The association of diastolic dysfunction with anaemia in patients with type 2 diabetes Mellitus

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الخلاصة

تم تشخيص أعتلال القلب الأنبساطي عند ٧١)١٧٪ (من اصل ١٧مريض مصاب بداء السكري مع فقر الدم بالمقارنة مع ١٢)٦٦٪ (من اصل ٤٤مريض مصاب بداء السكري والذين لديهم مستوى خضاب دم طبيعي .هناك أقتران هام بين أعتلال القلب الأنبساطي و فقر الدم في مرضى السكريالنمط الثاني المصابين بفقر الدم وبالتالي يمكن تعيين مرضى السكري الذين لديهم نسبة كبيرة لخطر الأصابة بأعتلال القلب الأنبساطي .فقر الدم هو حالة شائعة لدى المرضى الذين يعانون من داء السكري ويمثل عبء اضافي لمرضى السكري المتقدمين بالعمر والذين لديهم امراض وعائية اخرى.هذه الدراسة تبحث العلاقة بين أعتلال القلب الأنبساطي مع فقر الدم في المرضى المصابين بداء السكري النمط الثاني.هذه الدراسة هي دراسة أحصائية لمرضى السكري النمط الثاني اجريت في مستشفى الديوانية التعليمي (عدد المرضى ٧١مريض) ومستشفى الصدر التعليمي في النجف (عدد المرضى ١١مريض) للفترة من شهر كانون الاول ٢٠٠٩الى أيلول ٢٠١٠لدراسة حدوث أعتلال القلب الأنبساطي في المرضى المصابين بداء السكري النمط الثاني الذين لديهم فقر دم.تم فحص ٦٦مريض مصاب بداء السكري النمط الثاني بأستخدام فحص صدى القلب.نتائج فحص صدى القلب تم ربطها مع مستوى خضاب الدم وتمت مطابقة النتائج لمرضى السكري الذين لديهم فقر دم مع المجموعة الأخرى الذين لديهم مستوى خضاب دم طبيعي

Abstract

Background:

Anaemia is a common finding in patients with DM and constitutes an additional burden in patients with advancing age and co-morbid vascular disease. This study examines the association between diastolic dysfunction and anaemia in patients with type 2 DM.

Methods:

This is a cross-sectional study for diabetic patients who were attending the diabetic clinics in Ad Diwaniyah teaching hospital (number of patients was 37) and Al-sadir teaching hospital (number of patients was 28), Najaf from December 2009 to September 2010 to study the occurrence of adverse cardiac findings (diastolic dysfunction) in patients with type 2 diabetes mellitus and anaemia. A 65 type 2 diabetes patients were investigated using transthoracic echocardiography. Recordings and measurements were obtained according to the recommendations of the American Society of Echocardiography. The echocardiographic findings were correlated with Hb level. The patients with and without anaemia were compared.

Aim of the study:

This study was undertaken to show the relationship between anemia and diastolic dysfunction in patients with type 2 diabetes mellitus.

Results:

Diastolic dysfunction was diagnosed in 17 (81 %) of 21 diabetic patients with anaemia compared to 29 (66 %) out of 44 patients with a hemoglobin within the normal range.

Conclusion:

There is significant association between diastolic dysfunction and anaemia in type 2 diabetes patients, consequently this can be used to identify diabetic patients at increased risk of cardiac dysfunction.

Introduction

DM is a clinical syndrome charactersed by hyperglycaemia caused by absolute or relative deficiency of insulin [1] . The worldwide prevalence of DM has risen dramatically over the past two decades, from an estimated 30 million cases in 1985 to 177 million in 2000. Based on current trends, >360 million individuals will have diabetes by the year 2030 (15.2 million cases in 2000 and 42.6 million cases by the year 2030 in middle east). Although the prevalence of both type 1 and type 2 DM is increasing worldwide, the prevalence of type 2 DM is rising much more rapidly because of increasing obesity and reduced activity levels. DM increases with aging, prevalence is similar in men and women throughout most age ranges (10.5% and 8.8% in individuals >20 years) but is slightly greater in men >60 years. Worldwide estimates project that in 2030 the greatest number of individuals with diabetes will be 45–64 years of age [2] .

Diastolic dysfunction refers to a condition in which abnormalities in mechanical function are present during diastole [10]. The causes of diastolic dysfunction may be subdivided into a decrease in passive diastolic compliance and an impairment in active LV relaxation [12]. Abnormalities in diastolic function may occur in the presence or absence of a clinical syndrome of heart failure and with normal or abnormal systolic function [13]. The symptoms of heart failure from LV systolic and diastolic dysfunction are indistinguishable. There may be symptoms of heart failure (pulmonary edema and volume overload) in the setting of normal systolic function. In patients >70 years old who have heart failure symptoms, new onset AF or stroke, diastolic heart failure should always be suspected, especially if the LV EF is normal. Because the process of LV relaxation is more energy dependent than contraction, abnormalities of LV diastolic function occur earlier than systolic dysfunction in virtually all cardiac diseases [11].

DM is associated with increased cardiovascular complications, the most common of which are ischaemic cardiomyopathy and LV dysfunction. Diabetes is also associated with heart failure, mainly through its association with hypertension and coronary artery disease [1].

Anaemia is common in patients with diabetes and associated with an increased risk of diabetic complications and it has the potential to contribute to an excess of cardiac disease in diabetics [6]. In the general population, a decrease in Hb level is associated with a 41 % increase in cardiovascular disease. In patients with heart failure, anaemia has been linked to more severe cardiac dysfunction, increased brain natriuretic peptide and a worse prognosis even after adjustment for conventional risk factors such as coronary heart disease, smoking, hypertension, dyslipidaemia and renal dysfunction [8]. Anaemia has a range of effects on cardiac structure, including myocyte hypertrophy and interstitial fibrosis leading to LVH [9]. Over time functional changes occur, with impaired LV relaxation and compliance leading to diastolic dysfunction[7].

The second pattern represents abnormalities of both relaxation and compliance, it results from an increase in left atrial pressure compensating for slow relaxation. The E wave returns to normal producing a mitral pattern indistinguishable from normal called pseudonormalization (E/A ratio > 1). The third abnormal filling pattern, termed restrictive pattern, found in patients with severe decrease in left ventricular compliance, causes an increased E/A ratio (often above 2) and reflects a high left atrial pressure, usually to the extent that symptoms of left heart failure appear (15). Pseudonormal mitral flow velocity

pattern can be identified by performing a Valsalva maneuver which decreases preload, reverting this pattern to one that shows impaired LV relaxation (E/A ratio <1) (13).

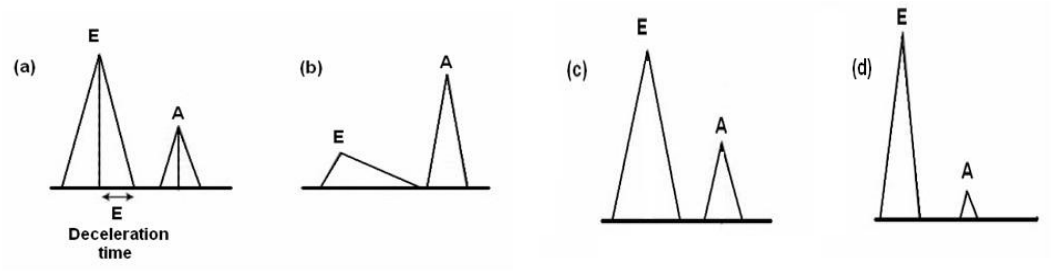


Figure-1: schematic drawing of mitral inflow patterns during different stages of diastolic dysfunction (a) normal; (b) slow filling (low peak E velocity with long deceleration time and high peak A velocity); (c) pseudonormal; (d) restrictive (high peak E velocity with short E deceleration time and with low or absent A wave).

Diastolic dysfunction can be graded as following:

*Grade 1 (mild dysfunction): impaired relaxation with normal filling pressure.

*Grade 2 (moderate dysfunction): pseudonormalized mitral inflow pattern with E/A ratio of 1-1.5.

*Grade 3 (severe reversible dysfunction) with E/A ratio greater than 2.

*Grade 4 (severe irreversible dysfunction) with E/A ratio greater than 2 [12].

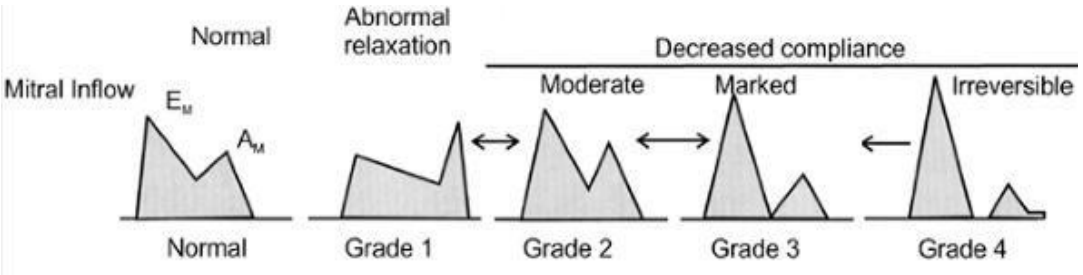


Figure-2: schematic representation of mitral inflow in a normal individual and in various grades of diastolic dysfunction.

Patients and methods

The study was performed in 65 patients with type 2 diabetes. The study group include 42 males and 23 females. The mean age of patients was 60 ± 10 years with a duration of diabetes of 10-20 years (from the time of diagnosis, independent of the time of onset of symptoms). All patients met the American Diabetic Association (ADA) diagnostic criteria for diabetes [2] [Symptoms of diabetes plus random blood glucose concentration ≥ 11.1 mmol/L (200 mg/dL) or Fasting plasma glucose ≥ 7.0 mmol/L (126 mg/dL)]. Previous history of ischemic heart disease, heart failure, stroke, transient ischemic attacks, hypertension or smoking status were taken. Blood pressure was measured in all patients. Standard biochemical indices in form of blood urea, serum creatinine, fasting lipid profile, blood glucose, ECG and Hb concentration were also obtained in all patients.

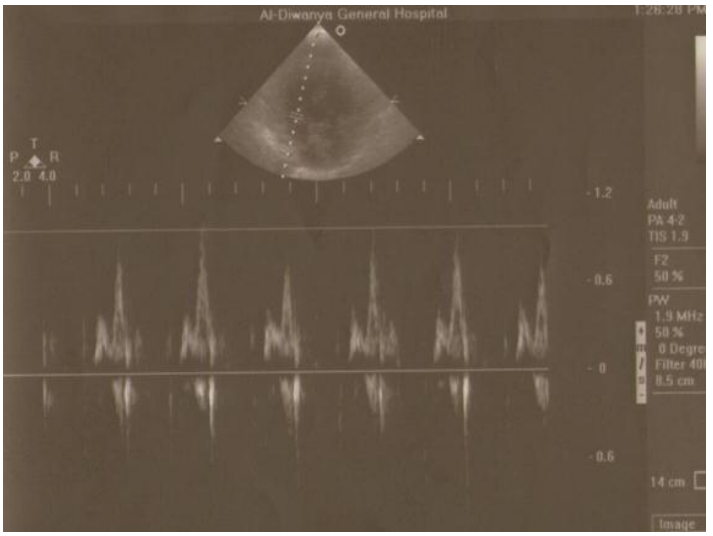
The treatment of patients included oral hypoglycemic drugs such as glibenclamide and metformin alone or in combination. Patients with hypertension

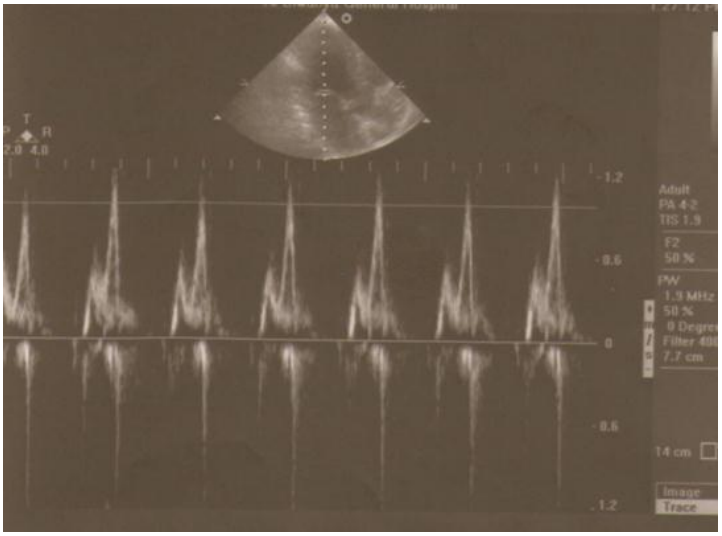
were on captopril, atenolol, amlodipine, lisinopril, enalapril and low dose aspirin. Other drugs used included simvastatin and atorvastatin. The presence of anaemia identified according to WHO definition (Hb < 13 g/dl in men and < 12 g/dl in women). The mean Hb level in anaemic diabetic patients was 10 ± 1 g/dl.

Exclusion criteria:

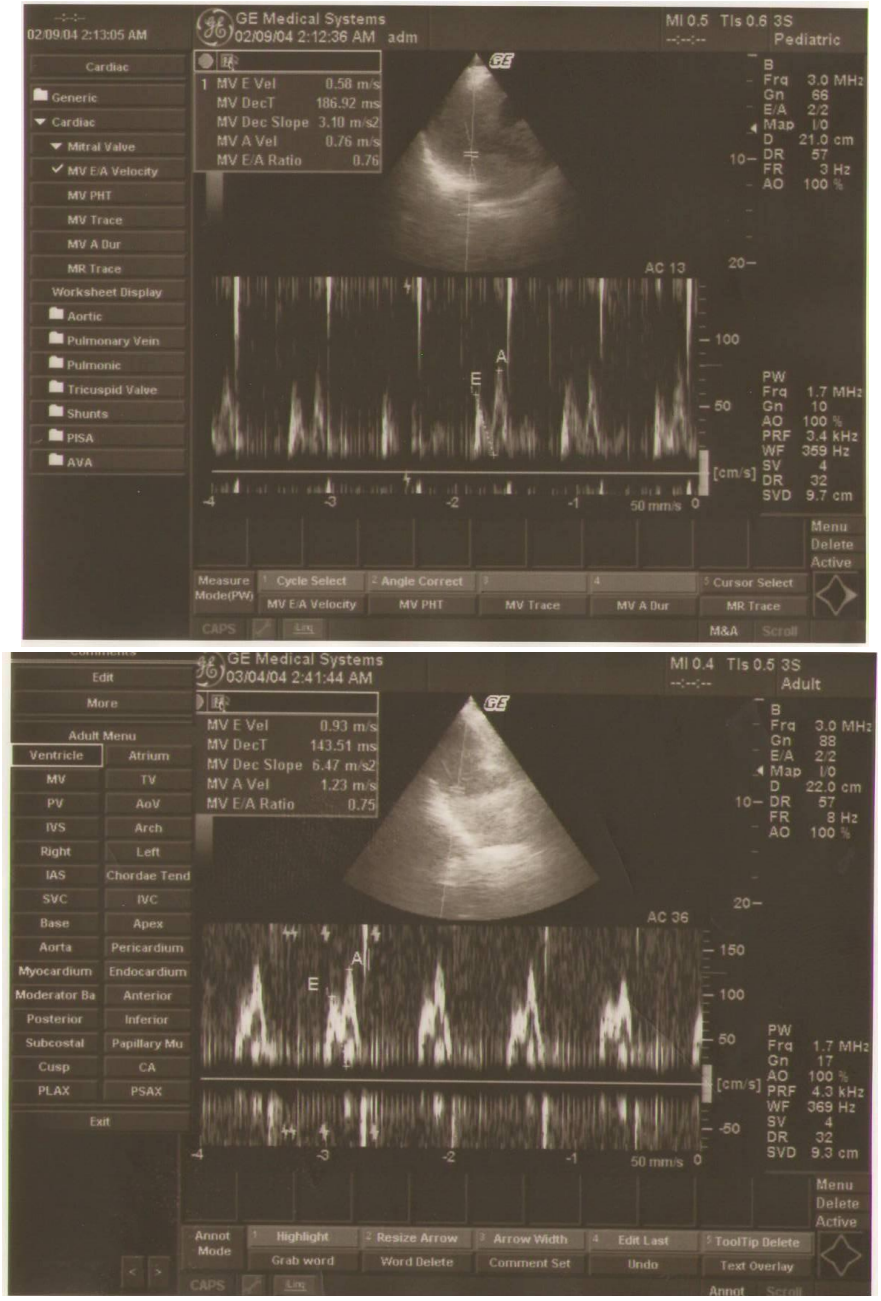
1. Patients with significant valvular heart disease (regurgitation or stenosis).
2. Patients with AF (mitral inflow A wave will be not present).
3. Evidence of LBBB on ECG (LBBB may cause a diastolic pattern of abnormal relaxation).
4. Non diagnostic imaging (imaging when the E and A wave are fused together producing a single wave).
5. Mechanical prosthetic heart valves.

Statistical analyses were performed using the chi-square test, a value of $P < 0.05$ was considered statistically significant. Immediately after blood was taken for these measurements, the patients were instructed to have echocardiography. The devices used were LOGIC 3 and PHILIPS. Transthoracic echocardiography examination was performed with parasternal and apical views were used to assess for diastolic dysfunction. The results obtained were analysed by two experienced physicians. Pulsed wave Doppler echocardiography was used and conducted in the mitral inflow area at the tips of mitral valve leaflets to measure mitral E and A waves velocities, E wave/A wave ratio, and deceleration time and rate. Other cardiac parameters measured using M-mode echocardiography were IVS wall thickness in diastole, LA dimension, and EF. In this study, imaging using pulmonary vein flow was not performed because of difficulty in imaging this flow. In cases of pseudonormalised filling pattern, patients were instructed to perform valsalva maneuver.





chocardiographic pictures from diabetic patients with anaemia in Ad Diwaniyah teaching hospital showing slow relaxation pattern diastolic dysfunction.



Echocardiographic pictures from diabetic patients with anaemia in Al-Sadir teaching hospital showing slow relaxation pattern diastolic dysfunction.

Results

Diastolic dysfunction in patients with diabetes and anemia:

Of the 65 patients with type 2 diabetes, 21 (32 %) patients had anaemia. Evidence of diastolic dysfunction on echocardiography was observed in 17 (81 %) patients with anaemia compared with 29 (66 %) out of 44 patients with a hemoglobin within the normal range. This mean that the majority of patients with anaemia were more likely to have cardiac diastolic dysfunction on echocardiography as showing in figure-7, table-3. (*P value = 0.03*) and table-2.

Hypertension in patients with diabetes and anemia:

At the time of review, 16 (76 %) out of 21 diabetic patients with anaemia were hypertensive, while 19 (43 %) out of 44 diabetic patients with normal Hb had hypertension. Regarding use of antihypertensive medications 14 (66 %)

from 21 diabetic patients with anaemia were on antihypertensives in contrast to 25 (57 %) from a total of 44 diabetic patients without anaemia who used these drugs. This is revealed in table-4. (*P value < 0.05*) and table-1.

Adverse cardiac history and anemia:

During survey of patients, past medical history of adverse cardiac events (heart failure, myocardial infarction and angina) was present in 11 (52 %) diabetic patients with anaemia while 19 (43 %) of those with a normal range Hb had such history. Diastolic dysfunction was observed to be more common in patients with a positive cardiac history and anaemia. In patients with no previous history of cardiac disease, those with anaemia were more likely to have abnormal diastolic function on echocardiography (80 %) compared with patients with Hb level in the normal range (68 %) [table-5, *P value > 0.05*].

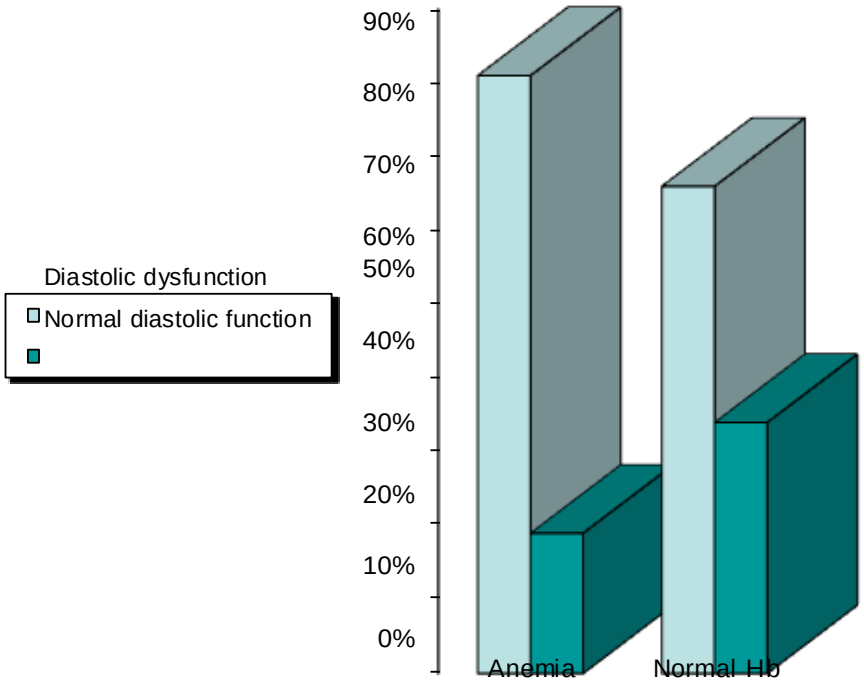


Figure-7: Prevalence of diastolic dysfunction in type 2 diabetes patients with and without anaemia.

Table 1 : Clinical characteristics of diabetic patients with and without anaemia.

Feature	Anaemia	Normal Hb	*P* value
Number of patients	21	44	
Age (years)	65 ± 3	57 ± 1	
Hb (g/dl)	10 ± 1	14 ± 1	0.41
DBP (mmHg)	80 ± 5	75 ± 5	0.10
SBP (mmHg)	145 ± 15	135 ± 10	0.004*
Use of antihypertensive medications (%)	66	57	0.005*
Duration of diabetes (years)	15 ± 5	10 ± 3	0.02*
FBS (mmol/L)	9.8 ± 9	6.5 ± 2	0.04*
Total cholesterol (mmol/L)	4.5 ± 1.3	4.1 ± 1.2	0.10
Serum triglycerides (mmol/L)	1.8 ± 0.2	1.7 ± 1	0.10
Serum creatinine (µmol/L)	98.4 ± 27.2	84.3 ± 12.8	0.05*

*** *P* value is significant.**

Table 2 : Echocardiographic characteristics in diabetic patients with and without anaemia.

Feature	Anemia	Normal Hb	*P* value
Number of patients	21	44	
IVS wall thickness (cm)	1.3 ± 0.3	1.1 ± 0.1	0.05*
Left atrial dimension (cm)	3 ± 0.5	3 ± 0.4	0.38
EF (%)	57.5 ± 8	60 ± 6	0.10
E wave peak (m/s)	0.86 ± 0.1	0.78 ± 0.1	0.05*
A wave peak (m/s)	0.95 ± 0.2	0.84 ± 0.1	0.04*
E/A ratio (%)	0.93 ± 0.3	0.92 ± 0.2	0.10
Deceleration time (m/s)	205.4 ± 30	200 ± 35	0.06*
Deceleration rate (m/s^2)	3.3 ±1.2	3.5 ± 1.1	0.39

*** *P* value is significant.**

Table 3 : Prevalence of diastolic dysfunction in diabetic patients with and without anaemia.

Parameter	Diastolic dysfunction	Normal diastolic function	Total number	*P* value
Anaemia	17 (81 %)	4 (19 %)	21 (32 %)	0.035*
Normal Hb	29 (66 %)	15 (34 %)	44 (68 %)	
Total number	46 (71 %)	19 (29 %)	65	

*** *P* value is significant.**

Table 4 : Diabetic patients classified according to blood pressure and prevalence of anaemia.

Parameter	Hypertension	Normal blood pressure	Total number	*P* value
Anaemia	16 (76 %)	5 (24 %)	21 (32%)	
Normal Hb	19 (43 %)	25 (57 %)	44 (68%)	0.01*
Total number	35 (54 %)	30 (46 %)	65	

*** *P* value is significant.**

Table 5: Incidence of adverse cardiac history in diabetic patients without and with anaemia.

	History of adverse cardiac events				Total number	*P* value
	Yes		No			
	Diastolic dysfunction	Normal diastolic function	Diastolic dysfunction	Normal diastolic function		
Anemia	11 (52 %)		10 (48 %)		21	0.68
	9 (82%)	2 (18%)	8 (80%)	2 (20%)		
Normal Hb	19 (43 %)		25 (57 %)		44	
	12 (63%)	7 (37%)	17 (68%)	8 (32%)		
Total number	30 (46 %)		35 (54 %)		65	
	21 (70%)	9 (30%)	25 (72%)	10(28%)		

Discussion

Anaemia is a common long term complication of diabetes. Diabetic patients are nearly twice as likely to have anaemia as non diabetics. It is possible that unrecognized anaemia may contribute to a high rate of cardiac dysfunction and heart failure observed in patients with diabetes [17]. Anaemia may be associated with adverse cardiac findings, particularly diastolic dysfunction, and this is consistent with
the clinical studies that have shown a link between anaemia and adverse cardiac outcomes in patients with heart failure [18]. The presence of anaemia in diabetes identifies patients with increased risk of morbidity and mortality [17]. In addition, correction of anaemia (with a hemoglobin target of 12.5 g/dl) significantly improved LV EF and New York Heart Association (NYHA) score both in non-diabetic and diabetic patients [20].

Anaemia has been identified as an important factor in the development of LVH in diabetic patients who develop chronic renal failure . Small studies suggest that anaemia reversal can either induce regression or prevent the development of LVH [20]. Other studies show that having anaemia along with diabetes may increase the likelihood of developing diabetic eye disease, developing heart disease or having a stroke. People who have both diabetes and anaemia are more likely to die earlier than those who have diabetes without anemia. High death rates are even more common in anaemic people with diabetes who also have heart failure and/or kidney disease [18].

The association between Hb and parameters of diastolic dysfunction was continuous across the full range of Hb levels, whereby patients with the lowest Hb levels had the worst diastolic dysfunction [6]. Although diastolic dysfunction was more common in

patients with anaemia, the ratio of patients with abnormal relaxation (mild diastolic dysfunction, grade 1) to those with the pseudonormal pattern (moderate diastolic dysfunction, grade 2) on echocardiography was similar in patients with and without anaemia [9].

In this study, the majority of diabetic patients with anaemia had evidence of diastolic dysfunction (81 %). Piyush M. *et al*. [6] demonstrated that most patients with anaemia had cardiac dysfunction (90 %), with the major abnormality being diastolic dysfunction associated with an increased LV mass and impaired relaxation, while 66 % of diabetics who are not anaemic had diastolic dysfunction. Thomas, M.C. *et al*. [17] found that 86.3 % of diabetic patients with anaemia have diastolic dysfunction assessed with pulsed wave Doppler echocardiography. Steinborn, W. *et al*. [8] and Rakusan, K. *et al*. have related anaemia with LV diastolic dysfunction. Sarnak, M.J. *et al*. [18] demonstrated the impact of anaemia on diastolic function and showed a correlation between anaemia and LV filling disturbances.

In our study, 76 % of diabetic patients with anaemia had hypertension compared to 43 % of diabetic patients with normal Hb level, the statistic difference is significant (*P value 0.01*). Piyush M. *et al*. [6] found 84 % of diabetic anaemic patients were hypertensive and 54 % of diabetics without anaemia had hypertension. Mohanram, A. *et al*. [20] found that the prevalence of hypertension was greatest in diabetic patients with anaemia than those without anaemia.

In this study, the incidence of history of adverse cardiac events was 48 % in anaemic versus 52 % in non anaemic diabetics, the difference is not significant statistically (*P value = 0.68*). Piyush M. *et al*. [6] observed a positive history of cardiovascular disease in 44 % of patients with anaemia and 30 % of patients with Hb level in the normal range, and the prevalence of previous myocardial infarction in patients with anaemia was not significantly different from those without anaemia. Cosson S. *et al* [21] also observed no difference in adverse cardiac events in diabetic patients with and without anaemia.

In patients with a positive cardiac history, systolic dysfunction was twice as common in patients with anaemia compared with those with normal Hb [6]. In patients with no previous history of cardiac disease, those with anaemia were more likely to have abnormal diastolic function on echocardiography compared with patients with normal range Hb [20,6].

Conclusions

Traditional cardiac risks such as hypertension, atherosclerosis, chronic renal failure, and dyslipidemia are common in diabetic patients and further compromise heart function. Management of these and other risk factors like anaemia should be instituted.

The measurement of haemoglobin, which is inexpensive test, may be a useful tool to identify diabetic patients at increased risk of cardiac dysfunction.

Anaemia contributes to an increased risk of cardiac disease in individuals with diabetes, manifesting in most of them as diastolic dysfunction on echocardiography.

Recommendations

Although there is a clear evidence of burden of anaemia on cardiac function in type 2 diabetes patients supported by many clinical trials, further researches are required to establish that correction of anaemia in patients with diabetes can improve the cardiac abnormalities and also emphasize the utility of anaemia as a cardiac risk factor.

Asymptomatic diastolic dysfunction is most frequent in diabetic patients and the coexistence of anaemia impart a more severe cardiac disease with a worse prognosis, so that, early screening in the course of the disease is warranted.

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