Analysis of Glycemic Control in Patients with Type 2 Diabetes Mellitus: A Case-Control Study

Noor-ul-Huda[1], Aqiba Sarfraz[2], Saima Saleem[1] and Abid Azhar[1]

[1]Dr. A. Q. Khan Institute of Biotechnology and Genetic Engineering, University of Karachi, Karachi, Pakistan
[2]Liaquat National Hospital and Medical College, Karachi, Pakistan.

Abstract: The incidence of DM (Diabetes mellitus) is rising all over the world. Inadequate glycemic control in patients having type 2 DM presents a higher risk of developing associated complications. This study was conducted to analyse the information on the management of diabetes in standard clinical practice. The study provides description of clinical profile of subjects with DM2 (Type 2 diabetes mellitus) under treatment with insulin and oral hypoglycemic drugs. A total of 500 patients diagnosed with DM2, and equal number of age and gender matched controls participated in the study. Clinical data including previous medical history of diabetes, medication taken for treatment, comorbidities, pre-prandial and post-prandial plasma glucose, and glycosylated haemoglobin (HbA1c) levels were collected. It was observed that among all participants 59.4% were obese and 30.6% were overweight. It was also found that 57.4% patients were suffering from hypertension while 56% were suffering from hyperlipidemia. Patient's data about family history revealed that 62.2% patients had both or either of the two parents suffering from diabetes. The mean fasting and random plasma glucose levels were found to be 178.6mg/dL and 245.4mg/dL respectively. Moreover, only 8% patients achieved glycemic goals and had HbA1c levels under normal limits. The study reveals that lack of awareness and poor self-care can increase the risk of comorbidities associated with type 2 DM. This study provides a basis for further investigations on quality of life of diabetic patients in various regions of Pakistan.

*Correspondence: Abid Azhar, Dr. A. Q. Khan Institute of Biotechnology and Genetic Engineering, University of Karachi, Karachi-75270, Pakistan Tel: 92-21-99261184. Email: abid.azhar@kibge.edu.pk

Introduction

The occurrence of type 2 Diabetes Milletus is a global public health challenge. According to the World Health Organisation (WHO), the global prevalence of type 2 DM, among adults over 18 years of age, is 8.5% making it the seventh leading cause of death. About 1.6 million deaths due to this disease in year 2016 have been reported[1].There has been a rapid increase in reported cases of diabetes which may cause an economic burden on healthcare systems in developing countries[2]. In line with the WHO statistics, the prevalence of diabetes is 9.8% in Pakistan[3]. Obesity and lack of physical activity increase the risk of developing diabetes[3]. In type 2 DM, a combination of biological and physical factors plays a key role to produce high blood glucose level[4, 5]. An important characteristic of type 2 DM is insulin resistance in muscle, liver and fat cells which make these tissues averse to both pancreatic insulin and insulin therapy[6]. Insulin resistance develops before the occurrence of hyperglycemia causing beta cells of pancreas to struggle by increasing insulin secretion[7, 8]. DM2 develops in insulin resistant individuals with the progressive

failure of pancreatic islet β-cells to produce adequate amounts of insulin to maintain normoglycemia which gradually decrease β-cell mass and function due to cell death[9, 10, 11]. In type 2 DM progression, the impairment in the operation of pancreatic islet β-cell begins before the emergence of prediabetes[12,13]. Therefore, this study aimed to identify the risk factors and assess the glycemic management of patients with type 2 DM in Pakistan.

Methods
Design of Study
The study was conducted from August 2016 to August 2018 among 500 type 2 DM patients. The patients were recruited from the Diabetes Clinic in Liaquat National Hospital which is a major tertiary care hospital in Karachi. All clinically diagnosed type 2 DM patients and patients with conditions of hyperlipidemia, obesity and hypertension to analyse the factors influencing glycemic control in patients. Patients with known familial history of diabetes were also included. Subjects with an age range of 18-85 years were considered in the study. The subjects in the control group comprised of similar number, age and gender as the case group and were exposed to the same environment as the patients. Apparently healthy individuals with normal range of blood sugar levels and blood pressure were considered in the control group. Exclusion criteria included all the patients with type 1 DM, hormonal abnormalities, mental illness and pregnant women. The American Diabetes Association (ADA) criteria of fasting glucose levels ($\geq$ 126 mg/dL) was used for the diagnosis of type 2 DM. Fasting plasma glucose was tested in all individuals after abstaining them from ingesting for at least 8 hours. The study was approved by the Institutional Review Board (IRB) of Dr. A. Q. Khan Institute of Biotechnology and Genetic Engineering, University of Karachi and Liaquat National Hospital and Medical College, Karachi (KIBGE/DG/AA-156/15-08-2016).

Data Collection
A questionnaire was administered after obtaining informed consent from subjects. The participants were interviewed in Urdu to obtain their anthropometric and clinical characteristics. The data on patients' age, gender, anthropometrics, random and fasting blood glucose levels were collected.

Biochemical Parameters
The following standards were used for diagnosis of Type 2 DM[14]: i) fasting plasma glucose (FPG) $\geq$ 126 mg/dL, ii) after 75-g oral glucose tolerance test (OGTT), 2-hour plasma glucose $\geq$ 200 mg/Dl, and iii) HbA1c $\geq$ 6.5%
The following cut-off levels for management of dyslipidemia and blood pressure (mmHg) set by American Association of Clinical Endocrinologists (AACE/ACE) were used for calculations[15]: i) LDLc<100 mg/dL, ii) HDLc>40 mg/dL, iii) blood pressure < 120/80 mmHg and iv) triglycerides <150 mg/dL,
The BMI was calculated by using following cut-off points for different categories[16]: i) underweight <18.5 kg/m^2,ii) normal weight 18.5–22.9 kg/m^2, iii) overweight 23-26.9 kg/m^2, and iv) obese $\geq$27 kg/m^2.

Statistical Analysis
The clinical characteristics and socio-demographic data were analysed using descriptive statistics. Frequencies and percentages were used for categorical variables while mean range was calculated for continuous variables. The SPSS (Statistical Package for Social Sciences) version 17.0 was used for these analyses. Data were expressed as mean ± standard deviation with Student's t-test for group comparison. Differences were considered statistically significant at p < 0.001.

RESULTS

Among the 500 participants, the proportion of males (N=270) was slightly higher than females (N=230). The participants were aged between 23 to 82 years.

Anthropometric Characteristics of Patients

The general characteristics of patients are shown in Table 1. Majority of patients participated in the study were obese(59.4%) or overweight (30.6%). Patients were also investigated for the presence of comorbidities associated to type 2 DM. It was found that 57.4% patients were suffering from hypertension and 56% were suffering from hyperlipidemia. Most of the patients (69.2%) were administered with oral anti-hyperglycemic drugs, while 30.8% patients were being treated with insulin. Patient's data about family history of diabetes was also documented and it was found that 62.2% patients had both or either of the two parents suffering from diabetes (Table 1).

Assessment of Age And BMI

The general characteristics of the patients compared with controls, matched by age and gender by using independent samples t-test are presented in Table 2. The average age of patients was 52.1 years while for control subjects it was 52.4 years (SD=10.9). The majority (54%) of patients were men, with females being older 52.2 years (10.3) than males 52.0 years (11.5). The mean age of patients at diagnosis was 44.1 years (9.87), with men being older 44.2 years (10.66) than women 44.0 years (9.09).

Table 1: The common characteristics of patients with DM2 (type 2 diabetes mellitus) (n=500)

Parameter	n (%)
Grouping upon basis of BMI	
Underweight	4 (0.80)
Normal	46 (9.20)
Overweight	153 (30.6)
Obese	297 (59.4)
Medical history of	
Hypertension	287 (57.4)
Hyperlipidemia	280 (56.0)
Treatment of type 2 diabetes mellitus	
Oral hypoglycemic	346 (69.2)
Insulin	154 (30.8)
Familial history of type 2 diabetes mellitus	
Subjects	311 (62.2)

Patients with DM2 presented an elevated mean BMI value (28.7kg/m^2) than control group (25.6 kg/m^2). The difference in BMI between patients of type 2 DM and control group was statistically significant.

Clinical characteristics of patients

The patients had mean glycemic and lipid profiles higher than clinical guidelines. The mean fasting and random plasma glucose levels were 178.6mg/dL and 245.4mg/dL respectively. The control of diabetes was checked through HbA1c quantification. The average HbA1c of the patients was higher (9.02%) than the clinical recommendation. In lipids, following mean serum LDL-cholesterol (107.57mg/dL), HDL-cholesterol (38.11mg/dL) and triglycerides (192.42mg/dL) levels were documented (Table 3).

Table 3: Biochemical parameters of patients with DM2 (type 2 diabetes mellitus)

Parameter	Mean (SD) [range] N=500
Fasting plasma glucose (mg/dL)	178.67 (79.75) [70-600]
Random plasma glucose (mg/dL)	245.46 (102.62) [69-672]
HbA1c (%)	9.02 (2.03) [5-16.7]
LDL-cholesterol (mg/dL)	107.57 (40.42) [87-281]
HDL-cholesterol (mg/dL)	38.11 (10.05) [6-74]
Triglycerides (mg/dL)	192.42 (146.26) [37-1158]

Comparison of random blood sugar of patients and controls

The difference between random glucose (246.07mg/dL) of patients with DM2 and control group (98.19mg/dL) was found to be significant (Table 3).

Table 3: The assessment of random glucose of patients with type 2 diabetes mellitus (DM)[a] and control group

	Type 2 DM (n=500)	Control (n=500)[b]	P value
Random glucose, mean (SD), [range]	246.07 (102.73) [69-672]	98.19 (16.58) [68-160]	<0.001
Females	254.05 (109.89) [80-672]	96.78 (14.89) [74-150]	<0.001
Males	238.14 (95.58) [69-586]	99.60 (18.28) [68-160]	<0.001

[a]For evaluation of means the standard2-tailed *t* test was applied
[b]Selected because of random plasma glucose levels (<200mg/dL), personal interview and questionnaire.

Frequency distribution of general and clinical characteristics of patients
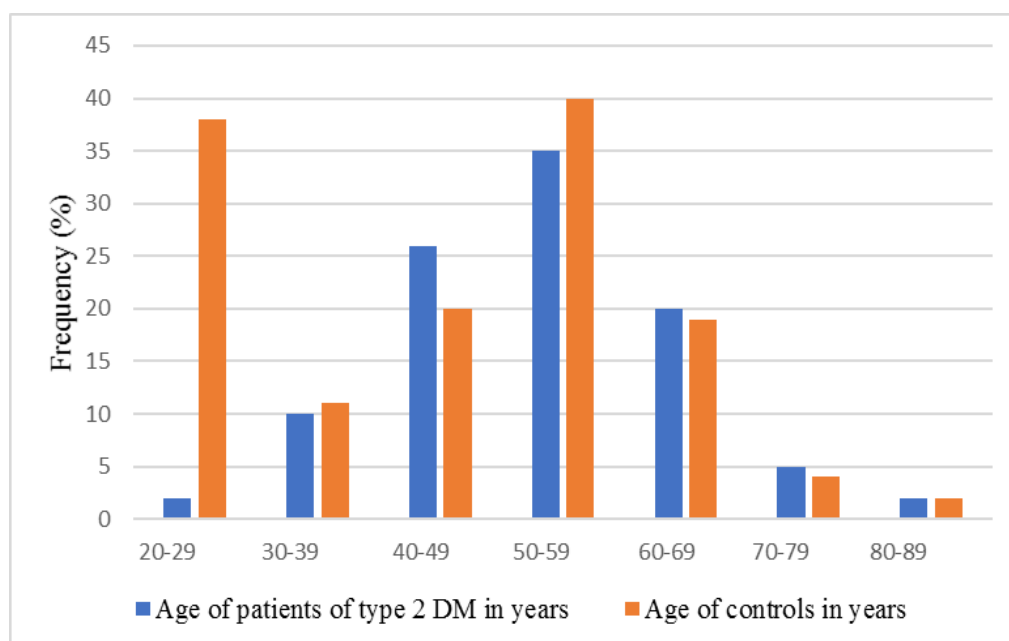
Age distribution of patients and control group is shown in Fig. 1. The maximum number of patients (35%) participated in the study were in age group (50-59) years, followed by age group (40-49) years (26.4%) and (60-69) years (20.0%) respectively. In the control group highest number (40.2%) of subjects belonged to age group (50-59) years, followed by age group (40-49) years (19.8%) and (60-69) years (19.2%) respectively (Fig. 1). The age range in which maximum number of patients (40.4%) were diagnosed with type 2 DM was (40-49) years (Fig. 2). The data demonstrates that majority of the patients (46.0%) participated in the study had diabetes diagnosed in the past 5 years, while (25.4%) and another (14.8%) patients had diabetes diagnosed in last (6-10) and (11-15) years respectively (Fig.3).

Among all recruited subjects only 6.0% had normal limits of fasting blood glucose levels, while all the rest had either suboptimal or poor glycemic control (Fig. 4). Random blood glucose of 26.4% patients was found within normal limits, while all the rest had elevated 2-hour post meal blood glucose levels and failed to achieve glycemic control (Fig. 5).

The glycemic management of patients with type 2 DM measured through HbA1c level shown in Table 5 indicate that the mean HbA1c was 9.10% for females and 8.95% for males and among all the patients only 8% had HbA1c values below 6.5%, of which 92.5% were on oral hypoglycemic drugs. The mean HbA1c of patients who were being treated with insulin was higher (9.80%) than those who had orally administered antihyperglycemic drugs (8.68%). The majority (92.0%) of patients had HbA1c levels above 6.5%, among them 32.8% were being treated with insulin and

67.1% had oral antihyperglycemic therapy. The glycated haemoglobin levels of only 8% patients were falling under normal limits as shown in Fig. 6while all the rest had elevated glycosylated haemoglobin levels and failed to achieve glycemic control.
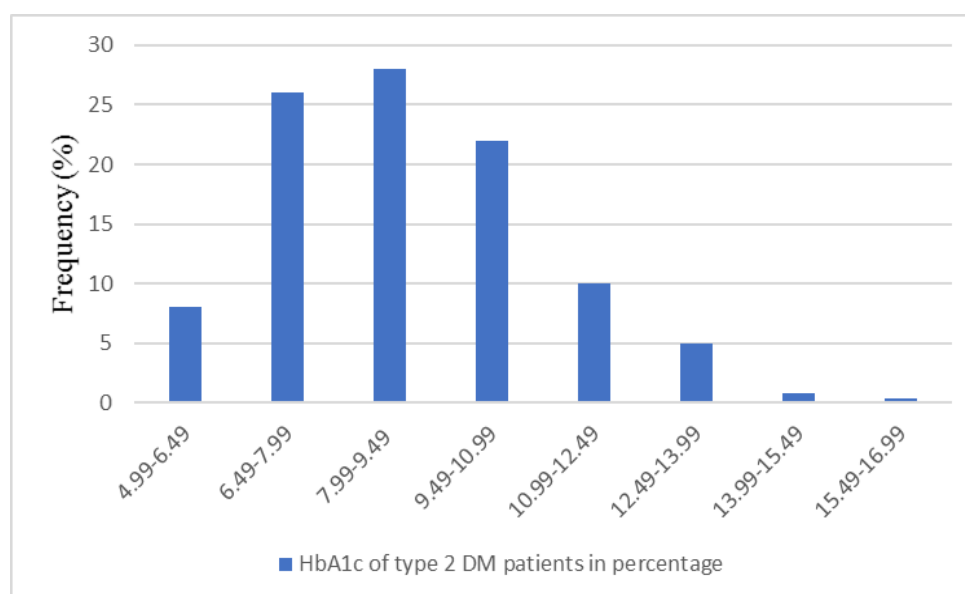

Figure 1. Frequency distribution of age of patients of type 2 DM and control subjects in years
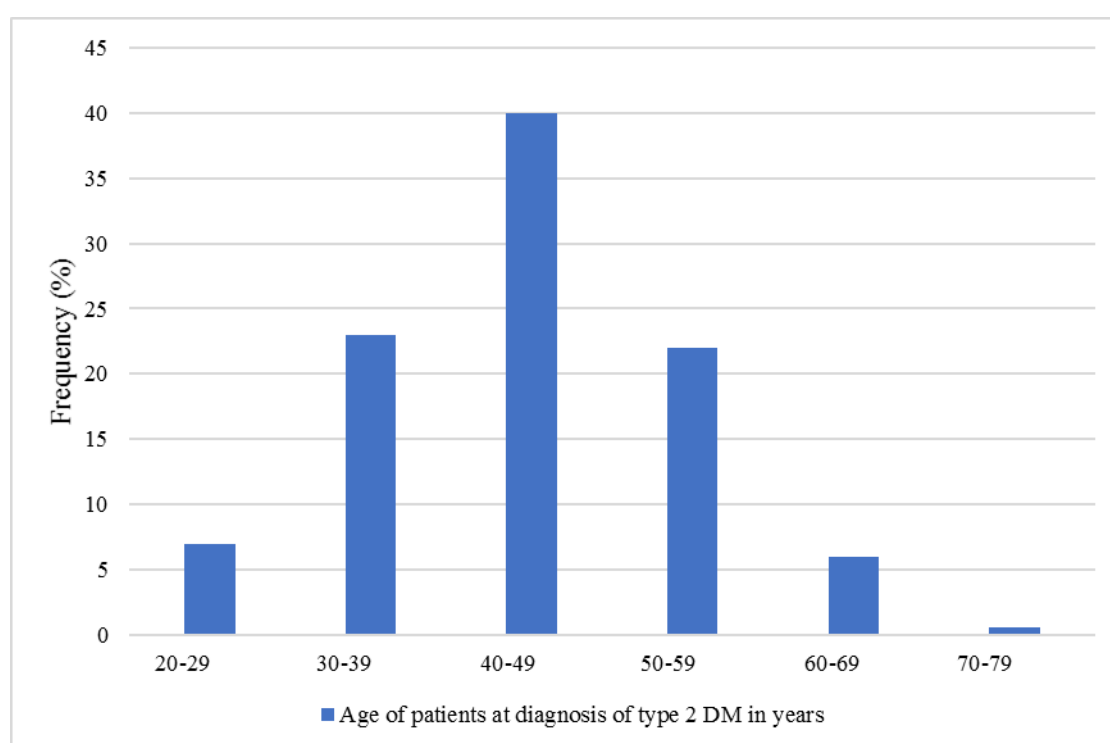
Figure 2. Frequency distribution of age of patients at diagnosis of type 2 DM
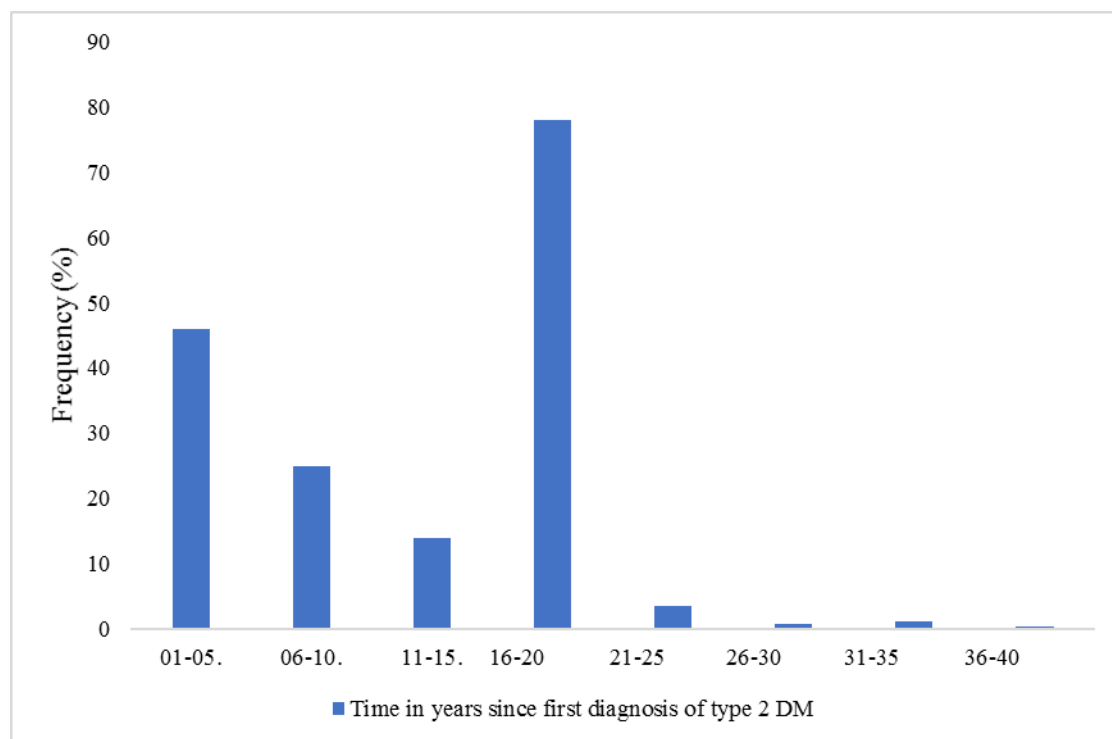
Figure 3. Distribution of duration of time since first diagnosis of type 2 DM
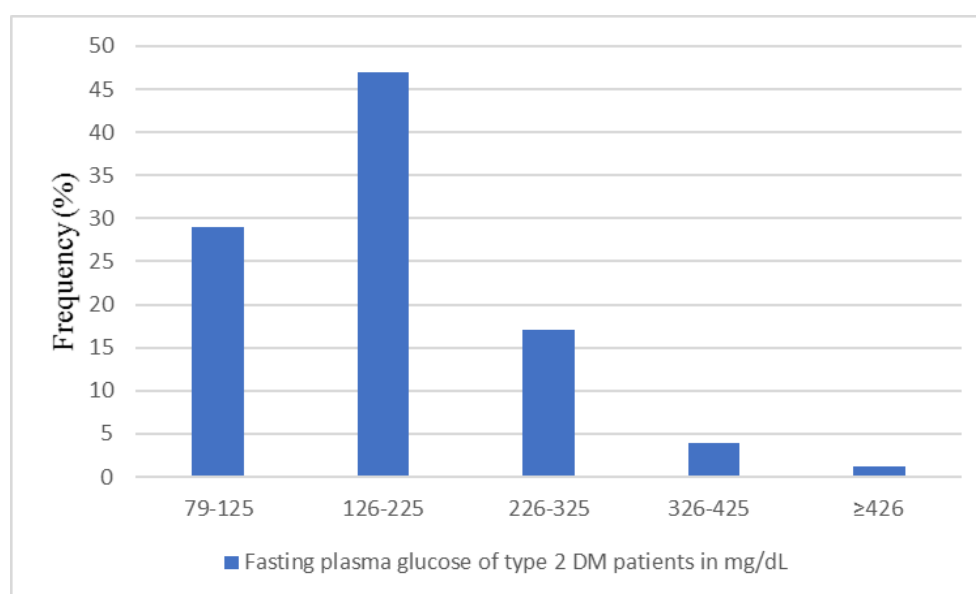
Figure 4. Frequency distribution of fasting blood sugar (FBS) of DMII patients in mg/dL
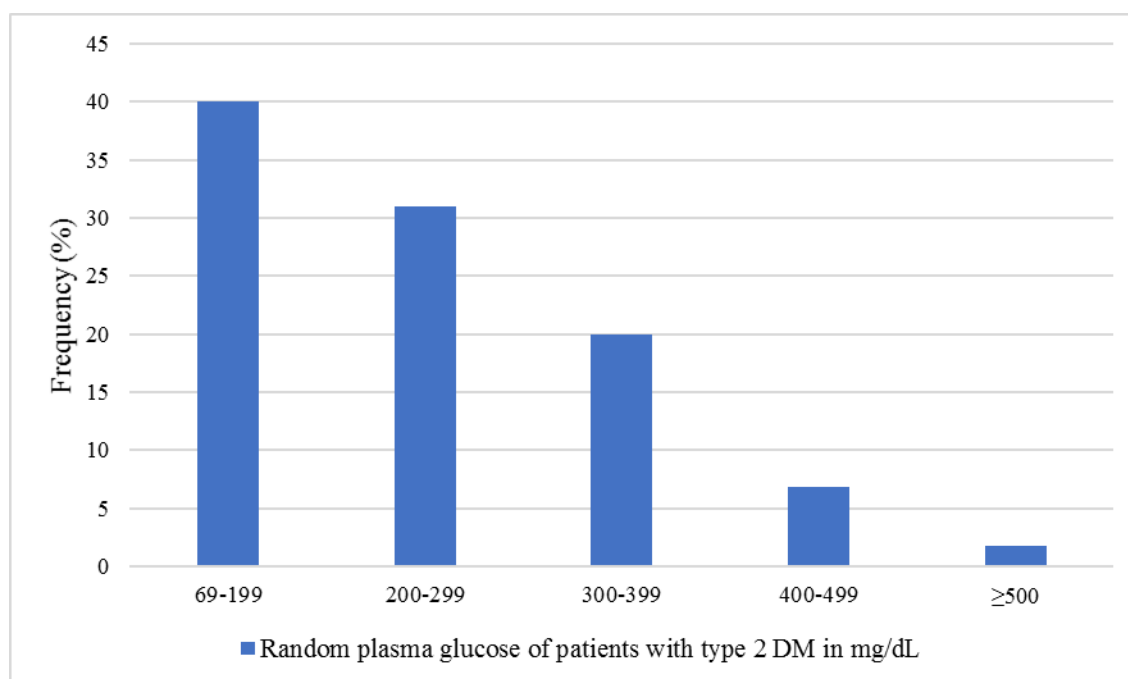
Figure 5. Frequency distribution of random blood sugar (RBS) of DMII patients in mg/dL

Figure 6. Frequency distribution of HbA1c of type 2 diabetes mellitus patients in (%)

Table 5: Glycemic control of patients with type 2 diabetes mellitus (DM2)

| Parameters	Mean (SD) [range]	n (%)	N
HbA1c (%)	9.02 (2.03) [5.00-16.7]	500 (100)	500
Females	9.10 (2.03) [5.3-14.1]	230 (46)	230
Males	8.95 (2.03) [5.0-16.70]	270 (54)	270
Insulin	9.80 (2.00) [5.91-16.10]	154 (30.8)	500
Oral hypoglycemic	8.68 (1.94) [5.00-16.70]	346 (69.2)	500
HbA1c<6.5%	6.06 (0.34) [4.9-6.4]	40 (8.00)	500
Insulin	6.0 (0.09) [5.9-6.1]	3 (7.50)	40
Oral hypoglycemic	6.06 (0.35) [4.9-6.4]	37 (92.5)	40

HbA1c$\geq$6.5%	9.28 (1.90) [6.5-16.7]	460 (92.00)	500
Insulin	9.87 (1.94) [6.5-16.1]	151 (32.83)	460
Oral hypoglycemic	8.90 (1.81) [6.5-16.7]	309 (67.17)	460

For evaluation of means the standard 2-tailed *t* test was applied

Patients With Controlled Biochemical Parameters
The percentage of patients with type 2 DM who had HbA1c, lipid levels and blood pressure under normal limits is shown in Figure 8. Among all patients of type 2 DM who participated in the study only 8% had normal HbA1c levels, while remaining 92% patients didn't meet glycemic control targets. The study has found that majority of patients had poor lipid management with only 39.6% of patients presenting HDL-cholesterol, 42.1% patients showing LDL-cholesterol and 49.1% having triglyceride levels falling under normal limits. The study also documented that blood pressure (BP) is not well controlled in the majority of patients with type 2 DM and found blood pressure controlled to < 130/80 mmHg in only 34% of patients (Fig.7).
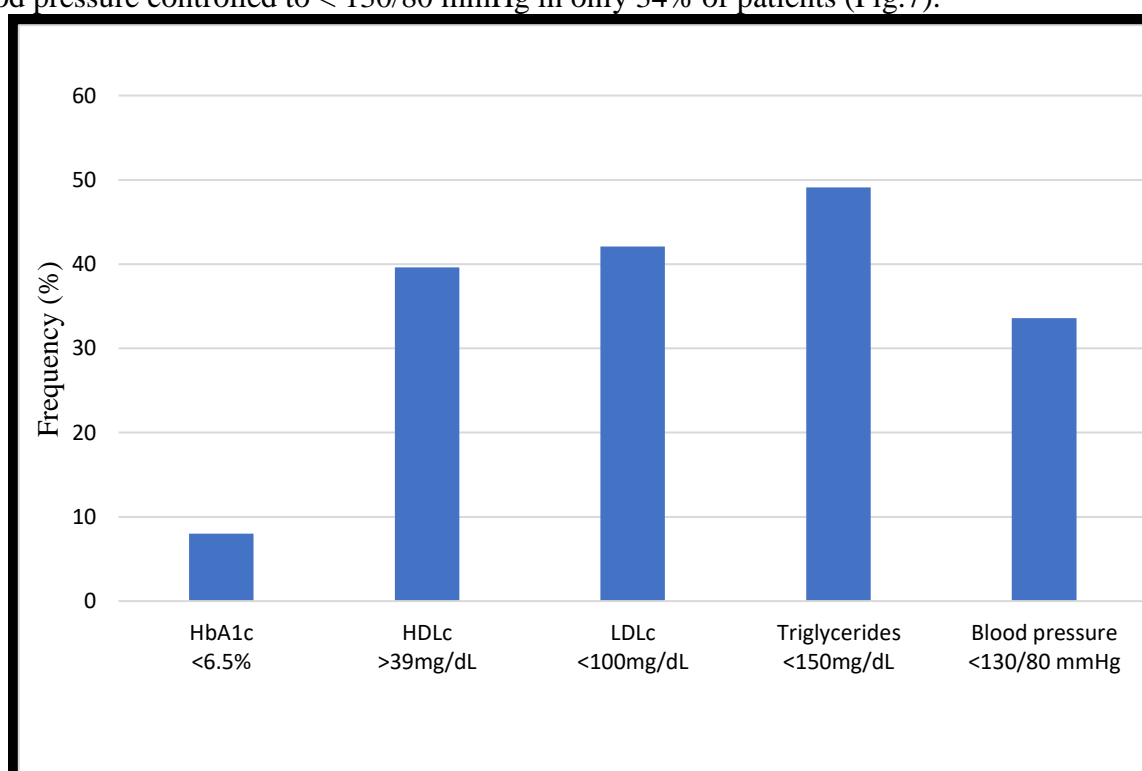
Figure 7. Percentage of patients with type 2 DM having HbA1c levels, lipid profile and blood pressure in normal range. The number of patients evaluable for the respective test whose HbA1c, lipid levels and blood pressure were falling under normal limits are shown in percentage

Discussion
Diabetes is a metabolic disorder, that can occur either by complete absence of insulin or a relative shortage of it, due to impaired insulin production and secretion[17]. Hyperglycemia and alterations in lipid and protein metabolism can be due to insulin resistance and glucose intolerance[18].
The possible risk factors associated with the progression of DM2 includes family history, obesity, chronic physical inactivity, race or ethnicity, history of impaired fasting glucose, impaired glucose tolerance, HbA1c 5.7% to 6.4% (38.8mmol/mol to 46.4mmol/mol), hypertension, abnormal high-density lipoprotein cholesterol and/or elevated triglyceride levels[19]. The poor glycemic control with presence of comorbidities like hypertension, dyslipidemia and obesity increase the risk of cardiovascular disease in comparison to normal subjects[20]. The study has

found that only a small percentage (8%) of patients achieved glycemic goals and had HbA1c levels between normal ranges. This can be attributed to lack of physical activity and poor medical compliance. Moreover, lack of self-care due to less awareness can be considered a major factor for poor glycemic control.

Among all patients 30.6% participants were overweight and 59.4% were obese. Overweight and obesity has been found to be major factors that may be responsible for the development of DM2 in the participants. According to the WHO (World Health Organisation), obesity, overweight and physical inactivity are major factors responsible for the development of DM2 in Pakistan (WHO, 2018). The results were consistent with previous findings in which obesity had been identified as a dominant risk factor for type 2 DM over other factors.[22]

Less awareness along with prolonged diabetes have been found to be linked with suboptimalglycemiccontrol[21].Some determinants of suboptimal glucose levels such as poor self-care management and increased stress about diabetes need to be addressed by health care providers for improving health and life quality of these patients[23].

Patients with uncontrolled diabetes may have increased risk of developing conditions such as diabetic retinopathy, neuropathy, nephropathy and macrovascular disease[24]. These health problems may become more serious in underprivileged sections of society facing lack of resources and access to basic health care facilities. More needs to be done to encourage therapeutic adjustment in line with current guidelines for the management of DM2 with the final objective of achieving glycemic goals to prevent diabetes and its complications.

The current study has some limitations, the study design (cross-sectional study) and thus, a contributory association cannot be implied by the demonstrated association. Secondly, the study was restricted to patients from a single major tertiary care hospital in Karachi, Pakistan.

Conclusions

The DM2 is a disorder is prevalent among Pakistani population. Lack of physical activity and obesity are identified as major factors for development of type 2 DM in Pakistan. The glycemic control of patients on both oral hypoglycemic drugs and insulin is suboptimal. The study indicates that methods for self-care management of diabetic patients should be devised and awareness programs should be run. Further, the study design can provide a guideline for investigations involving different hospitals in various parts of the country to provide better analysis on consequences of DM2 in Pakistan. Identification and management of modifiable risk factors can be implemented to provide better care to patients.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE
Not applicable.

HUMAN AND ANIMAL RIGHTS
No animals were used in this study. The study on humans was conducted in accordance with the ethical rules of the Helsinki Declaration and Good Clinical Practice.

CONSENT FOR PUBLICATION
Not applicable.

AVAILABILITY OF DATA AND MATERIALS
None.

CONFLICT OF INTEREST
The authors declare no conflict of interest, financial or otherwise.

REFERENCES
1. World Health Organization. Diabetes Fact Sheet; 2018. Available from: https://www.who.int/news-room/fact-sheets/detail/diabetes
2. Moucheraud C, Lenz C, Latkovic M, Wirtz VJ. The costs of diabetes treatment in low-and middle-income countries: a systematic review. BMJ global health. 2019 Feb 1;4(1):e001258.
3. World Health Organization. Diabetes country profiles; Pakistan. 2016. Available from: https://www.who.int/diabetes/country-profiles/pak_en.pdf?ua=1
4. Pinti MV, Fink GK, Hathaway QA, Durr AJ, Kunovac A, Hollander JM. Mitochondrial dysfunction in type 2 diabetes mellitus: an organ-based analysis. American Journal of Physiology-Endocrinology and Metabolism. 2019 Feb 5; 316(2):E268-E285.
5. Bonnefond A, Froguel P. Rare and common genetic events in type 2 diabetes: what should biologists know?. Cell metabolism. 2015 Mar 3;21(3):357-68..
6. Goedeke L, Perry RJ, Shulman GI. Emerging pharmacological targets for the treatment of nonalcoholic fatty liver disease, insulin resistance, and type 2 diabetes. Annual review of pharmacology and toxicology. 2019 Jan 6;59:65-87.
7. Reaven GM. Banting Lecture 1988. Role of insulin resistance in human disease. 1988. Nutrition (Burbank, Los Angeles County, Calif.). 1997 Jan;13(1):65-6.
8. Latres E, Finan DA, Greenstein JL, Kowalski A, Kieffer TJ. Navigating two roads to glucose normalization in diabetes: automated insulin delivery devices and cell therapy. Cell metabolism. 2019 Mar 5;29(3):545-63.
9. Kasuga M. Insulin resistance and pancreatic β cell failure. The Journal of clinical investigation. 2006 Jul 3;116(7):1756-60.
10. Butler AE, Janson J, Bonner-Weir S, Ritzel R, Rizza RA, Butler PC. β-cell deficit and increased β-cell apoptosis in humans with type 2 diabetes. Diabetes. 2003 Jan 1;52(1):102-10.
11. Böni-Schnetzler M, Meier DT. Islet inflammation in type 2 diabetes. InSeminars in immunopathology 2019 Jul 1 (Vol. 41, pp. 501-513). Springer Berlin Heidelberg.
12. Yang Y, Wang M, Tong J, Dong Z, Deng M, Ren X, Li H, Yang J, Meng Z, Sun J, He Q. Impaired glucose-stimulated proinsulin secretion is an early marker of β-cell impairment before prediabetes stage. The Journal of Clinical Endocrinology & Metabolism. 2019 Oct;104(10):4341-6.
13. Mezza T, Cinti F, Cefalo CM, Pontecorvi A, Kulkarni RN, Giaccari A. β-cell fate in human insulin resistance and type 2 diabetes: a perspective on islet plasticity. Diabetes. 2019 Jun 1;68(6):1121-9.
14. American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes—2019. Diabetes care. 2019 Jan 1;42(Supplement_1):S13-28.
15. Jellinger PS, Handelsman Y, Rosenblit PD, Bloomgarden ZT, Fonseca VA, Garber AJ, Grunberger G, Guerin CK, Bell DS, Mechanick JI, Pessah-Pollack R. American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease. Endocrine Practice. 2017 Apr 1;23:1-87.
16. Asian American Diabetes Initiative (download 2019). BMI Cutoff for Asians. Joslin Diabetes Center http://aadi.joslin.org/content/bmi-calculator.
17. Nolan CJ, Ruderman NB, Kahn SE, Pedersen O, Prentki M. Insulin resistance as a physiological defense against metabolic stress: implications for the management of subsets of type 2 diabetes. Diabetes. 2015 Mar 1;64(3):673-86.
18. Samuel VT, Shulman GI. The pathogenesis of insulin resistance: integrating signaling pathways and substrate flux. The Journal of clinical investigation. 2016 Jan 4;126(1):12-22.

19. American Diabetes Association. Standards of medical care in diabetes—2013. Diabetes care. 2013 Jan;36(Suppl 1):S11.
20. Lowe F, Feng W. Diabetes and Stroke: The Role of Glucose Regulation. The Diabetes Textbook: Clinical Principles, Patient Management and Public Health Issues. 2019:731-46.
21. Milo RB, Connelly CD. Predictors of glycemic management among patients with type 2 diabetes. Journal of clinical nursing. 2019 May;28(9-10):1737-44.
22. Schnurr, T.M., Jakupović, H., Carrasquilla, G.D. et al. Obesity, unfavourable lifestyle and genetic risk of type 2 diabetes: a case-cohort study. Diabetologia 63, 1324–1332 (2020).
23. Jannoo Z, Wah YB, Lazim AM, Hassali MA. Examining diabetes distress, medication adherence, diabetes self-care activities, diabetes-specific quality of life and health-related quality of life among type 2 diabetes mellitus patients. Journal of clinical & translational endocrinology. 2017 Sep 1;9:48-54.
24. Rangel EB, Rodrigues CO, De Sa JR. Micro-and macrovascular complications in diabetes mellitus: preclinical and clinical studies. Journal of diabetes research. 2019.