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DIASTOLIC DYSFUNCTION IN TYPE II DIABETES AND ITS CORRELATION WITH GLYCOSYLATED HAEMOGLOBIN

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ABSTRACT

Background: The alteration of left ventricular diastolic function is considered to be one of the earliest ultrasonographic signs of diabetic cardiomyopathy, which is a well-known chronic complication of diabetes mellitus. glycosylated haemoglobin (HBA_{1c}) is the standard marker for monitoring the control of glycemic status, although biological studies indicate that HBA_{1c} has a negative effect on the cardiovascular system, this effect has not been sufficiently studied so far. **Aim:** Highlight the role of HBA_{1c} as not only a marker, but also a risk factor for diabetic cardiomyopathy. **Materials and Methods:** in this case-control study, a total of 80 patients with type2 diabetes aged between 40-70 years, were selected from Tishreen University Hospital and been included in the case group and been compared with 80 non diabetic participants as a control group, the two groups were matched in terms of: age, gender, blood pressure and BMI, the two groups were scrutinized for Doppler echocardiography, ECG, stress ecg, both groups underwent an objective exam, full biochemistry profile, and Blood pressure measurement. HBA_{1c} analysis was performed for the case group. **Results:** in the case group Diastolic dysfunction of left ventricle was observed in 66 patients out of 80 (82.5%), the grades of Diastolic dysfunction were 33(50%) for grade I, 22(33.3%) for grade II, 11(16.7%) for grade III, 16(20%) patients of the case group had HBA_{1c} <7,19(23.75%) with HBA_{1c} between 7.1-8, 11(13.75%) with HBA_{1c} between 8.1-9, 20(25%) with HBA_{1c} >9, and 14(17.5%) without diastolic dysfunction all of them had HBA_{1c} <7. in the control group Diastolic dysfunction of left ventricle was observed in 30 participants out of 80 (37.5%), the grades of Diastolic dysfunction grades were 28(93.3%) for grade I, 2 (6.7%) for grade II, 0% for grade III. **Conclusion:** Diastolic dysfunction of left ventricle is a common finding in patients with type 2 diabetes, elevated levels of HBA_{1c} increase the risk of developing Diastolic dysfunction and with higher grades, Hence, it is a risk factor for diabetic cardiopathy.

KEYWORDS: Diastolic dysfunction, diabetes mellitus, HBA_{1c}, diabetic cardiomyopathy.

INTRODUCTION

Diabetes mellitus (DM) is a heterogeneous metabolic disease characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. It is associated with significant morbidity and mortality, reduced life expectancy and diminished quality of life due to diabetes-related complications. Recent estimates indicated that there are 415 million adults living with DM and this number is projected to reach 642 million by 2040.[1]

Diabetes mellitus is associated with high cardiac mortality attributed to coronary artery disease. Epidemiological as well as clinical studies have suggested the existence of diabetic cardiomyopathy independent of ischemic heart disease or other conditions leading to left ventricular dysfunction.[2]

Diabetic cardiomyopathy is defined as the presence of abnormal cardiac structure and performance in the absence of other cardiac risk factors, such coronary artery disease, hypertension, and significant valvular disease. Hyperglycemia, hyperinsulinemia, and insulin resistance mediate the pathological remodeling of the heart, characterized by left ventricle concentric hypertrophy and perivascular and interstitial fibrosis leading to diastolic dysfunction. A change in the metabolic status, impaired calcium homeostasis and energy production, increased inflammation and oxidative stress, as well as an accumulation of advanced glycation

end products are among the mechanisms implicated in the pathogenesis of diabetic cardiomyopathy.[3]

Several studies have indicated that left ventricular diastolic dysfunction represents the earliest preclinical manifestation of diabetic cardiomyopathy that can progress to symptomatic heart failure.[4]

AIM OF STUDY

This study aims to Highlight the role of HBA_{1c} as not only a marker, but also a risk factor for diabetic cardiomyopathy.

MATERIALS AND METHODS

This case-control study was conducted at the Cardiology Department in Tishreen university Hospital, between September 2018 and September 2019, and included 80 patients with type 2 diabetes aged between 40-70 years, and been compared with 80 non diabetic participants as a control group, the two groups were matched in terms of: age, gender, blood pressure and BMI, Patients with certain conditions, such as arrhythmias, moderate to severe valvular heart disease, prosthetic mitral valve, symptomatic ischemic heart disease, congestive heart failure with low EF, obesity with BMI>30, impaired renal function, sickle cell disease, blood pressure >= 140/90, Patients with indeterminate diastolic function, were excluded from our study As these conditions may affect the evaluation of the diastolic function or the accuracy of HBA_{1c} analysis. the two groups were scrutinized for Doppler echocardiography using siemens acuson x300 premium ultrasound machine, the LV diastolic function was evaluated according to the recommendations of the American Society of Echocardiography 2016. All participants underwent comprehensive clinical examination; a detailed medical history was taken including information related to: age, sex, smoking, associated diseases, past medical history and cardiac symptoms.

Blood pressure was taken in both arms to all participants after 10 minutes rest. Laboratory tests were performed for all participants, including: Complete blood count, serum creatinine, urea, glucose, lipid panel and HBA_{1c} analysis for the diabetic group. both groups underwent an ECG, stress ECG test.

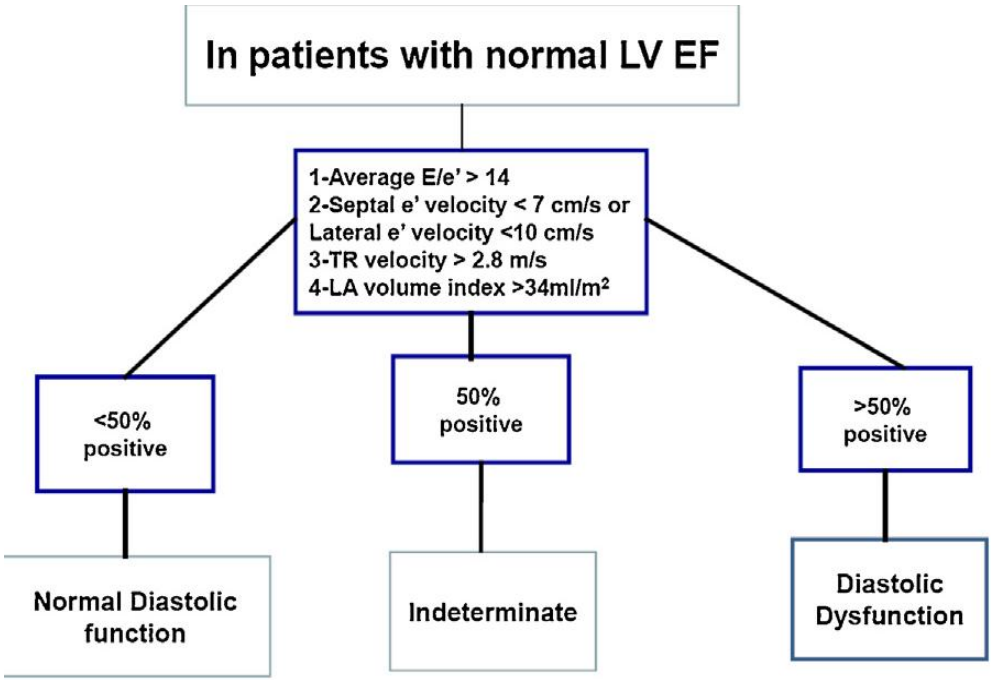
Definitions

Mitral E/A ratio: mitral valve E velocity divided by A-wave velocity, it is used to identify the filling patterns: normal, impaired relaxation (grade I), pseudonormal (grade II), and restrictive filling (grade III).

IVRT: Isovolumic relaxation time is the Time between aortic valve closure and MV opening. IVRT is=<70 msec in normal subjects and is prolonged in patients with impaired LV relaxation but normal LV filling pressures. When LAP increases, IVRT shortens and its duration is inversely related to LV filling pressures in patients with cardiac disease.

Mitral E/é: MV E velocity divided by mitral annular é velocity. é velocity can be used to correct for the effect of LV relaxation on mitral E velocity, and E/é ratio can be used to predict LV filling pressures.[5]

MPI: Myocardial performance index (MPI), or Tei index, is a Doppler echocardiographic parameter defined as the sum of the isovolumic contraction and relaxation times divided by the ejection time. It is considered a reliable parameter for global left ventricular function.[6]



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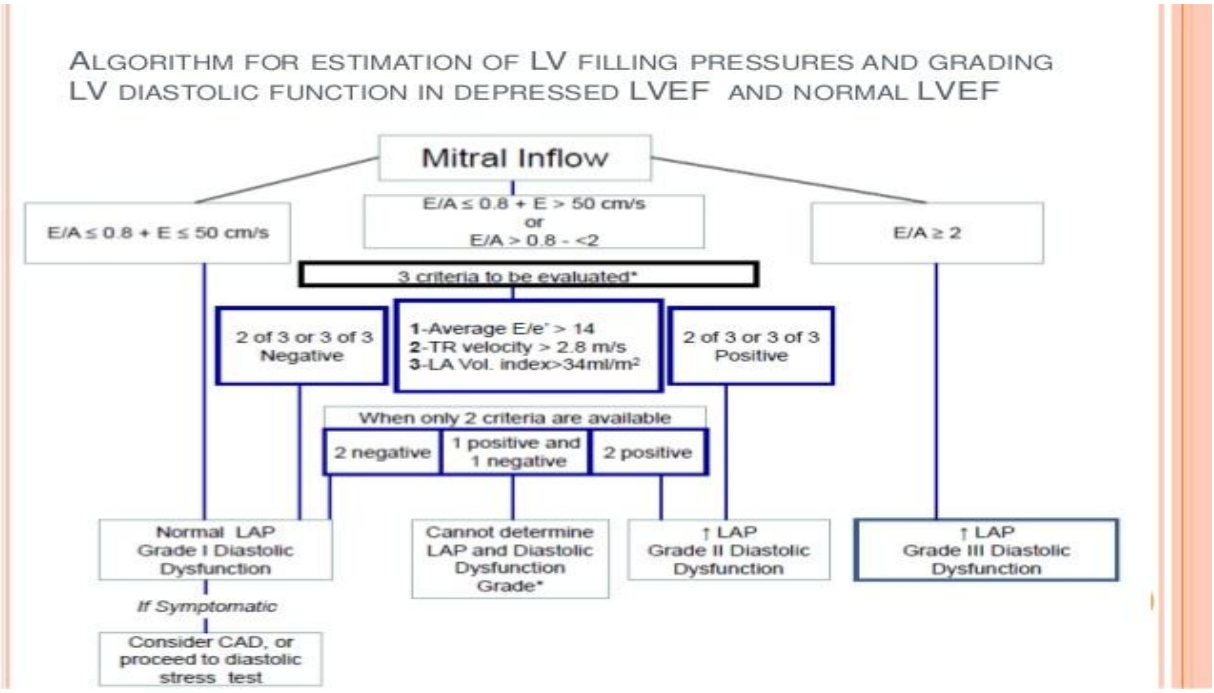

B

(A) Algorithm for diagnosis of LV diastolic dysfunction in subjects with normal LVEF. (B) Algorithm for estimation of LV filling pressures and grading LV diastolic function in patients with depressed LVEFs and patients with myocardial disease and normal LVEF after consideration of clinical and other 2D data. (5)

RESULTS

Table 1: Differences between the two study groups based on the diastolic function.

The variable		Variable classes	Case group		Control group		P
			N	%	N	%	
Diastolic dysfunction		absent	14	17.5	50	62.5	0.000**
		present	66	82.5	30	37.5	
grade of Diastolic dysfunction		I	33	50.0	28	93.3	0.000**
		II	22	33.3	2	6.7	
		III	11	16.7	0	0	
N_1=66	N_2=30	IV	0	0	0	0	

** Very important statistical significance (p<0.001)

Table 1: shows the differences between the case and control groups in terms of the presence and absence of diastolic dysfunction using the chi-square test, as it showed the presence of a statistically significant difference (p = 0.000) between the two groups. In terms of the grades of diastolic dysfunction, there was also a statistically significant difference (p = 0.000)) between the two groups.

Table 2: The differences between the two study groups based on the variables (E/A ratio, IVRT, E/é, MPI).

The variable	Case group		Control group		P
	M	SD	M	SD	
E/A ratio	1.17	0.739	1.01	0.3001	0.084
IVRT	87.81	26.514	79.45	18.258	0.021*
E/é	8.26	3.36	5.19	1.424	0.000**
MPI	0.44	0.127	0.35	0.077	0.000**

** Very important statistical significance (p<0.001), * important statistical significance (P<0.05).

Table 2. shows the differences between the case and the control groups in terms of (E/A ratio, IVRT, E/é, MPI) using the t.test for two independent samples, as it showed the presence of statistically significant differences between the two groups (p <0.05) in terms of (IVRT, E/é, MPI), but there were no significant differences between the two groups (p> 0.05) in terms of the E/A ratio.

Table 3: The relationship between HBA_{1c} and the presence of diastolic dysfunction and the grade of diastolic dysfunction in the case sample.

DD / HBA_{1c}	Diastolic dysfunction N=80				Diastolic dysfunction grade N=66					
	present		absent		I		II		III	
	N	%	N	%	N	%	N	%	N	%
<7	16	20	14	17.5	16	24.2	0	0	0	0
7.1-8	19	23.75	0	0	13	19.7	6	9.1	0	0
8.1-9	11	13.75	0	0	1	1.5	10	15.2	0	0
>9	20	25	0	0	3	4.5	6	9.1	11	16.7
P	0.000**				0.000**					

** Very important statistical significance (p<0.001).

Table 3: shows The relationship between HBA_{1c} and the presence of diastolic dysfunction and the grade of diastolic dysfunction in the case group using the chi-square test, as it showed the existence of a statistically very important relationship between HBA_{1c} and the presence of diastolic dysfunction and its grades.

Table 4: The relationship between HBA_{1c} and the variables (E/A ratio, IVRT, E/é, MPI).

		E/A ratio	IVRT	E/é	MPI	
HBA_{1c}	<7	0.000**	0.000**	0.000**	0.000**	P value
	7.1-8					
	8.1-9					
	>9					

** Very important statistical significance (p<0.001).

Table 4: shows the relationship between HBA_{1c} and the variables (E/A, IVRT, E/ é, MPI). in the case group using the nonparametric Kruskal-wallis test for the variables (E/A ratio, IVRT, E/é), and the One way Anova parameterized test on the variable (MPI), which showed a statistically very significant relationship between HBA_{1c} and each of the variables, (E/A ratio, IVRT, E/é, MPI), (P = 0.000) for each.

Table 5: The relationship of HBA_{1c} with diastolic dysfunction and its grade, and (E/A, IVRT, E/é, MPI) of the case group using Spearman's correlation coefficient for the rational data and the Pearson correlation coefficient for the quantitative data.

		Diastolic Dysfunction N=80	Diastolic dysfunction grade N=66	E/A ratio	IVRT	E/é	MPI
HBA_{1c}	*R	0.521	0.747	0.402	-0.542	0.824	0.883
	P	0.000**	0.000**	0.000**	0.000**	0.000**	0.000**

*R: Correlation coefficient value, ** Very important statistical significance (p<0.001).

Table 5 shows the existence of a statistically significant (P = 0.000) positive correlation (because R is positive) between HBA_{1c} and each of the diastolic dysfunction and its grade using Spearman's correlation coefficient, and the correlation strength was moderate with diastolic dysfunction and high with its grade. It also showed the existence of a positive and statistically significant correlation (P = 0.000) between HBA_{1c} and each of (E/A, E/é, MPI) using Pearson correlation coefficient, and the correlation strength was medium strength with E/A and high strength with E/é, And MPI. And the presence of an inverse, medium-strength and statistically significant correlation (P = 0.000) between HBA_{1c} and IVRT.

Table 6: The effect of HBA_{1c} on the incidence of diastolic dysfunction in the case group using binary logistic regression test.

	Diastolic dysfunction		
	B	P value	OR (CI: 95%)
HBA_{1c}	- 2.619	0.000	0.07 (0.016 – 0.327)

Table 6 shows the existence of a statistical significance (P = 0.000) of the effects of HBA_{1c} on the incidence of diastolic dysfunction, since as the value of HBA_{1c} decreases by one degree, the non-occurrence of diastolic dysfunction increases by 2.619 times. Meaning that an increase in HBA_{1c} is a risk factor for the development of

diastolic dysfunction with a probability of 0.07%, (OR=0.07 (CI: 95% (0.016 – 0.327)).

Table 7: The effect of HBA_{1c} on the Diastolic dysfunction grade in the case group.

	Diastolic dysfunction		
	wald	**P value**	**OR(CI: 95%)**
HBA_{1c}	12.337	0.000	2.322 (1.026 – 3.617)

Table 7. shows that for a patient whose HBA_{1c} values increase, the probability of higher grade of diastolic dysfunction has a statistically significant increase (P = 0.000) by 2.32% of the patient whose HBA_{1c} values are lower (OR = 2.322 CI: 95% (1.026 - 3.617) meaning that increased HBA_{1c} is a risk factor for advanced grade of diastolic dysfunction.

DISCUSSION

Diabetic complications are usually attributed to oxidative stress associated with glycation of major structural and functional proteins. This non-enzymatic glycation of long lived proteins such as collagen, albumin, fibrinogen, liver enzymes and globulins result in the formation of early and advanced glycation end products (AGEs) associated with the production of myriads of free radicles and oxidants that have detrimental effects leading to diabetic complications.[7]

As we mentioned earlier, several studies have indicated that left ventricular diastolic dysfunction represents the earliest preclinical manifestation of diabetic cardiomyopathy that can progress to symptomatic heart failure.[4]

In our study, we found that diastolic dysfunction is a common disorder among patients with type 2 diabetes (82.5%), compared to non-diabetics (37.5%), and this is consistent with international studies related to this topic. The grade of diastolic dysfunction was higher in diabetic patients, especially grade II (pseudonormal) and grade III (restrictive), by 33.3% and 16.7%, respectively, in the case group, compared to the control group, 6.7% and 0%, respectively. We found very significant differences (P <0.001), with diastolic function parameters between the two groups, in terms of E/é ratio and the myocardial performance index (MPI). The average E/é ratio was 8.26 for the case group, compared to 5.19 for the control group, and the average myocardial performance index for the case group was 0.44, compared to 0.35 for the control group. We found significant differences (P <0.05) regarding isovolumic relaxation time (IVRT), with higher IVRT values recorded in the case group (87.8ms) compared to the control group (79.45ms).

Our study did not find significant differences between the two groups regarding E/A ratio. We explain this by the fact that the E/A ratio increase in grade I diastolic dysfunction, while it decreases with higher grades, especially Grade III.

Prolonged sugar exposure produces early and advanced glycation end products affecting different proteins. A major example of early glycated proteins is HbA_{1C} which is further modified, through a series of reactions, into Hb-AGE. Under normal conditions Hb-AGE constitutes 0.42% of circulating Hb levels which increases to 0.75% in diabetic subjects.

Glycation is accelerated in diabetics where glucose uptake by erythrocytes is insulin independent and highly uncontrolled. Furthermore, glycated Hb is more readily oxidized and degraded by erythrocyte proteolytic enzymes than unglycated Hb enhancing oxidative stress by increasing the release of heme and free iron in association with free radicles. The released ferrous iron (II) reacts with hydrogen peroxide via the Fenton reaction forming ferric iron (II) and hydroxyl radicals. These reactive species contribute to further oxidative stress damaging lipids and proteins that alter cell membrane properties and lead to increased erythrocyte fragility. High exposure to oxygen during gas transport render erythrocytes even more vulnerable to oxidative damage. However, damage is normally prevented by anti-oxidant factors that maintain a balanced intracellular oxidation status. This balanced environment maintains an intact Hb structure which itself exerts a stabilizing effect on erythrocyte membrane structure. When Hb structure is altered due to persistent glycol-oxidative stress, Hb becomes more susceptible to degradation decreasing the life span of erythrocytes. Studies have shown a decreased life span of 6.9 d for 1% increase in glycated Hb levels.[7]

We found in our study that there is a very important relationship between HBA_{1c} and the presence of diastolic dysfunction and its grades, and this correlation is of moderate strength with respect to the presence of diastolic dysfunction (correlation coefficient = 0.521), and good with regard to the development of diastolic dysfunction grades (correlation coefficient = 0.747). We also found a very important relationship between the values of HBA_{1c} and all the parameters studied for the diastolic function, and there was a very good direct correlation between HBA_{1c} on the one hand, and each of the E/é ratio (correlation coefficient = 0.824), and myocardial performance index MPI (coefficient Correlation = 0.883). We noticed an inverse correlation between HBA_{1c} and IVRT (correlation coefficient = -0.542), which explains that IVRT is greatly reduced by the presence of high grades of diastolic dysfunction, especially in grade III, and from what we have seen previously, we evaluate HBA_{1c} is strongly proportional to elevated grades of diastolic dysfunction.

The study shows that there is a direct correlation of moderate strength between HBA_{1c} and the E/A ratio (correlation coefficient = 0.402), and the reason for that is that the E/A ratio increases significantly in advanced grades of diastolic dysfunction.

Our study shows the existence of a statistical significance (P = 0.000) of the effects of HBA_{1c} as values on the incidence of diastolic dysfunction, where it shows that as the value of HBA_{1c} decreases by one degree, the non-occurrence of diastolic dysfunction increases by 2.619 times. Meaning that increased HBA_{1c} is a risk factor for diastolic dysfunction, (OR=0.07 (CI: 95% (0.016 – 0.327)). We also found that for a patient whose HBA_{1c} values increase, the probability of higher grade of diastolic dysfunction has a statistically significant increase (P = 0.000) by 2.32% of the patient whose HBA_{1c} values are lower (OR = 2.322 CI: 95% (1.026 - 3.617)) meaning that increased HBA_{1c} is a risk factor for advanced grade of diastolic dysfunction.

Intracellular glyco-oxidative stress may contribute to vascular endothelial damage through several mechanisms:[1] accumulation of intracellular free radicals alters erythrocyte membrane properties leading to erythrocyte aggregation, increased blood viscosity and impaired blood flow. Shear stress, due to thicker abrasive blood consistency, affecting the vascular endothelium and triggering an inflammatory response that contribute to subsequent atherogenic events,[2] buildup of free radicles promotes the oxidation of ferrous Hb (Hb Fe2+) into ferric Hb (Hb-Fe3+) (methemoglobin), which is further modified, through several oxidation steps, into ferryl hemoglobin (Hb-Fe3+/Fe4+). The ferryl iron (Fe4+) is unstable and regains the Fe3+ state by reacting with specific amino acids in hemoglobin forming covalently cross-linked Hb multimers. The altered Hb structure promotes cellular damage and releases ferryl Hb into the subendothelial matrix. Silva et al demonstrated that ferryl Hb, rather than Hb, or methemoglobin, increased endothelial permeability and production of pro-inflammatory monocyte adhesion proteins that promote macrophage accumulation and a local inflammatory reaction preceding plaque formation;[3] Free Hb penetrates the vascular smooth muscle layer and inactivates endothelium-dependent relaxation induced by acetylcholine possibly through binding to nitric oxide (NO) which is a potent vasodilator which initiates vaso-relaxation in response to stimuli. Nitric oxide also inhibits formation of oxidized LDL which detrimental to endothelial integrity. Inactivation of NO is a major marker of endothelial dysfunction manifested in impaired vasoactive responses. Rodríguez-Mañas et al demonstrated that highly glycosylated Hb inhibited nitric oxide mediated relaxation to a larger extent than low glycated and unglycated Hb. The authors suggested that Hb-AGEs may exacerbate this effect as abundant in vitro and in vivo evidence demonstrates that AGEs inhibit nitric oxide production and function and,[4] Furthermore, accelerated degradation of erythrocytes releases heme which sensitizes endothelial cells to oxidative damage and promotes oxidation of endothelial proteins and low density lipoproteins (LDLs), Altogether, these adverse modifications trigger a proliferative inflammatory response in the subendothelial space which involves recruitment of a myriad of inflammatory and immune factors including monocytes, platelets, lymphocytes and increased production of various growth factors and cytokines such as IL-1 and TNF-α and adhesion molecules. Oxidized LDL particles are subsequently scavenged by macrophages forming lipid rich foam cells that contribute to the formation of fatty streaks and subsequent build-up of plaque. As atherosclerotic plaque builds up, further insult to the endothelium activates a vicious cycle of inflammatory/oxidation events and further progression of atherosclerosis.[7]

CONCLUSION

Diastolic dysfunction of left ventricle is a common finding in patients with type 2 diabetes, elevated levels of HBA_{1c} increase the risk of developing Diastolic dysfunction, Hence, it is a risk factor for diabetic cardiopathy.

REFERENCES

1. Amir A, Mohammad A, Omnia H, Ayman M. Pathophysiological mechanisms of diabetic cardiomyopathy and the therapeutic potential of epigallocatechin-3-gallate. Biomedicine & Pharmacotherapy, 2019; 109: 2155–2172.
2. Schannwell C, Schneppenheim M, Perings S, Plehn G, Strauer B.E. et al. Left Ventricular Diastolic Dysfunction as an Early Manifestation of Diabetic Cardiomyopathy. Cardiology, 2002.
3. Giulia B, Dirk V, Deborah E, Harald S, Steven R. Houser and Markus W. Diabetic Cardiomyopathy: Current and Future Therapies. Beyond Glycemic Control. Frontiers in Physiology, 2018; 9: 1514.
4. Hisashi Masugata, Shoichi Senda, Fuminori Goda, Yumiko Yoshihara, Kay Yoshikawa, Norihiro Fujita, Hiroyuki Daikuhara, Hiroyuki Okuyama, Teruhisa Taoka, Masakazu Kohno. Left ventricular diastolic dysfunction in normotensive diabetic patients in various age strata. diabetes research and clinical practice, 2008; 79.
5. Sherif N, Otto S, Christopher A, Benjamin B, Hisham D, Thor E, Frank F, Thierry G, Allan L, Patrizio L, Paolo M, Jae Oh, Bogdan P, Alan W, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Journal of the American Society of Echocardiography, 29(4).
6. Yasushige S, Paulo A, T. Dung N, Friedrich M, Michael S, and Torsten D. Myocardial performance (Tei) index is normal in diastolic and systolic heart failure induced by pressure overload in rats.

European Journal of Echocardiography, 2010; 11: 829–833.
7. Jumana S. Glycated hemoglobin and its spinoffs: Cardiovascular disease markers or risk factors?. World J Cardiol, 2015 August 26; 7(8): 449-453.