts both pro- and antioxidant effects. In the presence of hyperglycemia, the removal of testosterone by castration increases STZ-associated oxidative stress in rats, whereas supplementation with exogenous testosterone reduces ROS levels. This suggests a potential antioxidant/protective role for testosterone in the context of diabetes.

Glutathione (GSH) scavenges ROS and is converted to glutathione disulfide (GSSG), in a reaction catalyzed by glutathione peroxidase (GSH-Px). STZ-injected rats have a reduced ratio of GSH:GSSG, as well as higher levels of GSSG compared with controls, suggesting increased oxidative stress. Although one study found diminished GSH-Px activity levels in the hearts of diabetic mice models, another found no difference in GSH-Px activity between STZ-injected rats and controls. In STZ-injected rats, castration lowers protein levels of GSH-Px in the heart, which is restored by testosterone supplementation. GSH-Px activity is decreased by testosterone supplementation in nondiabetic animals, concomitant to increased oxidative stress. Testosterone restored GSH-Px activity in one study, but not in another.

Catalase is an antioxidant enzyme used to detoxify hydrogen peroxide by converting it into water and hydrogen. STZ-injected rats have decreased catalase protein levels and activity, compared with control rats, as well as signs of oxidative stress. Testosterone supplementation increases catalase protein levels in the hearts of diabetic rats. By contrast, testosterone propionate injection decreases the activity of catalase in nondiabetic animals. Gonadectomy decreases catalase activity, and testosterone propionate supplementation causes a further decrease.

Mice fed a high-fat diet and injected with STZ have decreased levels of superoxide dismutase (SOD), which scavenges superoxide, a free radical. Decreased SOD activity is observed in nondiabetic mice injected with testosterone propionate; however, testosterone supplementation in the diabetic model increases SOD protein levels in the heart. The reasons for the apparent differential effects of testosterone on oxidative stress in diabetic and healthy animals need to be investigated.

Nuclear factor-erythroid factor 2-related factor 2 (Nrf2) is a transcription factor and part of a cellular defense system against oxidative stress. Nrf2 increases levels of antioxidant enzymes, such as GSH-Px, GSH, Cat, and SOD1. Cardiomyocytes cultured in high glucose and palmitate have increased Nfe2l2 (alias Nrf2) expression. In STZ-injected mice, there is a transient increase in Nfe2l2 expression and greater nuclear translocation of the protein in the presence of hyperglycemia. However, over time, reduced Nfe2l2 levels are observed compared with controls. This suggests a
Figure 1  A: Pathways involved in the pathogenesis of diabetic cardiomyopathy (DbCM), with the impacts of testosterone highlighted. Pathways positively regulated by testosterone are indicated in green, negative regulation is indicated in red, and unknown effects are represented in gray or blue. B: Testosterone signaling. Testosterone binds to the androgen receptor in the cytoplasm, forming the androgen/androgen receptor (AR) complex. Upon dimerization, this complex translocates to the nucleus, binding to androgen response elements (AREs) in the promoters of specific gene thereby regulating gene transcription. Testosterone impacts numerous metabolic pathways generally promoting hypertrophy and attenuating oxidative stress in cardiomyocytes. ADA, adenosine deaminase; AGE, advanced glycation end products; GSH-Px, glutathione peroxidase; GSK-3β, glycogen synthase kinase-3β; HDAC4, histone deacetylase-4; HO-1, heme oxygenase-1; KC, protein kinase C; MEF2, myocyte enhancer factor-2; mTOR, mammalian target of rapamycin; NFAT, nuclear factor of activated T-cells; NHE-1, sodium-hydrogen exchanger-1; NLRP3, nucleotide-binding oligomerization domain like receptor pyrin domain containing 3; NOX, NADPH oxidase; Nrf2, nuclear factor-erythroid factor 2-related factor 2; PKC, protein kinase C; RAGE, receptor for AGEs; ROS, reactive oxygen species; SOD, superoxide dismutase; TLR4, toll-like receptor 4; XO, xanthine oxidase. Figure created with BioRender.com (Toronto, ON, Canada).
Cardiomyocytes cultured in high glucose have increased TLR4 and NF-κB protein, and addition of a ROS scavenger leads to decreased TLR-4 protein expression. TLR4 mRNA and protein levels are increased in STZ-injected animals, in conjunction with oxidative stress. Gene silencing of TLR4 in STZ-treated mice leads to reduced ROS production. Evidence suggests that Nrf2 can inhibit NF-κB signaling. HO-1 is believed to be a key mediator, and HMOX1 overexpression is able to reduce NF-κB DNA binding activity in cardiomyocytes.

NF-κB signaling in cardiomyocytes is activated by testosterone through an AR-dependent mechanism, which protects against superoxide-induced apoptosis. Because oxidative stress was elicited by superoxide and not high glucose in this study testosterone’s impact in diabetes may vary. It is plausible that NF-κB has opposing effects on oxidative stress, depending on the cell conditions. For instance, anti-oxidants that are targets of NF-κB signaling include HMOX1, Gpx1 (alias GSH-Px), and SOD1 and SOD2. Conversely, NF-κB is also known to increase the expression of NADPH oxidase (NOX) subunits, which are known to generate ROS, and XO. Specifically, the protective effect of testosterone may be due to increased Akt activity, which is known to have antioxidant functions. The increase in Akt upon testosterone administration was blunted by inhibiting NF-κB signaling. However, in the context of diabetes, inhibition of Akt is well-recognized. Therefore, NF-κB signaling may be harmful in cardiomyocytes exposed to high glucose because the inhibition of Akt blunts a protective role, whereas its pro-oxidative effects remain intact.

There are some pathways through which oxidative stress is stimulated by DbCM on which the impact of testosterone has not been investigated. NOX is responsible for the generation of ROS through the production of superoxide and hydrogen peroxide. Mouse models of diabetes exhibit increased NOX expression and NOX activates NF-κB in cardiomyocytes cultured in high glucose. Advanced glycation end products (AGEs) are proteins or lipids that are glycated after exposure to elevated concentrations of glucose or as a result of oxidative stress. Knockout of the receptor for AGEs (Ager; alias RAGE) in Western diet–fed mice reduces superoxide production, suggesting that AGE accumulation also leads to oxidative stress. Similarly, cardiomyocyte exposure to AGE led to increased NF-κB nuclear translocation, decreased Nfe2l2 expression and nuclear translocation of the protein, and decreased HMOX1 expression.

**Inflammation**

Inflammation represents the body’s response to injury or infection. Inflammatory pathways are activated when pattern recognition receptors bind damage-associated molecular patterns or pathogen-associated molecular patterns.
This leads to the release of pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), and IL-1β, which activate immune cells.72 These cytokines also stimulate the expression of intracellular adhesion molecule 1 (ICAM1) and vascular cell adhesion molecule 1 (VCAM1) on endothelial cells, which allow for leukocyte migration into the tissue, enhancing the inflammatory response.72

In the context of myocardial damage, cardiomyocytes are one of the first cells to show inflammatory activity, with the release of pro-inflammatory cytokines leading to recruitment of circulating immune cells.73 Inflammation in diabetes is stimulated by hyperglycemia and high concentrations of free fatty acid in the blood.73 Evidence suggests that oxidative stress may mediate the progression from hyperglycemia to inflammation.74,75 Inflammatory activity in the myocardium can lead to fibrosis, which leads to myocardial stiffness and diastolic dysfunction.76

The presence of sex differences in the occurrence inflammatory disease is well-established, with women generally at a greater risk than men.77 Some clinical trials of testosterone replacement therapy have identified an inverse relationship between testosterone levels and proinflammatory cytokines, whereas others have found no relationship.78 Focusing on the relationship between testosterone levels and proinflammatory cytokines, there is a paucity of work examining the modulatory effects of its modulation on the pathogenesis of DbCM. Although testosterone is known to modulate immune cell activity, there is a paucity of work investigating the impact of testosterone on cardiomyocyte-specific inflammation, in the context of diabetes or otherwise.79 One study found that testosterone increased levels of TNF-α in cardiomyocytes; however, the mechanisms responsible for this were not investigated.80

Tissue factor (TF) is a protein involved in the stimulation of the coagulation cascade. It is expressed at high levels in cardiomyocytes and is also believed to be involved in the pathology of DbCM.81 STZ-injected mice expressing reduced levels of TF have attenuated IL-6, and TLR4 expression compared with STZ-injected mice expressing normal levels of TF.82 Given the potential inhibitory role of testosterone on TF through androgen-dependent tissue factor pathway inhibitor-regulating protein (ADTPR), inhibition of TF represents one way in which testosterone may inhibit inflammation associated with hyperglycemia.83,84 ADTPR expression is increased through testosterone/AR binding to its promoter region. Although expression of this protein is confirmed in the heart, no research has been done on its direct impact on cardiomyocytes.83,84

Cardiomyocytes cultured in high glucose have increased NFKB1 (alias NF-κB) expression.85 Similarly, inhibition of NF-κB in STZ-injected rats leads to reduced TNF-α and IL-2.86 Knockdown of TLR4 expression using siRNA in STZ-injected mice leads to decreased cardiac levels of mRNAs encoding TNF-α, IL-1, ICAM-1, and VCAM-1.87 AGEs have been shown to increase NF-κB activation and TNF (alias TNF-α) expression in cardiomyocytes.71 Knockout of Ager reduces the expression of NFKB1, TNF, and IL6 in left ventricular homogenates of mice fed a high-fat diet.70 Because cardiomyocytes were not isolated, the extent to which cardiomyocyte-specific inflammatory activity is reduced by Ager blockade remains uncertain. AGE can also elicit inflammation through TLR binding. TLR4 binds AGE, which leads to increased NF-κB activity and increased IL-6 and TNF-α mRNA. These changes were blunted by inhibition of TLR4 binding to AGE.88 Overall, these results suggest that hyperglycemia and hyperlipidemia can trigger NF-κB signaling in cardiomyocytes, leading to the expression of proinflammatory cytokines.

Diabetes/hyperglycemia can also induce inflammation through activation of the nucleotide-binding oligomerization domain like receptor (NLR) pyrin domain containing 3 (NLRP3) inflammasome. This leads to the secretion of IL-1β and IL-18, which enhance inflammation.88,89 Cardiomyocytes cultured in high glucose display increased cell death, increased NLRP3 expression, and secretion of IL-1β, TNF-α, and IL-18.74,75 In STZ-injected and high-fat diet–fed rats, IL-1β expression and NLRP3 expression are higher relative to controls.75

Cytokines released by inflammation may also have an effect on cardiomyocytes. Whether IL-6 induces or protects against apoptosis in cardiomyocytes is controversial.90,91 Testosterone blunts the increase in cleaved caspase 3 in response to IL-6 administration, but has no impact on other apoptosis-associated proteins.91 TNF-α and IL-1β induce apoptosis in cardiomyocytes, whereas TNF-α, IL-1β, IL-6, and IL-18 promote hypertrophy.92 There is also evidence that inflammation can lead to reduced testosterone levels.92,93

Protein kinase C (PKC) is a serine/threonine kinase.94 Protein levels of PKC-β1, β2, and α, as well as total PKC activity, are increased in failing human hearts compared with healthy controls.95 Cardiomyocytes cultured in high glucose have increased expression of PKC-α and PKC-β2, and nuclear translocation of the protein. Inhibition of PKC reduces NFKB1 expression and protein nuclear translocation, and decreases TNF-α levels.85 This suggests that PKC is upstream of NF-κB. Because testosterone-AR signaling increases levels of PKCβ, the effects on inflammation in the context of diabetic models are worthy of investigation.86

Oxidative stress can directly cause inflammation in cardiomyocytes, and resolving oxidative stress inhibits NLRP3 activation in cardiomyocytes cultured in high glucose.74,75 Similarly, HO-1 appears to be protective against inflammation. Systemic overexpression of HMOX1 in STZ-injected mice ablates cardiac inflammation.47 Stimulation of HMOX1 expression by testosterone may therefore attenuate inflammation in DbCM.

Hypertrophy

Cardiac hypertrophy involves the increase in size of individual cardiomyocytes leading to an increase in overall
myocardial mass. This often occurs in response to mechanical pressure and can be a nonpathological process associated with stimuli such as exercise or pregnancy. However, if hypertrophy interferes with cardiac function due to being prolonged or excessive in nature, it is known as pathological cardiac hypertrophy.4

Epidemiological evidence suggests that hypertrophy is associated with diabetes, independent of hypertension.4 In fact, DbCM is first characterized by left ventricular hypertrophy leading to diastolic dysfunction.6,20 Hypertrophy is noted in cardiomyocytes cultured in high glucose and animal models of diabetes, suggesting that hyperglycemia directly contributes to hypertrophy.98 There is much evidence to suggest that testosterone promotes the development of myocardial hypertrophy.96,99–104

Mammalian target of rapamycin (mTOR) is a serine/threonine kinase, involved in increasing protein synthesis. In the case of cardiomyocytes, mTOR regulates hypertrophy in response to pressure.8,105 Administration of testosterone to isolated cells or animals increases cardiomyocyte hypertrophy through mTOR activation.99,101 However, there is a paucity of data on the potential role of mTOR in DbCM.106 mTOR inhibition attenuates hypertrophy in animal models of diabetes, but whether mTOR activity is actually elevated in the context of diabetes may depend on the type of model used.107,108

Nuclear factor of activated T-cells (NFAT) is a transcription factor known to promote hypertrophy,109 and cardiomyocytes cultured in high glucose have increased nuclear NFAT levels. However, the dependency of hypertrophy in cells cultured in high glucose on NFAT signaling has not been investigated.110 Testosterone enhances NFAT activity in cardiomyocytes.104 Glycogen synthase kinase-3β (GSK-3β) is a protein kinase associated with anti-hypertrophic activity.111 GSK-3β phosphorylates serine residues on NFAT, promoting its export from the nucleus.112 Testosterone promotes the phosphorylation/deactivation of GSK-3β, through a PI3K/Akt-dependent pathway. In fact, the hypertrophic effects of testosterone depend on GSK-3β phosphorylation.104 Conversely, inhibition of GSK-3β in STZ-injected rats diminishes hypertrophy.86 However, the chemical used to inhibit the GSK-3β pathway (meisoindigo), also inhibits Wnt/β-catenin, which may have been responsible for the anti hypertrophic effects.86

Myocyte enhancer factor—2 (MEF2) is a transcription factor associated with myocardial hypertrophy.113 Testosterone-induced hypertrophy in rats and isolated cardiomyocytes is dependent on MEF2 nuclear translocation and signaling. These effects are dependent on AR-binding.114

Calmodulin-dependent protein kinase II (CaMKII) mediates cardiac pathology, including DbCM.115,116 CaMKII can bind and phosphorylate histone-deacetylases (HDACs) present in the heart, including HDAC4. This results in the shuttling of HDAC4 out of the nucleus. HDAC4 is involved in suppression of MEF2 signaling, so its removal from the nucleus can increase MEF2 transcriptional activity.114,117 Testosterone-associated hypertrophy is dependent on CaMKII activity.114 Increased nuclear NFAT and decreased nuclear HDAC4 are noted in a rat model of diabetes.118 Although this suggests that diabetes may activate these pro-hypertrophic pathways, no hypertrophy was noted in this model. Overall, more work must be done to investigate the role of NFAT and HDAC4 in DbCM, especially in models presenting with hypertrophy. Similarly, whether HDAC4 mediates the dependency of testosterone-NFAT signaling on CaMKII should be further investigated.

Hypertrophy in cells exposed to elevated concentrations of glucose is dependent on PKC activation.98 Inhibition of PKC-β prevents hypertrophy in diabetic animal models.86,119 Elevations in maternal testosterone increase cardiac hypertrophy in rat offspring, concomitant with high cardiac levels of PKCδ, dependent on AR-testosterone signaling.96 TF is increased in the hearts of diabetic mice. Reduced expression of TF is linked to attenuated hypertrophy in STZ-injected mice.82 Because TF is linked to hypertrophy in models of diabetes, ADTPR may have an antihypertrophic role.

Increased Na+/H+ exchanger 1 (NHE1) activity is noted in hearts from mouse models of type 2 diabetes.120 SLC9A1 (alias NHE1) overexpression in mice is associated with increased nuclear NFAT and decreased nuclear HDAC4, as well as cardiac hypertrophy, whereas inhibition of NHE1 activity reduces cardiac hypertrophy.121–123 Whether testosterone regulates NHE1 activity in cardiomyocytes is not known.

Inhibition of XO activity leads to decreased cardiomyocyte hypertrophy in mice fed a high fat diet.54 Testosterone administered to late-gestational rats increases cardiac ADA and XO activity.55 However, hypertrophy was not directly measured in this study.

Inflammatory pathways may also lead to hypertrophy in DbCM, although crosstalk with testosterone has not been explored. Inhibition of NF-κB attenuates hypertrophy in high-glucose—cultured cardiomyocytes or in the myocardium of STZ-injected mice.36,38 AGEs increase hypertrophy in cardiomyocytes and knockout of the receptor for AGEs (Ager) leads to decreased cardiac hypertrophy in mice fed a high-fat diet.70 Silencing of TLR4 in STZ-injected mice decreases hypertrophy, providing further evidence for the inflammation—hypertrophy theory in diabetic animal models.87

Oxidative stress is also believed to be a cause of myocardial hypertrophy.23 Overexpression of the antioxidant HMOX1 in cardiomyocytes protects against hypertrophy.82 Similarly, PKC-β inhibition in STZ-injected rats leads to improvements in both myocardial hypertrophy and oxidative stress.124 Myocardial hypertrophy in the presence of hyperglycemia may occur due to inflammation or oxidative stress, so preventing oxidative stress in diabetic hearts may decrease hypertrophic remodeling.
Fibrosis

Cardiac fibrosis has been noted in patients and animal models of diabetes. Collagen I and II deposits and increased tissue growth factor (TGF)-β are noted in both the right and left ventricles of patients and experimental models. AGES, oxidative stress, and inflammation stimulate myocardial fibrosis. The role of increased myocardial fibroblast activity in the production of fibrosis in DbCM is well-established, but there are less data focused on the role of cardiomyocytes.

One theory is that the replacement of dead cardiomyocytes with fibrous tissue leads to increased myocardial fibrosis in DbCM. Cardiomyocyte apoptosis is largely triggered by oxidative stress and inflammation, as reviewed earlier. Additionally, hyperglycemia may cause the release of cytokines which stimulate other cells to produce fibres. Cardiomyocytes cultured in elevated concentration of glucose or glucose and high fatty acid exhibit increased expression of TGFβ, which is known to lead to fibroblast activation. IL-6 is also known to increase TGFBI expression, suggesting that inflammation may be responsible for this effect. Testosterone supplementation is insufficient to prevent IL-6–induced increased TGFBI expression, but this does not rule out a protective role against fibrosis through other pathways. It is also possible that the cardiomyocytes are secreting collagen and actin, directly causing myocardial fibrosis. Both hyperglycemia or hyperglycemia/fatty acids lead to increased collagen I and III and z-actin expression in cardiomyocytes.

The inhibition of Nrf2 signaling is believed to be responsible for the induction of fibrosis in high-glucose environments. As mentioned previously, early stages of diabetes entail increased Nfe2l2 expression, which is reversed as the disease progresses. Knockdown of Nfe2l2 is associated with increased expression of z-smooth muscle actin and collagen I. Unfortunately, the impact of testosterone on Nrf2 signaling is not known.

Similarly, NF-kB signaling may be responsible for fibrosis in DbCM. Inhibition of NF-kB in STZ-injected rats decreases myocardial fibrosis. GSK-3β inhibition in STZ-injected rats reduces myocardial fibrosis. AGE exposure increases cardiomyocyte expression of collagen I and TGF-β1. These cells also display greater NF-kB and GSK-3β activation, as well as decreased Nrf2 activation.

In addition to inflammation and oxidative stress, PKC may be involved in fibrosis, because inhibition of PKC-β in STZ-injected rats leads to decreased collagen I compared with controls. The putative protective effect of Nrf2 and detrimental roles of GSK-3β, NF-kB, and PKC in the stimulation of cardiomyocyte fibrosis is in concordance with their effects on inflammation and oxidative stress pathways. Evidence from animal models suggests that oxidative stress causes myocardial fibrosis to which cardiomyocytes may contribute.

Although evidence suggests that testosterone promotes myocardial fibrosis, no studies have investigated the direct impact of testosterone on the induction of fibrosis in cardiomyocytes. Similarly, the extent to which cardiomyocyte matrix protein expression and profibrotic cytokine expression actually increases myocardial fibrosis in an in vivo context cannot be inferred from studies using isolated cardiomyocytes.

Table 1 Summary of Animal Models Used to Study Diabetic Cardiomyopathy

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<thead>
<tr>
<th>Animal model</th>
<th>Observed effects</th>
<th>Effect of testosterone</th>
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<tr>
<td>STZ-injection</td>
<td>Increased oxidative stress</td>
<td>Decreased oxidative stress</td>
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<tr>
<td></td>
<td>Reduced antioxidant defense</td>
<td>Increased antioxidant defense</td>
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<tr>
<td></td>
<td>Inflammation</td>
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<tr>
<td>(mRen-2)27 transgenic rats injected with STZ</td>
<td>Increased oxidative stress</td>
<td>NR</td>
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<td></td>
<td>Increased fibrosis</td>
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<td></td>
<td>Increased hypertrophy</td>
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<tr>
<td>High fat/fructose diet (Western diet)</td>
<td>Increased oxidative stress</td>
<td>NR</td>
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<td>Increased inflammation</td>
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<tr>
<td>Obese db/db mice</td>
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<tr>
<td>Hyperamylinemia</td>
<td>Increased hypertrophic signaling</td>
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<tr>
<td>GK (Goto-Kakizaki) rats</td>
<td>Increased hypertrophy</td>
<td>NR</td>
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NR, not reported.
Conclusion and Future Directions

Overall, there is limited work directly investigating the impact of testosterone in animal models of diabetes. Given the presence of sex differences in the development of DbCM, it is important to investigate the potential impact of sex hormones such as testosterone on the development of this condition. Because evidence suggests that the impact of testosterone is dependent upon glycemic status, it is difficult to infer the role of testosterone in DbCM based on studies in nondiabetic animals (Table 1). Therefore, the influence of testosterone on the development of DbCM must be investigated by examining how testosterone administration directly impacts this pathology.

Disclosure Statement

None declared.

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