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EFFECT OF DIABETES MELLITUS ON HEART FAILURE – A REVIEW

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ABSTRACT

Diabetes mellitus, a group of metabolic disorders is characterised with hyperglycemia because of insufficient insulin production or loss of insulin sensitivity of the cells. Heart failure patients with diabetes are associated with higher adverse events compared to those without diabetes. Pathophysiological changes associated with diabetes includes structural and functional alterations, metabolic disturbances such as insulin resistance, vascular disease, endothelial dysfunction, myocardial fibrosis, oxidative stress, accumulation of advanced glycation end products, impaired calcium homeostasis, free fatty acid metabolism, activated leukocytes, cardiac autonomic dysfunction lead to heart failure. American Diabetes Association recommends life style changes along with monotherapy of metformin. Preventive measures of heart failure are the possible initial approaches which would result in positive outcomes. Insulin has positive inotropic effects (increased intra cellular calcium concentration), antioxidant effects (increase the activity of antioxidant enzymes), antiapoptotic effects, anti-inflammatory effects (prevent leukocyte adherence to endothelium) and vascular effects. Considering the therapeutic effects and adverse events, SGLT-2 inhibitors should be used as primary choice of drugs in patients with DM & HF. Our review focusses on pathophysiological events of DM, treatment patterns and non-pharmacological (life style changes &).

KEYWORDS: Heart Failure, Diabetes, Pathophysiological Effects.

INTRODUCTION

Definition: Diabetes mellitus is a metabolic disorder characterised by hyperglycemia due to the deficiency of insulin or decreased secretion of insulin or decreased action of insulin.[1] Heart failure is a clinical syndrome caused by the inability of heart to pump sufficient blood to meet the metabolic needs of the body or Heart failure is a progressive clinical syndrome that results from any disorder; that impairs the ability of the ventricle to fill with or eject the blood thus render the heart unable to pump blood at a rate sufficient to meet the metabolic demands of the body.

Epidemiology: Diabetes is a factor for cardiac diseases affecting heart muscles leading to systolic and diastolic HF. On estimation, 366 million people had DM in 2011, which would rise to 550 million by 2030 (2). In the year 2000, India topped the world with highest number of diabetics (31.7 million) followed by China (20.8 million), US (17.7 million). By 2030, DM may rise to 79.4 million in India.[2]

A survey by Kaiser permanente database has shown that patients with diabetic HF approximately doubled from 33 cases /1000 - 45 to 54 years to 68 cases/1000 – 55 to 64 years age group and again 135 cases/1000 – 65 to 74 years.[3] Heart failure incidence were two fold higher in diabetic men and five fold higher in women.[4] Incidence of HF was 30.9 per 1000 people in patients with diabetes and 12.4 per 1000 people in subjects without diabetes.[5] The prevalence of DM in patients with HF was increased from 12.3% (1993-1998) to 21.1% (2003-2007) (6). It was recently found that with each 1% increase in HbA1c there is a 30% risk of developing HF.[7]

Pathophysiology

I. Structural alterations of myocardial cells: Atheroma in patients with diabetes is more extensive and atheroma diffuse involving distal vessels in both the coronary & peripheral circulation. Pathological and anatomical alterations of microvascular and myocardial endothelium involves increased adhesiveness, impairment of relaxation, fibrinolysis & permeability. Causes such as hypertrophy of myocardial cells, interstitial and perivascular fibrosis, increased thickening of the capillary basement membrane and formation of microaneurysms in the small capillary vessels result in LV hypertrophy. The reduction of blood supply form microvascular disease & vasa varosum effect in diabetics further results in the damage of small and medium arterioles of diabetic heart.[8]

II. Functional alterations of Diabetic cardiomyopathy (DCM)

Reduced left ventricular ejection fraction is the main cause of systolic myocardial dysfunction. Altered diastolic functioning of left ventricle appears in diabetic population and is responsible for 30% of patients ending up with symptomatic HF and diabetes. Raised circulatory advanced glycated end products (AGE) and increased production of ROS results in the accumulation of collagen in myocardium which leads to myocardial fibrosis further leading to diastolic dysfunction. Failure of diastolic relaxation of left ventricle results in the reduction of filling and cardiac reserve on exercise. Left ventricle hypertrophy, myocardial dilation results in the left ventricle diastolic and systolic dysfunction.[8]

III. Metabolic disturbances

A. Insulin resistance: DM is characterised by insulin resistance. Insulin resistance develops in multiple organs such as skeletal muscle, liver, adipose tissue and heart. Obese patients have increased plasma levels of free fatty acids and inflammatory mediators derived from the adipose tissue bind to toll like receptors and activate NF-KB. This triggers inflammation which leads to upregulation of inflammatory genes, IL-6, TNF-alpha. Free fatty acids activate toll like receptors leading to phosphorylation of insulin receptor resulting in down regulation of GLUT-4 causing insulin resistance. Insulin resistance associated with increased free radicals leads to decreased production of NO and bioavailability which leads to reduced cellular levels of NO which facilitates pro inflammatory markers. The insulin signaling is lost in vascular endothelial cells leading to endothelial dysfunction that cause expression of adhesion molecules and atherosclerotic plaque. Damage to insulin receptor in the vascular endothelium decrease glucose uptake by skeletal muscle. Aggregation of platelets is faster in diabetics than healthy individuals.[9]

B. Vascular disease: Persistent hyperglycemia with other conditions like arterial hypertension, dyslipidemia as well as genetic susceptibility are the major causes of vascular disease.[9] This includes.

i. Microvascular: Structural and functional alterations of small vessels lead to HF in diabetics.[4] In general, vascular smooth muscle receives continuous regulatory nerve signals and receive NO from endothelial cells and have continuous flow of metabolic products. Hyperglycemia results in the inhibition of NO production in arterial endothelium. In diabetes, NO bioavailability is reduced either due to insulin deficiency or insulin resistance in endothelial cells.[10] In diabetics, thickening of capillary basement membrane and interstitial

fibrosis was significantly found greater on biopsy when compared to control subjects.[4] The resultant effects of diabetes are defects in the autonomic nervous system, endothelium and local metabolism leads to microvascular disease.[10] Autopsy studies reveals that endothelial and sub endothelial proliferation with fibrosis is seen in coronary micro vessels.[4]

ii. Macrovascular: Plasma of diabetics contain high triglycerides & low HDL cholesterol. Small LDL particles can easily penetrate & strongly adhere to arterial wall than large LDL particles thus small LDL are more atherogenic & more susceptible to oxidation. Oxidized LDL is proatherogenic because the particles once get oxidized acquire new properties which are recognized as foreign particle by immune system. This oxidized LDL produces multiple abnormal biological responses like attracting leukocytes to intima of vessel, improving the ability of leukocytes to ingest lipids, differentiate into foam cells. Foam cells stimulating the proliferation of leukocytes, endothelial cells & smooth muscle cells, all these steps are involved in formation of atherosclerotic plague.[10]

C. Endothelial dysfunction: Blood vessel tone, platelet activation, leukocyte adhesion, thrombogenesis and inflammation are regulated by endothelium. Vasodilatory, antiatherogenic and anti-inflammatory are net effects of healthy endothelium.[10] Endothelial dysfunction is seen in the coronary vessels of diabetics that lead to reduced blood flow. Reduced levels of plasma nitric oxide is induced by high glucose concentration in diabetics. Hyperglycemia causes down regulation of NO synthase and NO production. Dysfunction of endothelium impairs not only NO but also increases the synthesis of vasoconstrictors & prostaglandins. Reduction of antioxidative defence decreases NO bioavailability in diabetics which is assosciated with increased vascular oxidative stress. Free radical superoxide react with endothelium derived NO and inhibits eNOS. This is one of most important interaction mechanism involved in the endothelial dysfunction in diabetic patients.[4] Acute hyperglycemia may impair endothelial derived vasodilation in healthy humans.[11]

D. Myocardial fibrosis: Abnormal gene expression and abnormal signal transduction caused by hyperglycemia may activate the pathogen leading to apoptosis. Hyperglycemia may even directly includes necrosis of myocytes which result in depletion of collagen.[4]

E. Oxidative Stress: Poor glycemic control in diabetics leads to chronic hyperglycemia. Elevated levels of glucose with in the cell undergoes oxidation and stimulates production of ROS & increases oxidative stress. Increased ROS species cause oxidation and modification

of the structure of cellular proteins, nucleic acids & membrane lipids. Damage to cellular structure & impairment of cellular functions leads to necrosis and activation of genes that damage cell. High levels of ROS species results in cardiac dysfunction with a sufficient decrease in effectiveness of antioxidant defense.[4] Immune system produces ROS as a way to destroy pathogens. Oxidative stress occurs when the cellular production of ROS exceeds the capacity of anti-oxidant defenses with in the cells.[10] Activity of anti-oxidative enzymes and endothelial nitric oxide synthase are inhibited by protein nitrosylation. Reduction of NO bioavailability is a predictor of CVS problems. Reduced NO & oxidation of free fatty acids stored intracellularly generates ROS leading to vascular inflammation. Endothelial dysfunction in diabetes is due to impaired NO bioavailability and increased synthesis of vasoconstrictors & prostanoids. Mitochondrial ROS increases intracellular glucose metabolites, AGE synthesis & Methyl glycol.[9]

F. Accumulation of advanced glycation end products (AGE): Mitochondrial ROS rises the intracellular glucose metabolites. Methylglyoxal play a major role in pathophysiology of diabetic complications via ROS, endothelial pathway & AGE accumulation. Generation of AGE stimulates AGE receptors and cause cellular damage.[9] Hyperglycemia cause glycation of numerous macromolecules. Accumulation of AGE in the tissue results in morphological changes of heart. AGE accumulation causes decrease in elasticity of vessel wall and myocardial dysfunction.[4]

G. Impaired calcium homeostasis: Cardiac contractility is majorly regulated by intracellular calcium. Any disturbance in calcium homeostasis contributes to alteration in cardiac performance. Decreased response of ATPases decreases the ability of sarcoplasmic reticulum to take up calcium, decreased activities of sodium-calcium & calcium-ATPase contribute to this effects. Diabetes reduced activity of sarcoplasmic reticular calcium pump & diminished rate of calcium removal from cytoplasm in diastole, may be responsible for diastolic dysfunction.[4]

H. Free fatty acid metabolism: In normal conditions free fatty acids are the primary source of energy for myocytes, glycolysis is important for aerobic exercise and is increased during ischemia. In diabetics, glucose metabolism is altered along with the increased myocardial oxygen consumption & increased free fatty acid in serum. Factors that limit glucose utilization in diabetics are slow rate of glucose utilization & transport into myocardium is associated with depletion of glucose transporters GLUT 1 & 4. Metabolism of high levels of

free fatty acids uses high oxygen & results in intracellular accumulation of toxic intermediates which influence myocardial performance negatively by reduced availability of ATP (4). Free fatty oxidation produce high levels of citric acid which inhibit fructokinase leading to reduction of glycolysis & promotes synthesis of glycogen which in turn leads to lactic acid accumulation there by promote free fatty acid degradation. Lack of defense response in Diabetic Cardiomyopathy leads to Myocardial ischemia or injury & includes early impairment of diastolic dysfunction.[11]

I. Inflammation – activated leukocytes

Reactive oxygen species are produced by activated leukocytes & mitochondria. Hoko ma *et al* found that the expression significantly increased in diabetes.[10] Inflammatory response involves leukocyte activation mediated by cytokines & chemokines. In diabetic & prediabetic state immune activation occurs, followed by insulin resistance which ultimately are the factors that initially increases the cardiovascular risk. Abnormalities such as reduced vasodilator production, increased vasoconstrictor secretion & growth factor endothelin subjects with metabolic syndrome enhance vasoconstriction associated with release of pro-inflammatory cytokines. These pro-inflammatory markers exacerbate injury in various mechanisms including vascular permeability, apoptosis, increased ROS & invasive leukocyte.[10]

J. Cardiac autonomic dysfunction (CAN)

Diabetics with impaired autonomic function show higher HR than nondiabetics.[11] In diabetics CAN is associated with high CV risk and may contribute to impaired diastolic function. CAN in diabetes is responsible for abnormal vasculature response of coronary vessel. Abnormality in sympathetic innervation of heart might be responsible for abnormalities in LV filling. Systolic & diastolic dysfunction in T2DM was related to altered sympathetic function.[4] Several studies have confirmed that cardiac neuropathy has the propensity to cause a reduction in cardiac ejection fraction ; impair systolic dysfunction & decrease diastolic filling, thus having an important contribution to the deterioration of diastolic myocardial function & DCM. Cardiac autonomic neuropathy is portrayed by a significant decrease in HR variability & an abnormality in parasympathetic-sympathetic balance, in which decrease in parasympathetic tone secondary to autonomic neuropathy leads to relative over activity of sympathetic system. Resting tachycardia interfere by reducing the heart's pumping ability into peripheral circulation and also interfere with ventricular

chambers capillary to fill the blood. Ventricular tachycardia interfere by reducing the time of ventricular filling and interfere the timely atrial contraction.[8]

In conclusion CAN is associated both strongly and independently with functional and structural pathogenic substrate of DCM in both T1 & T2 Diabetics. This is explained partially by significant reduction in HR and alteration in parasympathetic-sympathetic balance of heart, leading to parasympathetic reduction and sympathetic overactivity.[8]

Treatment goals of diabetes

✓ The main goal for treatment of diabetes is to maintain blood sugar under control.

✓ To prevent micro and macrovascular complications.

Treatment of Diabetes Mellitus

Start with monotherapy

Monotherapy: Metformin is usually given in a dose of 500-1000mg OD to BD with a max dose 2250mg/day. Side effects includes muscle pain, weakness, lactic acidosis, diarrhoea, abdominal pain.

Dual therapy

If HbA1C is greater than or equal to 9% dual therapy is preferred. If HbA1C target not achieved after 3 months, dual therapy is recommended. Metformin and SU or TZD or DPP4 I or SGLT2 I or GLP 1 RA or Insulin. If HbA1C is greater than or equal to 10% i.e., blood glucose is greater than or equal to 300mg/dl.

Triple therapy

If HbA1C target did not achieve after approximately 3 months proceed to triple therapy. Metformin + SU+TZD / DPP4 I / SGLT 2 I / GLP 1 RA/ Insulin. If HbA1C target did not achieve after 3 months, switch to combination injectable therapy.[15]

Treatment of Diabetes in Patients with HF

In the Framingham study, patients had a risk of HF 2.4 fold and 5 fold in males and females respectively. Lower the glycemic control, higher will be the risk of heart failure. If there is increase in HbA1C by 1%, there will be the increase in the risk of HF by 8%. The prevalence of HF in elderly diabetic patients was approximately 20%. Diabetics with pre-existing HF had a higher CV risk compared with those without HF.[12]

Insulin

Patients with diabetes and heart failure need insulin as either monotherapy or in combination with other hypoglycemic agents in order to achieve adequate blood glucose level.[12] Insulin has anti natriuretic action which leads to the raised sodium and fluid retention in diabetics. The consensus group gave a neutral position to insulin in patients with diabetes and HF.[13]

Positive inotropic effect of insulin: Insulin has a direct positive ionotropic effect which is not dependent on its modulation of its glucose metabolism. Increased intracellular calcium levels mediates this effect. Insulin phosphorylates the heat shock protein 27 which associates with the actin filaments in the cardiomyocytes. It has the major role in the maintenance of the structure and function of the cells. The phosphorylated heat shock protein 27 is associated with improved myocardial contractility.[14]

Antioxidant effect of insulin: Compromised insulin signaling has shown the increase in oxidative stress and mitochondrial dysfunction. Insulin acts by decreasing the formation of peroxy nitrite free radical there by checks the oxidative destruction. Insulin elevates the antioxidant enzymatic activity in the myocardium.

Antiapoptotic effect of insulin: Anti apoptotic processes are carried out by the translocation and binding of intracellular hexokinases to the mitochondrial membrane. Firstly, decreased oxidative damage to the cell is caused by the suppression of free radical generation and then inhibits the release of cytochrome C from the mitochondrion into the cytosol.[14] This prevents the opening of mitochondrial permeability transition pores. Unbinding of hexokinase from the mitochondria leads to the mitochondrial permeability transition pores to open which causes the greater permeability of mitochondrial membrane further leads to mitochondrial swelling and apoptosis. Akt gene mediates the association of hexokinase to the mitochondrial membrane. Insulin inhibits the apoptosis by the upregulation of eNOS and NO.

Anti-inflammatory effect of insulin: Insulin shows anti-inflammatory where as hyperglycemia shows proinflammatory. Anti -inflammatory effect is associated with to its anti-oxidant. Insulin has shown to inhibit leukocyte adherence to endothelium. This avoids leukocyte aggregation in the myocardial wall &attenuate inflammation.

Vascular effect of insulin: Insulin increases blood flow to myocardium & coronary sinus reducing coronary resistance. Insulin induced coronary vasodilation is associate with NO

synthesis. Insulin upregulates expression of eNOS and thus facilitates vasodilation. It also shows cardioprotective effects by glucose dependent and independent mechanisms. The use of insulin should be reserved for patients whose blood glucose cannot be controlled by safer drugs.[14]

Table. 1: Oral hypoglycemics.

Class of drugs	Examples	Dose	Side effects	Other information
Biguanides	Metformin	Initial dose 500mg PO OD, maximum dose 2550mg/day	Lactic acidosis, Weight gain,	The consensus group gave a high priority to metformin in patients with DM & stable HF[13]
SGLT-2 inhibitors	Dapagliflozin	Initial dose 5mg PO OD	Weight gain, UTI, AKI, DKA, fracture, dehydration	It is recommended that SGLT-2 inhibitors are the first line therapy in with DM &HF
DPP-4 inhibitors	Sitagliptin Saxagliptin	50-100 mg 2.5-5 mg	HF	DPP-4 is given. Reduce neutral position in patients with DM & HF.
Glinides	Nateglinide	0.5-2 mg	HypoglycemiaGIT disturbances,	Given a neutral position
GLP-1receptor agonist	Liraglutide Semaglutide	0.6-1.8 mg (SC once daily) 0.25-1 mg (SC once a week)	Weight gain, GI	This class was given neutral position in patients with DM & HF.
Sulfonylureas	Glimepride Gliclizide Glipizide	1-8 mg 40-80 mg 5-40 mg	Hypoglycemia weight gain	This class was given a neutral position for the treatment of DM & HF.[13]
Thiazolidinediones (TZD's)	Rosiglitazone Pioglitazone	4-8 mg 15-45 mg	Hypoglycemia weight gain edema, fractures	TZD's should not be used in patients with symptomatic HF and should be discontinued when HF appears.
Alpha glucosidase inhibitors	Acarbose Voglibose Miglitol	25-100mg 0.2mg 25-50mg	Flatulence, abdominal bloating & diarrhoea	Given a neutral position & did not given high priority due to GI effects.

Table. 2: Treatment of Heart Failure.

Class of drugs	Examples	Initial Dose	Max. dose	Side effects
Beta blockers	Metoprolol Carvedilol	12.5-25mg QD 3.125mg BID	200mg QD 50mg BID	Masks the symptoms of hypoglycemia, elevates the conditions like insulin resistance.
ACE-inhibitors	Captopril, Enalapril	6.25mg TID 2.5mg BID	50mg TID 10-20mg BID	Dry cough, fatigue, dizziness, loss of taste
Diuretics	Spironolactone	12.5-25mg QD	25mg QD or BD	Enhances insulin resistance
Angiotensin receptor blockers	Losartan Valsartan	25-50mg QD 20-45mg TID	50-150mg QD 160mg BID	Confusion, diarrhea, Hyperkalemia

Life style modifications

➢ Overweight diabetic patients must limit the fat intake. Patientsmust be encouraged to do

regular physical activity like brisk walking for 35-45 mins every day.

➢ Avoid smoking. This shows an immediate and lasting benefits in diabetics with heart failure.

Table. 3: Diet Plan for Diabetes Patients.

Food item	Amount	Protein (gm)	Calories (k.cal)
Early morning	-		-
Fenugreek seeds with 1 cup of water	One cup	-	-
Tea (without sugar)		4	35
Marie biscuits	2	1	56
Breakfast			
Stuffed methi/ palak paratha	2 (small size)	7	200
Curd (or)	50 gm (1 cup)	3	30
Egg white/paneer bhurji	1 medium bowl	6	130
Plain roti (no oil)	2 small	3	150
Mid- morning			
Apple / guava/ orange	1	-	40
Lunch			
Salad (10 min before lunch)	1	-	85
Capsicum + ghobi veg.	1 medium bowl	1	130
Dal	1 soup bowl	6	175
Phulka (no ghee)	2	6	
Evening			
Milk / green tea/ herbal tea / lemon water.	1 cup	2	35
Roasted chana	1 cup	5	85
Dinner			
Salad (10 min before dinner)	2	4.5	150
Phulka (no ghee)			
Lauki veg	1 cup	2	85
Curd	1 cup	3	30
Late night			
Skimmed milk (no sugar)	1 glass	4	120
Total	-	**49.5**	**1286**

CONCLUSION

Development of HF in patients with DM is responsible for increase in mortality. The pathophysiological changes occurred in DM are insulin resistance, microvascular, vascular changes, endothelial dysfunction, myocardial fibrosis, oxidative stress, accumulation of AGE, impaired calcium homeostasis, free fatty acid metabolism, activated leucocytes along with structural and functional changes in the combination with systolic and diastolic dysfunction. Considering all the side effects and therapeutic efficacy, the preferred class of drugs in patients with diabetes & HF are SGLT-2 inhibitors and biguanides. Life style changes such as regular physical activity and dietary modifications may be beneficial. Maintaining tight

glycemic control along with ACE-I for HF may show the positive results.

ABBREVIATIONS

DM: Diabetes

HF: Heart failure

ROS: Reactive oxygen species

AGE: Advanced glycation end products

IL-6: Interleukin-6

NO: Nitric oxide

eNOS: Endothelial nitric oxide synthase

CAN: Cardiac autonomic dysfunction

ATP: Adenosine triphosphate

DCM: Diabetic cardiomyopathy

LV dysfunction : Left ventricle dysfunction

SGLT-2: Sodium glucose linked trasporter-2

DPP-4: Dipeptidyl peptidase-4

REFERENCES

1. Salim Bastaki. (Diabetes mellitus and its treatment). Int J Diabetes & Metabolism, 2005; 13: 1111-134.
2. Chinmay D. Deshmukh and Anurekha Jain. (Diabetes Mellitus : A Review). Int. J. Pure App. Biosci, 2015; 3(3): 224-230.
3. V. Baliga and R. Sapsford. (Diabetes metillus and heart failure- an overview of epidemiology and management). Diabetes & vascular Disease Research, 2009; 6(3): 164-171.
4. Jacek Kasznicki, Jozef Drzewoski. (Heart failure in diabetic population- pathophysiology, diagnosis and management). Arch Med Sci., 2014; 10(3): 546-556.
5. Lehrke, MD, Nikolaus Mark, MD. (Diabetes Mellitus and Heart Failure). The American Journal of Medicine, Michael, 2017; 130: 6S.
6. Yasuhiko Sakata, Hiroaki Shimokawa. (Epidemiology of Heart Failure in Asia). 2013; Circulation Journal Vol.77.
7. Stephan von Haehling, Gerd Hsenfub, Stefan D. Anker. (Diabetes and Heart Failure). 2016; JACC VOL. 68: 13.
8. Christiana Voulgari, Dimitrios Papadogiannis, Nicholas Tentolouris. (Diabetic

cardiomyopathy: from the pathophysiology of the cardiac myocytes to current diagnosis and management strategies). Vascular Health and Risk Management, 2010; 6: 883-903.

9. Francesco Paneni, Joshua A. Beckman, Mark A. Creager and Francesco Cosentino. (Diabetes and vascular disease disease: pathophysiology, clinical consequences and medical therapy:part I). Europea Heart Journal, 2013; 34: 2436-2446.
10. Besty B. Dokken. (The Pathophysiology of Cardiovascular Disease and Diabetes: Beyond Blood Pressure and Lipids). Diabetic Spectrum, 2008; 21.
11. Lars Ryden. (Diabetes mellitus and congestive heart failure). Eur Heart J. 1999; 20.
12. Sai Fullah Nasir, David Aguliar. (Congestive Heart Failure and Diabetes: Balancing Glycemic Control with Heart Failure Improvement). Am J Cardiol, 2012; 110(9Suppl): 50B-57B.
13. Chern-En Chiang *et al.* (2018 consensus of the Taiwan Society of Cardiology and the Diabetes Assosciation of Republic of China (Taiwan) on the pharmacology management of patients with type-2 diabetes and cardiovascular diseases). Journal of Chinese Medical Association, 2018; 18: 189-222.
14. Keng Wooi, Meredith L. Allen, Ajay Desai, Duncan Macrae, Nazima Pathan. (Cardioprotective effects of insulin). Circulation, 2012; 125: 721-728.
15. James Thrasher. (Pharmacologic Management of Type 2 Diabetes Mellitus: Available Therapies. The American Journal of Medicine, 2017; 113: 6S.
16. Clyde W. Yancy et al. (Guideline for the management of Heart Failure). 2017.