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Original Article

Evaluation of Low Dose Metformin Response and Dyslipidemia Levels in Patients with Pre-diabetes

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ABSTRACT

Objective: This study aimed to investigate the effectiveness of low-dose metformin on the HbA1c and plasma lipid levels in pre-diabetic individuals.

Methods: Between 2018 and 2020, 357 patients with HbA1c levels of 5.7–6.4% were included in the study. The level of HbA1c and lipid response was evaluated in cases followed up for a minimum of 9 months with 1000 mg/day metformin.

Results: A complete response was observed in 39% of the group with HbA1c levels of 6–6.4%, whereas that in the group with HbA1c levels of 5.7–5.9% was 77%. While the response obtained before the age of 40 was 70%, the response was obtained in 36% of the cases over the age of 40. A decrease in non-HDL cholesterol components was observed in 23% of the pre-diabetes cases using low-dose metformin.

Conclusion: Low-dose metformin causes a decrease in A1c, as well as in non-HDL lipid components at varying rates. Although the basis of macrovascular complications of diabetes mellitus is laid during the pre-diabetes, the threshold levels required for the administration of statin and fenofibrate are different in patients with DM and pre-diabetes. Pre-diabetes cases can be treated like cases with isolated lipid increases. In these cases, a response to varying levels of non-HDL lipid components can be obtained in some of the patients, along with an HbA1c response with low-dose metformin. Especially in the pre-diabetic dyslipidemia group, the importance of metformin was observed in the group in which we could not arrange statin and fibrate treatment.

INTRODUCTION

Pre-diabetes is an expression used to describe cases wherein the plasma glucose level is high but does not reach the limit to confirm the diagnosis of diabetes mellitus (DM); it is essentially the "preliminary" diagnosis of DM. Since 2005, the American Diabetes Association (ADA) has been using the term "pre-diabetes" for the terms Impaired Fasting Glucose and Impaired Glucose Intolerance.[1] According to the ADA data, patients with fasting plasma glucose in the range of 100–125 mg/dL, postprandial 2nd-h blood glucose in the range of 140–199 mg/dL, and HbA1c in the range of 5.7–6.4% were categorized as those with "pre-diabetes" since 2014. According to the World Health Organization (WHO), measurement of HbA1c level is not included in the diagnostic criteria of pre-diabetes, whereas the ADA, Turkish Diabetes Foundation, and Turkish Endocrine and Metabolism Association accept patients with 5.7–6.4% HbA1c as those with pre-diabetes.

The US National Health and Nutrition Survey reports that 35% of US individuals over 20 years of age and 50% over 65 years of age had pre-diabetes between 2005 and 2008, based on their fasting plasma glucose or HbA1c levels.[2] According to the global growth rate, the number of individuals with pre-diabetes is estimated to reach 472 million by 2030, and the regions with the highest increase are expected to be in South-east Asia and the Western Pacific Region.[3] According to TURDEP-II data in 2012, the prevalence of pre-diabetes increased to 30.4% from a mere 6.7% in the 2002 TURDEP-I study performed 10 years earlier.[4] One of the reasons for the approximately 5-fold increase in pre-diabetes cases could be the increase in awareness about the diagnosis of DM.

Patients with Type-2 DM may have a history of pre-diabetes that can extend up to 8–12 years in the pre-DM Type-2 period. The risk factors for pre-diabetes and Type-2 DM are the same.[5] While the detection of disease during the pre-diabetes stage makes it possible to cure the disease or reduce the rate of progression to DM, it is not possible to do so if the disease progresses to DM. Although the WHO has recommended a change in lifestyle with treatment to

patients with Type-2 DM,[6] polyclinic observations indicate that patients do not comply with these recommendations. In the Indian Diabetes Prevention Program (IDPP-1) study, it was observed that the use of metformin alone reduced the risk of progression to diabetes by 26.4%, metformin combined with lifestyle change reduced the risk by 28.2% compared to the control group.[7]

It is known that the initial period of cerebrovascular disease, cardiovascular disease (CVD), and peripheral vascular disease, which are some of the macrovascular complications of DM, corresponds to the pre-diabetes period.[8] In the San Antonio Heart Study,[9] there is an evidence that the risk of CVD begins to increase long before the onset of clinical diabetes. Well-known risk factors for CVD, such as dyslipidemia, hypertension, and obesity are quite common among people with pre-diabetes.[10] The findings of the Paris prospective study cohort study and EPIC-Norfolk study indicated that the CVD risk of pre-diabetic patients was 2-times that of normoglycemic individuals. It has been observed that pre-diabetics with an increased risk of CVD generally have high triglyceride levels and are obese. The diagnostic components of metabolic syndrome can be recognized 3–4 years earlier than those with pre-diabetes.[11]

Several studies have examined the effects of metformin on lipid values. A meta-analysis has reported that metformin decreases the levels of total cholesterol, LDL cholesterol, and triglycerides.[12] Although the mechanism with which metformin decreases lipid levels is not clear, certain studies on the subject have shown that it involves the reduction of Acyl-CoA-Cholesterol-Acyl-Transferase activity in the intestinal tract,[13] reduction of lipid synthesis in hepatocytes,[14] increase in VLDL catabolism,[15] and facilitation of fat excretion with very low amounts of feces.[16]

We aimed to evaluate the HbA1c response of patients with pre-diabetes that were treated with low-dose metformin, and to investigate whether the levels of plasma lipids were affected by metformin in these patients.

MATERIALS AND METHODS

Patients

Our study was conducted retrospectively on 357 patients over the age of 18 who had presented to the diabetes outpatient clinic between 2018 and 2020. Only those patients who were diagnosed with pre-diabetes based on HbA1c levels of 5.7–6.4% during the first visit and were subsequently administered 1000 mg/day metformin were included in the study. Patients who required a dose increase, lifestyle change, metformin combinations, or other oral antidiabetics and those with iron-deficiency anemia and hemoglobinopathy were excluded from the study because these conditions affected the HbA1c level. Patients with severe metformin intolerance or an inability to adapt to the treatment were also excluded from the study. Data of patients who were followed up regularly for 9–12 months were included in the study.

The lipid profiles of the patients during the first visit were examined and those who received statin and/or fibrate treatment due to dyslipidemia were not included in the study.

It was accepted that the progression to DM was prevented if the HbA1c level was maintained below 6.5%.

A decrease in the HbA1c level to below 5.7% was accepted as a complete response.

Non-HDL cholesterol levels below 130 mg/dL, LDL cholesterol levels below 130 mg/dL, and triglyceride levels below 150 mL/dL were also evaluated as complete responses.

HbA1c measurement was carried out by HPLC method.

Sample size

A total of 357 subjects was included in the study. The primary hypothesis checked in the study was the comparison of the first and control measurements of the cholesterol panel and HbA1c levels. Examination of the primary hypotheses revealed a statistically significant difference between the first measurements and the control measurements. This suggested that the power of the test was high and the sample size was enough to test these hypotheses.

Statistical analysis

Descriptive statistics of the obtained data were calculated as the arithmetic mean, standard deviation, median and 25–75th percentiles, number, and percentage frequencies depending on the type of variables and were given in tables (Table 1). The Shapiro–Wilk test was used to determine if the measured characteristics were normally distributed. The significance of the differences between the first and control measurements was examined by the Wilcoxon signed rank test. Control measurements of HbA1c were divided into two groups as <5.7 or >5.7, and these two groups were compared in terms of the measured characteristics using the Mann–Whitney U test. Pearson's Chi-squared test was used to compare the gender distribution in these two groups. Moreover, the changes between the first and control measurements of HbA1c were compared. The Kruskal–Wallis test and the Dunn's multiple comparison test were used to compare groups. $P<0.05$ indicated statistically significant differences. The statistical program SPSS (ver. 23) was used for the statistical analysis.

RESULTS

A total of 357 participants with a mean age of 53.9±11.6 years (range 19–97 years) were included in the study, of which 262 (73.4%) were women. The descriptive statistics of age, glucose, AST, ALT, and non-HDL cholesterol with only one measurement are presented in Table 1. The table also contains descriptive statistics of the cholesterol panel and the differences between the control measurements, the first measurements, and the two measurements for HbA1c. The numerical characteristics and differences between the two measurements were not normally distributed.

Table 1. Descriptive statistics

	n	Mean	SD	Min	Max	Percentiles		
						25th	Median	75th
Age (year)	357	53.92	11.596	19	97	46.00	54.00	62.00
Glucose (mg/dl)	357	113.37	20.351	83	219	101.00	109.00	120.00
Cholesterol (mg/dl)	357	221.21	47.316	105	425	189.00	220.00	249.00
c cholesterol (mg/dl)	357	200.38	41.777	101	324	171.00	198.00	228.00
Triglyceride (mg/dl)	357	165.26	70.342	22	475	114.50	155.00	203.00
c triglyceride (mg/dl)	357	137.75	61.485	36	456	93.00	128.00	171.00
LDL (mg/dl)	357	138.53	41.292	46	321	112.00	136.00	162.50
c LDL (mg/dl)	356	120.42	36.003	45	229	95.00	117.00	143.00
HDL (mg/dl)	357	53.60	13.228	24	98	44.50	52.00	60.00
c HDL (mg/dl)	357	52.90	13.470	26	129	44.00	51.00	60.00
Non-HDL cholesterol (mg/dl)	357	166.04	44.375	63	327	136.00	165.00	194.00
HbA1c (%)	357	5.984	0.2167	5.6	6.4	5.800	6.000	6.150
Control HbA1c (%)	357	5.817	0.3995	4.8	7.4	5.500	5.700	6.100
Delta cholesterol (Control–1st measurement difference)	357	−20.83	34.992	−164	93	−34.00	−13.00	0.00
Delta triglyceride (Control-1st measurement difference)	357	−27.51	56.256	−273	291	−49.00	−15.00	0.00
Delta LDL (Control–1st measurement difference)	357	−18.44	30.501	−149	48	−29.00	−10.00	0.00
Delta HDL (Control–1st measurement difference)	357	−0.69	8.687	−44	79	−4.00	0.00	2.00
Delta HbA1c (Control–1st measurement difference)	357	−0.16751	0.401273	−1.300	1.300	−0.40000	−0.20000	0.10000

LDL: Low density lipoprotein; HDL: High density lipoprotein; HbA1c: Hemoglobin A1c; SD: Standard deviation; Min: Minimum; Max: Maximum.

When the first measurements were subtracted from the control measurements, a significant decrease was observed in both the cholesterol panel (Triglyceride, cholesterol, LDL, and HDL) and HbA1c control measurements (Table 2).

In the control measurements, 181 people (50.7%) with an initial HbA1c level of 5.7% and below were observed to have HbA1c levels above 5.7%, while the remaining 176 people (49.3%) had an initial HbA1c level above 5.7%. When the two groups with HbA1c levels above 5.7% were compared in terms of other characteristics, the results presented in Table 3 were obtained. Based on the obtained results, the mean age, glucose, non-HDL cholesterol, and ALT of patients with HbA1c >5.7% in the control measurement were observed to be significantly higher. However, no significant difference in terms of other measurements was found between the patients with control HbA1c level >5.7% and those with HbA1c level of <5.7% (Table 3).

The control HbA1c level of 36 (37.9%) men was measured as 5.7% and below, while the control HbA1c level of 145 (55.3%) women was determined as 5.7% and below. This result suggested that the proportion of women with a control HbA1c level of 5.7% and below is significantly higher than that of men (p=0.004).

Table 2. Evaluation of the changes between the first measurement and the control

	Mean	SD	p-value
Cholesterol (mg/dl)	221.21	47.316	<0.001
c cholesterol (mg/dl)	200.38	41.777	
Triglyceride (mg/dl)	165.26	70.342	<0.001
c triglyceride (mg/dl)	137.75	61.485	
LDL (mg/dl)	138.72	41.180	<0.001
c LDL (mg/dl)	120.42	36.003	
HDL (mg/dl)	53.60	13.228	0.020
c HDL (mg/dl)	52.90	13.470	
HbA1c (%)	5.984	0.2167	<0.001
Control HbA1c (%)	5.817	0.3995	

*Wilcoxon signed ranks test. LDL: Low density lipoprotein; HDL: High density lipoprotein; HbA1c: Hemoglobin A1c; SD: Standard deviation

Moreover, there were 24 participants (6.7%) whose first measurement was the same as the control measurement, 237 participants (66.4%) whose control measurement was smaller than the first measurement, and 96 participants (26.9%) whose control measurement was greater than the first measurement, suggesting an increase in the HbA1c level. These results indicated that more than half of the participants had a significant decrease in the HbA1c level.

Table 3. Results of comparison between the two groups with HbA1c levels of 5.7 and above

	HbA1c target	n	Mean	SD	Percentiles			*p-value
					25th	Median	75th	
Age (year)	HbA1c >5.7	176	56.87	11.244	48.00	57.00	65.00	<0.001
	HbA1c =<5.7	181	51.06	11.239	44.00	50.00	58.00	
Glucose (mg/dl)	HbA1c >5.7	176	117.55	22.696	103.00	112.50	126.00	<0.001
	HbA1c =<5.7	181	109.31	16.874	100.00	106.00	114.00	
Non-HDL cholesterol (mg/dl)	HbA1c >5.7	176	170.43	43.106	141.00	170.00	199.75	0.046
	HbA1c =<5.7	181	161.77	45.288	133.50	161.00	191.00	
Delta cholesterol (Control-1st	HbA1c >5.7	176	−22.72	34.169	−36.75	−14.00	0.00	0.228
measurement difference)	HbA1c =<5.7	181	−18.99	35.772	−33.00	−9.00	0.00	
Delta triglyceride (Control-1st	HbA1c >5.7	176	−32.64	60.473	−61.75	−21.50	0.00	0.100
measurement difference)	HbA1c =<5.7	181	−22.52	51.506	−41.00	−10.00	0.00	
Delta LDL (Control-1st	HbA1c >5.7	176	−20.63	30.918	−31.75	−11.00	0.00	0.192
measurement difference)	HbA1c =<5.7	181	−16.31	30.023	−27.00	−10.00	0.00	
Delta HDL (Control-1st	HbA1c >5.7	176	−0.97	8.037	−4.00	0.00	2.00	0.820
measurement difference)	HbA1c =<5.7	181	−0.43	9.290	−4.00	0.00	2.00	

*Mann–Whitney U test. LDL: Low density lipoprotein; HDL: High density lipoprotein.

Table 3 presents the results of comparisons between these three groups in terms of other characteristics (Table 4).

DISCUSSION

Although metformin was less effective than lifestyle changes in preventing diabetes among patients with pre-diabetes in the DPP study, DPP and DPPOS were reported to be cost-effective over the 10-year follow-up period.[17]

In the IDPP study, lifestyle change alone, metformin monotherapy, and lifestyle change+metformin treatment had no significant benefits in terms of diabetes development.[18] In the DPP studies, the response to metformin in the medical treatment arm was 24.8%,[19] while that to treatment with another arm, Metformin 850 mg, was 31%.[20] In our retrospective study, it was observed that the patients did not fully comply with the recommended lifestyle changes in the polyclinic follow-up.

Considering the results of this study in general, it was observed that women were more often diagnosed with pre-diabetes. Of the patients, 26.6% were male and 73.3% were female, and women showed a better response to treatment than men. While the complete response was obtained in 41.2% of all women, only 28.4% of the male group showed a complete response. The rates of both pre-diabetes and the response to treatment were significantly higher in women than those in men.

Regarding the age groups, 10% of the patients were between the ages of 18–40 years, while 90% were over 40 years old. While a complete response was observed in 70% of patients in the 18–40-year age group, only 36% of patients aged over 40 years old showed a complete response. While the frequency of pre-diabetes cases increased significantly among patients over 40 years of age, the response to treatment of patients was better if the diagnosis was made under 40 years of age.

In the study by Grundy et al.[21] on pre-diabetes and microvascular complications in 2012, the authors did not find metformin to be effective on pre-diabetic patients over 60 years of age. In our study, 35.9% of patients over 60 years of age showed a complete response to low-dose metformin, which was unexpectedly remarkable.

The DPP study revealed that the use of metformin in the medical treatment arm reduced the rate of progression to diabetes by 24.8%,[19] and the use of 850 mg metformin in patients with BGT, in another arm of the same study, reduced the risk of progression to diabetes by 31% compared to placebo.[20]

Regarding the importance of early diagnosis, a complete response was obtained in 28.2% of the patients with HbA1c levels of 6–6.4%, which increased to 47.98% in the group with HbA1c levels of 5.7–5.9%. While a complete response was obtained in 39.6% of the patients with regression in HbA1c levels to 6–6.4%, complete response was observed in 77.57% of the patients with regression in HbA1c levels to 5.7–5.9%. This indicated that patients with early pre-diabetes responded to treatment better.

Among all the patients, only 21 (5.8%) had HbA1c levels of 6.5% and above, in which progression to diabetes was observed. This indicated that the treatment of pre-diabetes with low-dose metformin significantly stopped their progression to diabetes, which was observed in 94% of the patients in our study.

While there is no cure for DM, pre-diabetes is a "preventable" condition; so, the development of diabetes can also be prevented in patients whose pre-diabetes can be corrected or maintained as pre-diabetics. The cost of metformin treatment at 2 × 500 mg/day, which is an effective treatment and

Table 4. Results of comparison between the three groups according to the changes observed in HbA1c

	HbA1c Change	n	Mean	SD	Percentiles			*p-value
					25th	Median	75th	
Age(year)	1. measurement and Control measurement are the same	24	56.542	10.181	53.250	55.000	60.750	0.093
	Control measurement <1st measurement	237	53.034	11.429	45.000	52.000	61.000	
	Control measurement >1st measurement	96	55.469	12.173	47.000	56.000	65.000	
Glucose (mg/dl)	1. measurement and Control measurement are the same	24	109.000	16.054	94.750	107.000	118.750	<0.001
	Control measurement <1st measurement	237	111.211	18.799	100.500	107.000	116.000	
	Control measurement >1st measurement	96	119.802	23.525	103.500	115.000	128.750	
Cholesterol (mg/dl)	1. measurement and Control measurement are the same	24	226.917	46.454	194.250	224.500	260.500	0.762
	Control measurement <1st measurement	237	221.679	48.320	189.000	223.000	249.000	
	Control measurement >1st measurement	96	218.635	45.293	187.500	217.000	248.000	
c cholesterol (mg/dl)	1. measurement and Control measurement are the same	24	210.333	49.598	170.000	205.000	260.000	0.644
	Control measurement <1st measurement	237	200.409	40.952	172.000	198.000	228.000	
	Control measurement >1st measurement	96	197.833	41.797	169.250	197.500	226.000	
Triglyceride (mg/dl)	1. measurement and Control measurement are the same	24	155.042	63.792	112.750	139.500	181.000	0.041
	Control measurement <1st measurement	237	159.118	66.177	107.500	151.000	198.000	
	Control measurement >1st measurement	96	182.969	78.993	127.000	170.500	210.750	
c triglyceride (mg/dl)	1. measurement and Control measurement are the same	24	130.333	54.787	89.000	115.000	144.250	0.033
	Control measurement <1st measurement	237	133.017	59.030	88.000	124.000	163.500	
	Control measurement >1st measurement	96	151.281	67.295	106.250	141.000	182.500	
LDL (mg/dl)	1. measurement and Control measurement are the same	24	148.792	51.489	117.250	140.500	172.250	0.709
	Control measurement <1st measurement	237	138.143	41.051	112.000	135.000	161.000	
	Control measurement >1st measurement	96	136.906	39.136	110.250	137.000	168.500	
c LDL (mg/dl)	1. measurement and Control measurement are the same	24	126.958	41.645	93.750	121.500	164.250	0.769
	Control measurement <1st measurement	237	120.287	35.529	97.500	116.000	143.000	
	Control measurement >1st measurement	95	119.116	35.903	90.000	119.000	142.000	
HDL (mg/dl)	1. measurement and Control measurement are the same	24	55.833	12.576	44.500	55.500	65.750	0.072
	Control measurement <1st measurement	237	54.536	13.416	46.000	52.000	60.000	
	Control measurement >1st measurement	96	50.719	12.587	42.000	51.000	58.000	
c HDL (mg/dl)	1. measurement and Control measurement are the same	24	57.083	13.478	47.250	56.000	67.750	0.009
	Control measurement <1st measurement	237	53.937	13.991	44.000	52.000	61.000	
	Control measurement >1st measurement	96	49.302	11.378	40.250	50.500	56.000	
Non-HDL cholesterol (mg/dl)	1. measurement and Control measurement are the same	24	167.250	44.872	135.250	167.000	193.500	0.985
	Control measurement <1st measurement	237	166.169	45.483	136.000	165.000	194.500	
	Control measurement >1st measurement	96	165.417	41.854	137.500	164.500	196.000	
HbA1c (%)	1. measurement and Control measurement are the same	24	5.954	0.215	5.800	6.000	6.075	0.079
	Control measurement <1st measurement	237	6.002	0.216	5.800	6.000	6.200	
	Control measurement >1st measurement	96	5.947	0.215	5.800	5.900	6.100	
Control HbA1c (%)	1. measurement and Control measurement are the same	24	5.954	0.215	5.800	6.000	6.075	<0.001
	Control measurement <1st measurement	237	5.607	0.252	5.500	5.600	5.800	
	Control measurement >1st measurement	96	6.299	0.282	6.100	6.300	6.400	
Cholesterol_change (mg/dl)	1. measurement and Control measurement are the same	24	−16.583	25.543	−32.000	−14.000	0.000	0.934
	Control measurement <1st measurement	237	−21.270	36.398	−35.000	−12.000	0.000	
	Control measurement >1st measurement	96	−20.802	33.679	−31.750	−13.000	0.000	
Triglyceride_change (mg/dl)	1. measurement and Control measurement are the same	24	−24.708	31.800	−51.750	−22.000	0.000	0.867
	Control measurement <1st measurement	237	−26.101	53.349	−44.000	−14.000	0.000	
	Control measurement >1st measurement	96	−31.687	67.227	−62.750	−18.500	0.000	
LDL_change (mg/dl)	1. measurement and Control measurement are the same	24	−21.833	37.370	−32.250	−10.500	−1.000	0.769
	Control measurement <1st measurement	237	−17.857	30.185	−28.500	−10.000	0.000	
	Control measurement >1st measurement	96	−19.031	29.677	−29.750	−10.000	−0.250	
HDL_change (mg/dl)	1. measurement and Control measurement are the same	24	1.250	4.580	−2.750	0.500	4.750	0.161
	Control measurement <1st measurement	237	−0.599	9.343	−4.000	0.000	2.000	
	Control measurement >1st measurement	96	−1.417	7.706	−4.000	0.000	2.000	

*Kruskal–Wallis test and post hoc Dunn test. LDL: Low density lipoprotein; HDL: High density lipoprotein; HbA1c: Hemoglobin A1c; SD: Standard deviation; Min: Minimum; Max: Maximum.

can improve the patient's condition even if the recommended lifestyle changes are not adequately followed, remains insignificant compared to the oral antidiabetics used in DM, insulin regimens, and the cost of micro and macrovascular complications that may develop due to DM.[21]

Besides increasing the risk of CVD, it has been reported in the meta-analysis of 129 studies that pre-diabetes causes an increase in cardiovascular deaths and all-cause deaths.[22] In three different studies[23,24] using different doses of metformin in patients of different sexes, ethnicities, and ages, total cholesterol levels were observed to decrease by 3–13% in the patient groups. In the BIGPRO-1 study, it was reported that the use of metformin significantly decreased the fasting triglyceride level.[25] Another study that examined the effect of metformin on serum lipoproteins and platelet functions reported that 2 g/day metformin given to 24 patients with non-diabetic Type-2b hyperlipidemia decreased the total cholesterol levels by 8.1% and

LDL cholesterol levels by 9.6%.[26] In our study, examination of the lipid responses indicated an improvement in the levels of all lipids in patients with an improvement in pre-diabetes condition and demonstrating a complete HbA1c response. The antiatherosclerotic activity of metformin was also observed to decrease the levels of total cholesterol, LDL, and VDLD while maintaining the levels of HDL. Simultaneously, metformin has been shown to reduce oxidative stress in the endothelium and cause a decrease in blood pressure.[27]

In this study, we observed that low-dose metformin treatment alone not only controlled the lipid components including non-HDL cholesterol but also pre-diabetes. It was observed that among the patients whose pre-diabetes improved was observed were those who showed a better response to non-HDL and its components.

The high levels of non-HDL cholesterol were observed in 82% of all the patients, of which, 23% showed a non-HDL response. The high levels of triglycerides were observed in 52% of all the patients, of which, 40% showed a decrease in triglyceride level to below 150 mg/dL. LDL cholesterol levels of 130 mg/dL and above were observed in 211 patients, which decreased to below 130 in 39% of those patients. In the group with complete response to HbA1c level, 61% of the patients had LDL cholesterol levels of below 130 mg/dL.

When the lipid responses were examined, it was observed that patients demonstrating a complete HbA1c response showed better responses to all lipids. Since they do not meet the diagnostic criteria of "DM," lipid targets of patients with pre-diabetes are evaluated as patients without DM. There is a lack of consensus on the treatment goals of dyslipidemia in patients in this gray area.[28]

A more positive response was obtained in non-HDL cholesterol and its components in patients over 60 years of age (29%), compared to the lower age groups (19%). We believe that low-dose metformin treatment may contribute positively to patients aged over 60 years in terms of the risk factors for CVDs.

Statin treatment conditions for patients with pre-diabetes were similar to those for patients with non-pre-diabetic hyperlipidemia. However, while pre-diabetes alone is a risk factor for CVD, pre-diabetes along with dyslipidemia is a more serious risk factor. However, while dyslipidemia should be treated when LDL cholesterol level is above 70 mg/dL in DM patients, no such information is available for patients with pre-diabetes. Although some of the patients staying in this grey area also meet the criteria of metabolic syndrome, there is a lack of consensus regarding the treatment goals of dyslipidemia. Levels of target lipids in patients with pre-diabetes should be similar to those of patients with diabetes. This is a situation that should be considered to prevent CVDs.

CONCLUSION

Our study demonstrated that irrespective of whether the patients diagnosed with pre-diabetes and administered low-dose metformin followed the recommended lifestyle changes, they had a significant complete and partial response to the HbA1c levels. Moreover, although metformin was not an antilipidemic agent, a significant response to triglycerides, LDL cholesterol, and non-HDL cholesterol was obtained. It was also observed that patients with a complete response to HbA1c levels had a better response to non-HDL cholesterol levels, the rate of pre-diabetes detection was significantly higher in female patients than males, and the rate of response to treatment was higher. Simultaneously, patients with HbA1c levels of below 6% showed a better response and were more likely to achieve treatment goals if they undertook early treatment. Pre-diabetes, as stated in the study, is an "atherogenic" condition like diabetes, and it has been shown that the initiation of macrovascular complications of diabetes started during the pre-diabetic period, due to which, the importance of pre-diabetes treatment emerges at this point. However, due to the lack of consensus on the targets for the treatment of dyslipidemia and they do not meet the diagnostic criteria for DM, the treatment initiation level and target lipid level in dyslipidemia are similar to those in normoglycemic dyslipidemic patients. Therefore, DM and its macrovascular atherogenic complications can be prevented if pre-diabetes is controlled. In our study, treatment of pre-diabetics with low-dose metformin not only achieved normoglycemia but also decreased the levels of triglyceride, LDL cholesterol, and non-HDL cholesterol levels.

Limitation of study

Since our study was retrospective, we do not have information about the body mass indexes and weights of the patients. We are also unable to provide real data on the effect of lifestyle changes on HbA1c. These constitute a limitation on our study.

Ethics Committee Approval

This study approved by the Kartal Dr. Lütfi Kırdar City Hospital Clinical Research Ethics Committee (Date: 28.04.2021, Decision No: 2021/514/200/39).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Conflict of Interest

None declared.

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Prediyabetli Hastalarda Düşük Doz Metformin'e Glisemik Yanıt ve Dislipidemi Yanıtı

Amaç: Çalışmamızla prediyabetik bireylerde düşük doz metforminin HbA1c ve plazma lipid düzeyleri üzerindeki etkinliğini araştırmayı amaçlanmıştır.

Gereç ve Yöntem: 2018–2020 yılları arasında HbA1c düzeyi %5.7–6.4 arasında olan 357 hastanın dahil edildiği çalışmamızda 1000 mg/gün metformin ile minimum dokuz ay takip edilen olgularda HbA1c düzeyi ve lipid yanıtı değerlendirildi.

Bulgular: HbA1c düzeyleri %6–6.4 olan grubun %39'unda tam yanıt gözlenirken, HbA1c düzeyleri %5.7–5.9 olan grupta bu %77 yanıt elde edildi. Kırk yaş öncesi elde edilen yanıt %70 iken, 40 yaş üzeri olgularda %36 yanıt elde edilmiştir. Düşük doz metformin kullanan prediyabetli olguların %23'ünde nonHDL lipit bileşenlerinde azalma gözlenmiştir.

Sonuç: Düşük doz metformin, A1c'de ve ayrıca nonHDL lipid bileşenlerinde değişen oranlarda azalmaya neden olur. Diabetes mellitus'un makrovasküler komplikasyonlarının temeli prediyabet döneminde atılsa da DM ve prediyabetli hastalarda statin ve fenofibrat uygulaması için gereken eşik değerler farklı olup prediyabetikler izole lipid artışı olan olgular gibi tedavi edilebilmektedir. Düşük doz metformin ile HbA1c yanıtının yanı sıra değişen seviyelerde HDL olmayan lipid bileşenlerine yanıt alınabilmektedir. Özellikle prediyabetik dislipidemi grubunda statin ve fibrat tedavisi verilemeyen olgularda kısmi lipit yanıtının olumlu etkileri gözlemlenebilmektedir.

Anahtar Sözcükler: Dislipidemi; düşük doz metformin; prediyabet.