Dietary and Pharmacological Management of Plasma Glucose, Triglyceride and Glycated Hemoglobin among Patients with Type 2 Diabetes Mellitus

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Abstract

Introduction: Diabetes mellitus type 2 (DM2) is among leading causes of mortality in Occupied Palestinian territories and providing data on its level of management using pharmacological and dietary approaches is important to provide policy makers of possible gaps in clinical practice.

Aims: we aimed to study the level of control of recently diagnosed patients with DM2 and patterns of pharmacological treatment and dietary intakes in relation to clinical endpoints.

Methods: we used semi-structured questionnaire, medical records, anthropometric measurements and biochemical measurements to assess plasma glucose, Glycated hemoglobin (HbA1C), medical and medication history, measurement of obesity

Results

105 participants were included in this analysis with few missing data for some sub-analysis. Average age was (56.8 ± 8.1 y), medians for glucose (160 (150, 180)mg/dl), Triglyceride (TG (155 (140, 170) mg/dL), HbA1C (8 (7, 9)%). Metformin was associated with best HbA1C control compared to groups who used insulin ($p < 0.01$). Also, HbA1C and glucose were different across fish intake categories. Nuts were associated with modest improvement in HbA1C. Plasma TG was not modified by study variables.

Conclusion

Metformin, fish intake and nuts intake were associated with improvement in glucose and HbA1C among diabetic patient in Palestinian territories.

Introduction

Diabetes mellitus type 2 (DM2) is a chronic health condition through which human body has impaired glucose regulation. In DM2 there is impairment in insulin sensitivity and insulin secretion. The main manifestation of DM2 is hyperglycemia which happens due impairment in uptake and utilization of glucose in synthesis of fat, glycogen and protein (1). The recent increase in the rate of DM2 is associated with changes in society, economic growth and nutrition transition which is associated with increase in rates in obesity and DM2. Awareness about DM2 symptoms, complications and management is linked to improvement in disease outcomes (2). DM2 is associated with macrovascular and microvascular complications such as end-stage renal diseases, retinopathy, neuropathy and lower extremity amputation which cause disease mortality and morbidity and deteriorated life quality. Among all complications, cardiovascular diseases (CVD) is the main cause of death and disability among patients with DM2, with DM2 is associated with 2 to 4 folds increase in the CVD mortality rate(3). The diagnosis of DM2 is based on clinical symptoms and measurement of glucose and glycated hemoglobin according to American diabetes association cut off points

In a work published in 2019, DM was the fourth leading cause of death in Palestine, the prevalence is 9.1% in patients aged 20–79 y and predicted to increase to 20.6%. The Palestinian Healthcare system is a mixture of governmental, non-governmental, United Nations Relief and Work agency and Palestinian medical services(4). Diabetes can be prevented by effective lifestyle management such as healthy diet, regular physical activity, normal body weight and avoiding tobacco. The Palestinian ministry of health reported that half of patients with DM2 have obesity. Increase in fruit intake, vegetables and whole grains is valuable in preventing chronic diseases. Also, regular physical activity improves insulin sensitivity(4).

Emerging new pharmacological treatments does not ease the path to curing this disease. Metformin remains the first choice medication for combating DM2 in most international guidelines. Previously, the use of metformin was hampered by lactic acidosis that could happen as a complication of metformin use in certain health conditions. The mechanism of action of metformin is discussed elsewhere (5). In patients DM2 with glucose levels that can't be adequately regulated by oral hypoglycemic are prescribed insulin as addition to oral hypoglycemic or insulin alone. The use of insulin ranges from one to four times. Despite the use of insulin, many patients fail to achieve adequate control of plasma glucose(6). In United States of America (USA), it is estimated that 29.1% of patients with DM2 uses insulin either as insulin alone or insulin with oral hypoglycemic.

There is consensus among researchers that weight loss of about 5% of body weight or more is associated with improving glycemic control in patients with DM2 and preventing DM2 in patients with prediabetes. The main recommendations include restricting energy intake, reducing total fat and saturated fat, increasing fiber intake and increasing physical activity (7). Dietary biochemical markers were studied in Swedish cohort to find a significant association between whole grains, beef, fish were significantly and glucose control(8). Fish consumption among patients with DM2 is associated with reduced risk of mortality(9).

CVD is the leading cause of death in developing countries including Palestine. The aggregation of certain risk factors including; high level of triglyceride, Low density lipoprotein (LDL), very low density lipoprotein (VLDL), glycated hemoglobin (HbA1C), hypertension, microalbuminia, low concentration of high density lipoprotein (HDL) and high body mass index (BMI)is associated with increase in the risk of CVD. Dyslipidemia is a major factor that contributes to CVD(10). Diabetic dyslipidemia is usually managed with statins and some studies suggest that the disease could be managed by intake of omega 3 fatty acids(11).

The goal of this study was to describe glycaemia control characteristics among patients with DM2 including pharmacological management and dietary management.

Methods

Population and Sample Size

The newly reported DM2 cases who visited Palestinian Ministry of Health Primary Health Care diabetic clinics in the West Bank in 2019 reached 5,671 (573 in Nablus alone). Reaching a total number of 248008 DM2 cases in the West Bank according to Palestinian Ministry of Health records.

Sample Size and Sampling Technique

Using the Robert Mason equation, the sample size of the participants totaled (105) and the convenient sampling method was used to select them Participants were included in the current study if they are DM2 patients from Almakhfya clinic in Nablus city from both genders and are more than 30 years old, and were excluded if they had Alzheimer's patient.

Data Collection Tool

A structured questionnaire was used to collect the data through interviewing the participants. The questionnaire included the following sections.

Socio-Demographic Data; (Sex, residency location, marital status, educational level, monthly income, occupational status). Information regarding the medical History were obtained from record of information about a person’s health, including information about illnesses

(current and past), surgeries, medicines taken and health habits, such as diet and exercise.

Anthropometric measurement included weight which was measured using an electronic scale in kilograms with precision of ± 0.1. Participants were weighed wearing light clothes without shoes. Height was measured using a stadiometer. BMI and WC were obtained.

Dietary Assessment.

The FFQ modified from Shen *et al*. (2019)(12), was used to assess the omega-3 FAs intake, participants were instructed to describe accurately with details the food portion size during the interview. The participants’ responses to FFQ were converted by recoding the answers into numeric values. The recoding was conducted as follows: three points were given for “more than 3 times” answers; two points were given for “1–3 times” answers; one point was given for “0 times”. Additionally, for yes or no questions, the answers “yes” were converted into two points and “no” into one point. Data from FFQ was converted manually into average daily 18 intake data using the fact sheet for omega-3 FAs provided from United States Department of Agriculture .

Biochemical Tests

To determine blood glucose level, HbA1c and blood triglyceride levels, blood samples were collected over the period of two months (from 24thof September, 2019 till the 5th of November, 2019) during the clinic’s day hours. In collaboration with the laboratory administration and after participants’ approval, blood samples were collected at a medical laboratory with the help of nurses working at Almakhfya Clinic in Nablus city. Blood was drawn from fasting participants. Biochemical tests were done soon after blood collection with the help of nurses at Almakhfya Clinic.

Validity and Reliability

After a translator translated the data collection tool into Arabic, content validity was used. Finally, the tool was reviewed by experts, the ten copies of the questionnaire were distributed to the doctors from An-Najah National University for their opinion and to ensure the

reliability of the questions and the ease of understanding among the participants and to ensure the relevance of the questionnaire to subject under study.

Pilot Study.

A pilot study was conducted on (5%) of the sample size and was included in the sample size. It was conducted to determine the clarity of the questionnaire and to estimate the time 19 necessary for the data collection. The reliability scale (Alpha Cronbach) was computed, with a

result of 0.83. This value indicates that the instrument is acceptably valid.

Field work and procedure

125 blood samples (5.0 ml each) were collected from each participant in EDTA tubes, centrifuged at 4000 rpm at room temperature for 10 minutes to separate cells from the plasma and stored at -60°C until analysis. Half of the samples were stored at AlMakhfya clinic's laboratory for further biochemical tests (analyzed by nurses and recorded in participant's medical files) such as HbA1c,

blood triglycerides level and blood glucose level.. The rest of samples were stored in the laboratory of the Department of Public Health at

the An-Najah National University to determine the amount of EPA and DHA in plasma. Medical records for each participant was used to obtain all information needed for the research (including medications).

Statistical Analysis Study variables were checked for normality and summarized as median, interquartile range, or percentages. Measures of obesity, glycaemia and dyslipidemia were compared across study variables categories using ANOVA or non-parametric comparison. Study variables (outcomes) were compared across various categories of BMI, pharmacological treatment of DM2. Measures of obesity, glycemia and dyslipidemia were compared across food intake categories of many important food groups using ANOVA. Bivariate correlation was calculated between variables of interest. All data was analyzed using SPSS 21.

Results

This study included 105 participants from patients with Diabetes mellitus who consult the Palestinian Ministry of Health. The study included almost equal percentages of males and females. Our study sample were mostly females. Most of our study group have bachelor's degree and older than 46 y. Most of our study participants were smokers. Continuous variables are described in Table 1.

In this study group, females had higher BMI than males, smokers and not working people had lower WC. Main study variables including measures of glycaemia including HbA1C and plasma glucose. In addition to TG are not different according to categories of sex, education, occupational status, chronic diseases and smoking status.

In Table 3 participants who obese had significantly higher HbA1C than overweight participants.

Our study indicates that participants who used metformin had the lowest HbA1C compared to adults who use insulin and metformin and insulin mixture. Moreover, glucose was the lowest in the group who used insulin alone, but this did not reach statistical significant. It is worthy to mention that groups who used insulin had lower BMI than group who used BMI.

The last table indicates that increase in fish intake increases the HbA1C and glucose significantly ($p < 0.05$), whereas the intake of nuts was associated with lower HbA1C.

Discussion

This study included 105 participants who are being treated for DM2 in outpatient clinics of Palestinian Ministry of Health. Our study group had mainly adequate control of HbA1C and TG. This study group showed that obese patients who used metformin were in better control of DM2 than other groups who used insulin, although use of insulin was not very common. Consumption of fish and nuts although showed protective effect in Patients with DM2 but this relationship was fluctuating with groups in the highest category of fish consumption having higher plasma glucose and HbA1C. The only factor that was associated with TG is body fat, TG was low and use of atorvastatin is common.

The Palestinian society is continuously changing because there is a shift from traditional Mediterranean diet to westernized foods and readily prepared food. The classical risk factors for CVD are increasing including smoking, obesity, dyslipidemia and type 2 diabetes mellitus (DM2) (13). DM2 happens at rate of 10% in Palestinian Occupied territories and its risk factors include: age, positive family history, high TG level and high waist to hip ratio (14). The American Diabetes Association estimates that the yearly cost of treating a person with DM2 is 5 times more than a person without DM2 (13, 243 USD versus USD 2,560). Blindness, leg amputation and people with DM2 may die from CVD. Cost for DM2 comes from medications such as insulin and oral hypoglycemic, hospitalization, consultation and treatment for complications(15). In our study group, fat mass correlated significantly with plasma glucose, and adults who are obese have higher HbA1C than adults who are less obese. Sex, education, working status and smoking were not significantly related to measures of glyceamia.

Majority of our study group used metformin to control DM2. Fewer number of participants used combination of insulin and metformin and insulin alone. HbA1C was the lowest among the group who used metformin. At the same time, the group that used metformin were more obese. Metformin which is dimethylbiguanide has become first line therapy for oral glucose lowering agent to manage DM2 (16). The primary role of metformin in prevention of DM2 is through suppression of hepatic glucose production. Also, metformin may interfere with energy metabolism through activation of AMP-activated protein kinase and also through inhibition of gluconeogenesis (17). The benefits of metformin for human health is beyond its effect on lowering glucose levels. Metformin is associated with weight loss in cohort studies and the mechanisms involved include reduction in hepatic gluconeogenesis and reduction in insulin production. Other evidence indicate that metformin reduces weight due to modifying appetite regulatory centers, altering gut microbiome(18). Use of metformin is more common among obese participants. In our study, users of insulin were fewer than users of metformin. Worldwide, the number of persons who used insulin in 2018, 405.6 million (95% CI 315·3 million–533·7 million) and this number is projected to increase by 100 million by 2030. The ultimate goal of use of insulin is to reduce disability related lost years, however use of newer oral anti-hyperglycemic drugs and aiming for higher HbA1C, the use DALYs that will be averted will increase (19).

In our study frequent consumption of fish is associated with fluctuations in plasma glucose levels, with people with more modest consumption of fish are more likely to have better glycemia control values. Fish consumption is associated with reduced levels of inflammatory markers.The anti-inflammatory related to consumption of fish is associated with reduced production pro-inflammatory eicosanoids derived from arachidonic acid and increased conversion of Eicosapentanoic acid (EPA) and decosahexanoic acid (DHA) to anti-inflammatory to eicosanoids (e.g PGE3, TXA3, LTA5), resolvins and protectins. Other components include Se, taurine and proteins(20). We showed previously in studies from Inuit people of Canada, that consumption of fish is associated with increase in blood glucose (21). The consumption of fish is associated with increase in metals and organic pollutants (POPs) which is associated with increased risk of DM2 which could lead to reduced insulin secretion(22). One study on fish collected from Mediterranean Sea indicated that fish is associated with contamination. Author was unable to find studies that link fish consumption to other socioeconomic and life-style factors.

Nuts and tree nuts are botanically defined as dry fruits with a single seed and an ovary wall which becomes hard at maturation. In Palestine, among edible nuts in Palestine are; almonds, cashews, macademia and walnuts, peanuts. Consumption of 5 servings of nuts per week was inversely associated with lowering DM2 in Nurses' Health Study, but other studies did not show significant relationships (23). Our study indicates that HbA1C is reduced by nuts intake, but plasma glucose was not reduced by nuts intake. There was no consistent association between nuts intake and obesity. According to author knowledge, most Palestinian people consume salted nuts, but how intake of salt in this case affect CVD needs further studies.

Our data indicate that there is no association between TG and plasma glucose and HbA1C. Increase in plasma triglyceride (TG) is a leading cause of cardiovascular disease in patients with diabetes mellitus (DM2). In human plasma triglycerides are always carried by lipoproteins such as VLDL and LDL, insulin regulates VLDL concentrations through lipoprotein lipase. Hyperglycemia is not always associated with increase in plasma TG but insulin, so when there is insulin resistance associated with increase in insulin the level of plasma TG will increase(24). 84% of the study group used Atorvastatin which represents the most suitable method to lower the risk of CVD in patients with DM2(25). Having high TG is common among patients who use statins to control the cholesterol which is associated with more common CVD related to increase in TG. The level of TG is low in this group indicating that the level of insulin resistance did not induce hypertriglyceridemia, but other data is needed to analyze CVD risk in this study group(26).

Conclusion

In summary, in a study among a group of patients with DM2 we found that patients with normal, excellent and good HbA1C were more common, and that better glucose and HbA1C control was among patients who used metformin compared to insulin. Modest consumption of fish and nuts helped to control plasma Glucose and HbA1C, whereas other dietary items were not related to the control of glycemia. Also, the use of atorvastatin to control dyslipidemia was very frequent among our study participants and plasma TG was low but whether this was related to better protection from CVD is inconclusive. Our work is not without limitation including its cross sectional design and small number of participants.

Table 1
Description of Main Study Outcomes according to Study Variables Categories

Variable		HbA1C	Glucose	TG	WC	BMI
Sex	0	8.0 ± 8.0	159 ± 226	152 ± 614	106 ± 62	30.1 ± 25.6**
	1	7.7 ± 6.6	160 ± 250	160 ± 263	99.5 ± 77	33.4 ± 35.1
Educational Status	1	7.6 ± 8	165 ± 209	157 ± 176	109.5 ± 51	32.6 ± 25.1
	3	7.6 ± 3.6	178.5 ± 235	158 ± 234	101.0 ± 55	32.4 ± 24.7
	5	8.0 ± 3.9	155 ± 241	155 ± 588	99.0 ± 77	31.1 ± 35.1
	6	8.0 ± 8.0	156 ± 33	160 ± 65	110 ± 37	31.0 ± 35.1
Occupational status	0	8 ± 8	155 ± 226	160 ± 614	98.5 ± 77*	31.1 ± 25.6
	1	7.7 ± 6.6	165 ± 250	155 ± 263	110.0 ± 59	32.0 ± 35.1
Chronic diseases	0	8 ± 8	160 ± 250	160 ± 614	102 ± 77	32.0 ± 35.1
	1	8 ± 8	164 ± 53	155 ± 263	97 ± 48	26.0 ± 25.1
Smoker	0	8.0 ± 6.3	160 ± 226	155 ± 617	102 ± 77*	31.0 ± 26.6*
	1	8.0 ± 8.0	160 ± 250	160 ± 173	97.0 ± 48	32.0 ± 35.1

Table 2
Description of Study Variables

Variable		N (%)
Sex	0	49 (46.7%)
	1	56 (53.3%)
Educational Status	1	30 (28.6%)
	3	22 (21%)
	5	42 (40%)
	6	11 (10.5%)
Occupational status	0	49 (46.7%)
	1	56 (53.3%)
Chronic diseases	0	93 (88.6%)
	1	12 (11.4%)
Smoker	0	32 (30.5%)
	1	73 (69.5%)
Variable	n	Median
HbA1C	95	8 (7, 9)
Glucose	98	160 (150, 180)
TG	97	155 (140, 170)
% Fat	98	35 (33, 35)
WC	98	101.5 (96, 114)
BMI	105	31.8 (28.7, 35.1)
Age	105	56.8 ± 8.1

Table 3
Comparison between Study Outcomes across Pharmacological category treatments.

Variable	Insulin (n = 7)	Metformin (n = 80)	Insulin + Metformin (n = 8)	P-value
HbA1C	8.50 ± 4	7.65 ± 6.6	9.50 ± 6.5	0.015
Plasma glucose	187 ± 156	158 ± 235	165 ± 203	0.21
Triglyceride	150 ± 158	155 ± 263	108 ± 614	0.67
Body Fat	34 ± 7	35 ± 23	33 ± 19	0.94
WC	100 ± 28	105 ± 62	99 ± 77	0.71
BMI	29 ± 30	32 ± 27	29.2 ± 25.6	0.07

Table 4
Comparison between Study Outcomes across BMI categories.

Variables	BMI (5)	BMI (n = 31)	BMI (n = 69)	P-value
HbA1C	9.9 ± 6.2	7.6 ± 5.7	8.0 ± 6.6	0.039
Plasma glucose	159.0 ± 50	160.0 ± 183	160 ± 250	0.970
Triglyceride	155± 158	150 ± 213	155 ± 588	0.92
Body Fat	29.0 ± 11	33 ± 10	35 ± 23	0.04
WC	87 ± 16	98.5 ± 52	110 ± 55	0.71
BMI	21.80 ± 4.93	27.91 ± 4.88	33.56 ± 22.05	0.006

Table 5
Comparison between Study Outcomes across Food intake categories.

Fish	**HbA1C**	**Glucose**	**TG**	**BMI (Kg/m2)**	**WC (cm)**
1 (n = 16)	9.0 ± 6	165 ± 92	167 ± 103	30.7 ± 34.3	99 ± 60
2 (n = 11)	7.4 ± 5.4	166 ± 142	155 ± 116	31.6 ± 20.9	112 ± 34
3 (n = 7)	9.0 ± 6.1	196 ± 212	145 ± 263	32.0 ± 12.7	106 ± 17
4 (n = 22)	8.0 ± 8.0	155 ± 235	140 ± 614	32.0 ± 18.9	99 ± 62
5 (n = 32)	7.0 ± 4.0	155 ± 121	160 ± 85	31.6 ± 18.9	103.5 ± 44
6 (n = 5)	8.0 ± 4.0	156 ± 105	161 ± 96	34.5 ± 14.6	115.5 ± 28
7 (n = 2)	8.8 ± 0.6	195 ± 59	94 ± 26	28.1 ± 6.0	98.0 ± 4
F, p-value	2.4, 0.035	2.22, 0.05	0.41, 0.87	0.54, 0.78	1.67, 0.14
Meat					
1	8 ± 6.6	164.5 ± 250	160.0 ± 579	31.2 ± 34.3	100.5 ± 77
2	9.2 ± 7	162 ± 197	103.0 ± 119	30.1 ± 13.3	99.0 ± 28
3	7.6 ± 3.5	163 ± 150	152.0 ± 184	31.7 ± 20.4	101.0 ± 59
5	8.5 ± 4.0	140 ± 80	147.5 ± 91	32.2 ± 20.8	105.0 ± 33
6	8.0 ± 2.0	158 ± 68	152.5 ± 27	39.5 ± 3.7	120.5 ± 6.0
7	7.0 ± 0.0	160 ± 0	160.0 ± 0	28.7 ± 0.0	91.0 ± 0.0
8	6.8 ± 0.4	155 ± 47	170 ± 53	32.4 ± 5.6	106.0 ± 27.0
	1.8, 0.10	0.83,0.55	1.1, 0.40	1.5, 0.18	1.2, 0.30
Nuts					
1	8.0 ± 6.6	158.0 ± 216	156 ± 579	31.1 ± 25.6	101.0 ± 77.0
2	8.0 ± 8.0	164.0 ± 250	160 ± 153	32.7 ± 35.1	110.0 ± 56.0
3	6.8 ± 3.0	155.0 ± 68	150 ± 135	33.1 ± 17.8	98.0 ± 37.0
4	7.1 ± 1.1	138.5 ± 43	98.5 ± 93	31.9 ± 5.0	105.0 ± 14.0
F, p-value	2.5, 0.07	1.7, 0.16	1.5, 0.21	0.26, 0.86	2.7, 0.05
Carbohydrate	8.0 ± 8.0	160 ± 152	156 ± 176	30.0 ± 26.9	108 ± 69
1	7.0 ± 1.0	155 ± 10	170 ± 17	30.5 ± 10.2	111.5 ± 26
2	7.8 ± 6.6	160.0 ± 250	155 ± 588	32.1 ± 35.1	100 ± 62
3					

Fish	HbA1C	Glucose	TG	BMI (Kg/m2)	WC (cm)
	1.0, 0.37	0.8, 0.47	0.16, 0.85	2.20, 0.12	0.60, 0.55
Egg	8.0 ± 6.0	161 ± 101	156 ± 90	30.7 ± 14.4	110 ± 57
1	7.9 ± 8.0	158 ± 250	155.0 ± 260	29.5 ± 33.3	99.0 ± 41
2	8.0 ± 8.0	160 ± 226	155.0 ± 617	32.4 ± 27.4	102 ± 62
3					
F, p-valuetmk	0.35, 0.71	0.55, 0.58	0.02, 0.98	0.88, 0.42	0.14, 0.87

Table 6: Correlation coefficients between measures of

glucose control and measures of obesity and TG:

Variable	R (p)
(HbA1C, plasma glucose)	0.5 ($p < 0.0001$)
(plasma glucose, TG)	0.1 ($p = 0.30$)
(plasma glucose, fat)	0.3 ($p = 0.002$)
(plasma glucose, WC)	0.1($p = 0.38$)
(plasma glucose, BMI)	0.1 ($p = 0.42$)
(HbA1C, TG)	0.1 ($p = 0.32$)
(HbA1C, fat)	0.18 ($p = 0.09$)
(HbA1C, WC)	-0.03, ($p = 0.78$)
(HbA1C, BMI)	-0.13, ($p = 0.21$)

Abbreviations

BMI; Body Mass Index. CVD; Cardiovascular diseases. DHA; Decosahexanoic acid. DM2; Type 2 diabetes mellitus. EPA; Eicosapentaenoic acid. FA; Fatty acid. FFQ; Food frequency Questionnaire. HbA1C; Glycated Hemoglobin A1C. LDL; low density lipoprotein TG; Triglyceride. USA; United States of America. USD; United States Dollar. VLDL; Very low density lipoprotein. WC; waist circumference

Declarations

Ethics Approval and Consent to Participate

This study was approved by Najah University IRB board. Informed consent was obtained. All methods were carried out in accordance with relevant guidelines and regulations (declaration of helsinki).

Consent for publication

NA

Availability of Supporting Data

Data is available upon request

Competing Interests

None

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None

Author Contributions:

NN designed and implemented the study, MA and FB and NN collected data and drafted the paper. AS provided review.

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Figures

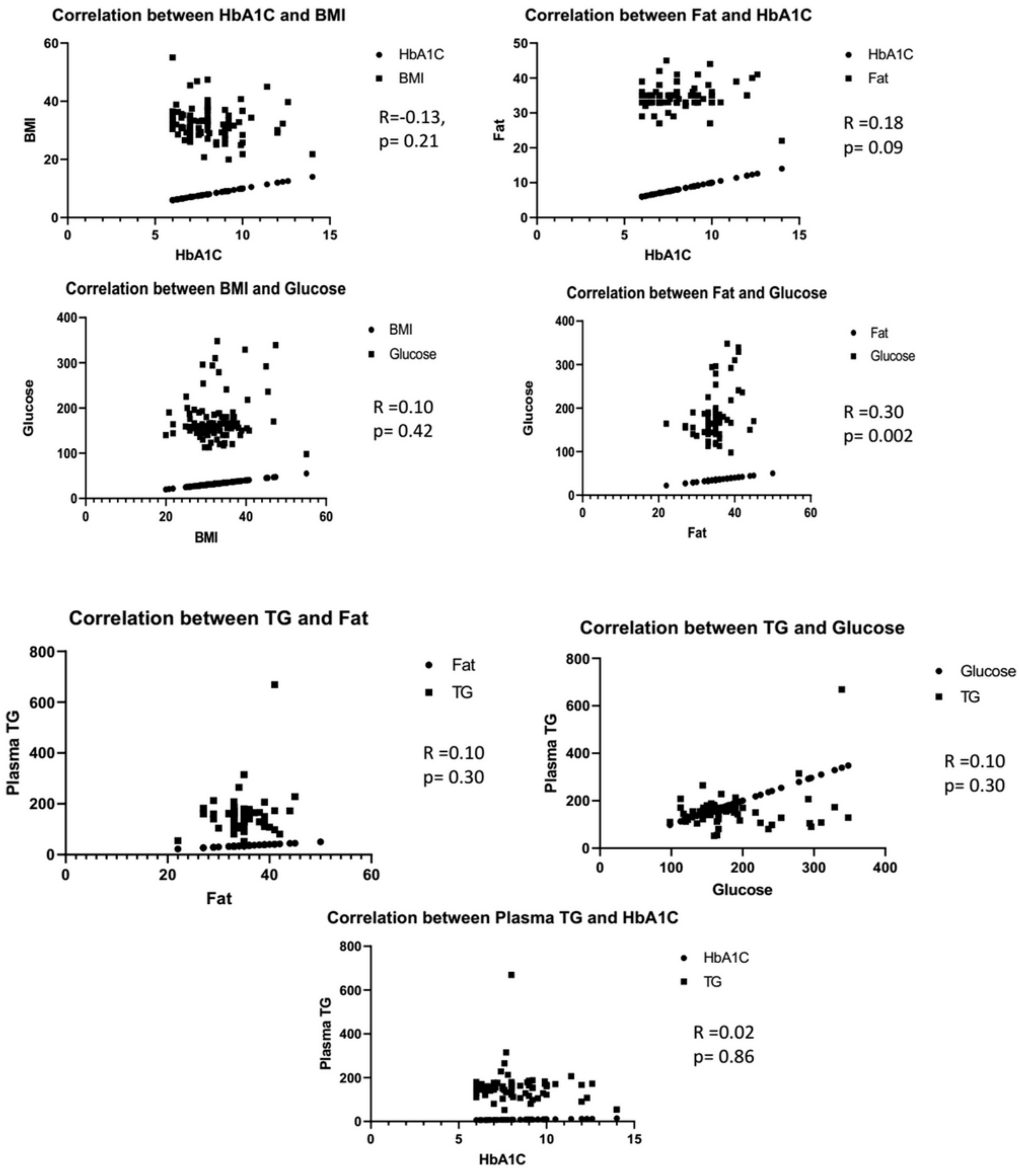

Figure 1

Correlation coefficients between measures of glucose control and measures of obesity and TG

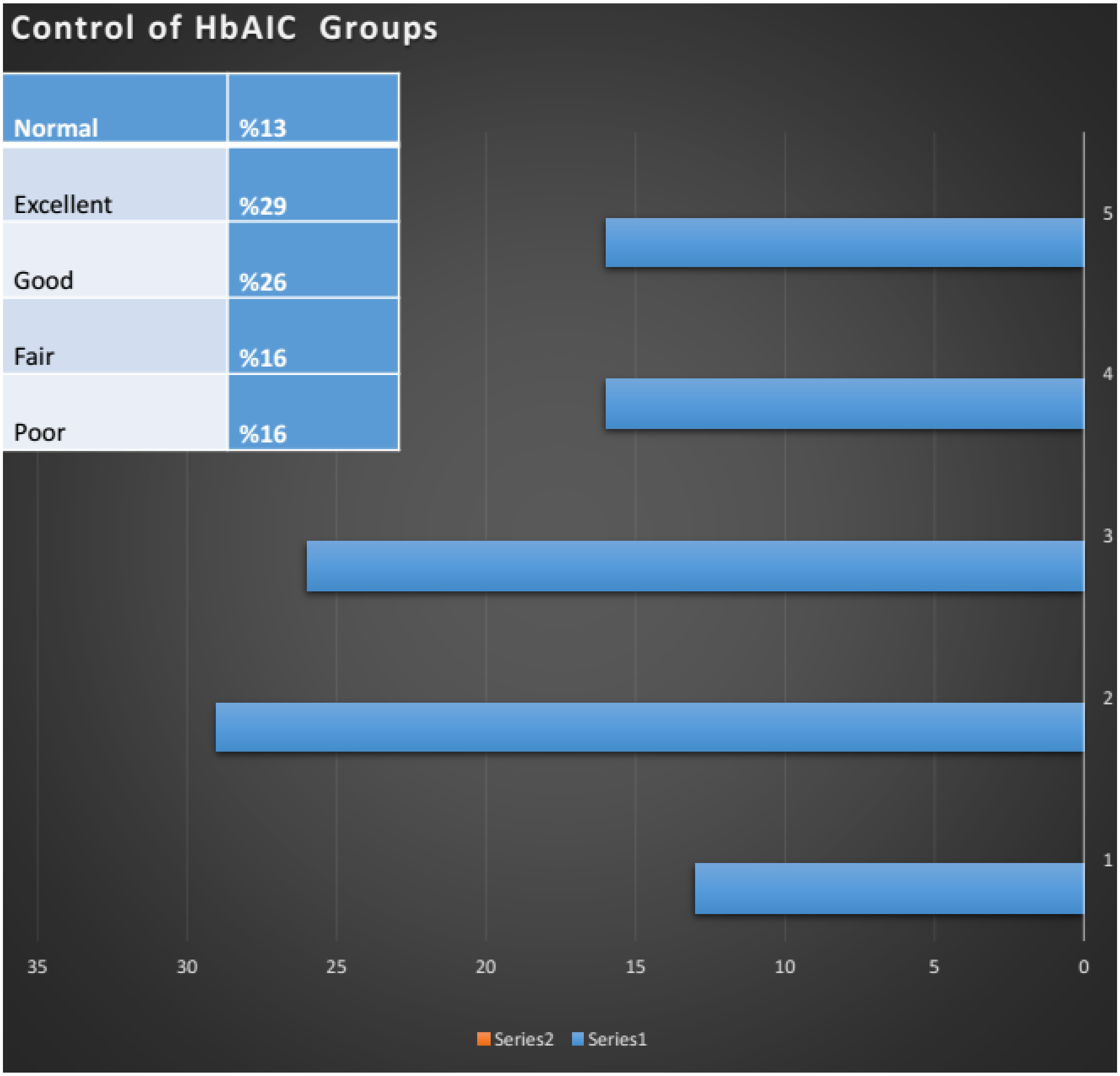

Figure 2

Categories of Glycaemia Control in Study Group