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The effect of nutrition theraphy on oxidative stress, inflammation, glycemic control in type 2 diabetes patients

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Summary. *Aims:* Type 2 diabetes mellitus is a metabolism disease which is seen frequently among adult population in Turkey. The aim of this study was to determine the medical nutrition theraphy effect on oxidative stress, inflammation, glycemic control in type 2 diabetes patients. *Methods:* An interventional study was carried on 35 type 2 diabetes ages between 20-65 years old at the Department of Endocrinology of Başkent University İstanbul Hospital in 2015. In 3 month period a personal nutrition theraphy was applied. Biochemical parameters, anthropometric measurements and body analysis were also determined. The three day food consumption and biochemical parameters were requested at the beginning and at the end of the study. *Results:* When the impact of the blood values of the new medical nutrition theraphy which the patients practiced during the first visit and the follow up visit were compared; it was seen that there was a significant decrease on fasting plasma glucose, fasting insulin, HbA1c, CRP, TG and MDA values ($p<0.05$). The mean diabetic age of the patients was 7.63±6.22 years. When diabetic age of the patients was increased, there was a positive correlation between the fasting plasma glucose and HbA1c values ($p<0.05$). *Conclusions:* Type 2 diabetes patients were evaluated 3 month of medical nutrition theraphy and it was seen that the personal medical nutritional theraphy contributed to providing glisemic control and decreasing oxidative stress and inflammation.

Key words: glycemic control, inflammation, oxidative stress, medical nutrition therapy, Type 2 diabetes

Introduction

Type 2 diabetes mellitus is a metabolism disease which is seen frequently among adult population in Turkey and especially in developing countries in particular. Type 2 diabetes is seen between the ages of 40 and 59 and it consists of the 90% percent of the whole diabetic occasions. Type 2 diabetes is the most increasing disease. According to the datas of World Health Organization (WHO), there were 171 millions of diabetic patients in the year of 2000 and it is expected that this will be 366 millions in 2030. International Diabetes Federation (IDF) expects that there are 425 millions of diabetic adult patients around the world. It is also expected that the prevalance of diabetics will reach 592 millions by 2035. So, 8.03% of the world population have diabetics and 6.9% have impaired glucose tolerance (1).

According to the Turkey datas of IDF, in 2012 the prevalance of diabetic disease was found as 8.3%. The epidemiologic studies identifying the prevalance of type 2 diabetes in Turkey started in 1990. According to the The Turkish Diabetes Epidemiology *Study* I and II (TURDEP-I and TURDEP-II) studies which was practiced by TURDEP on 25.000 ≥19-year-old people in 1997 and 2010, the prevalance of type 2 diabetes disease was increased from 7.2 to 13.7%, which comes up to 95%, in 12 years period of time. It was determined that the prevalance of diabetic disease was 14.6% among men and 12.4% among women. In our country, the number of the type 2 diabetics patients

are 10.3 millions. In an attempt to determine the heart disease and the risk factors in parallel with the disease in adults, in the Turkish Adult Risk Factor Study (TEKHARF), the prevalance of type 2 diabetic disease was specified as 11.3% among over 35-year-old people in the years of 1997 and 2005, and this number comes up to 3.3 millions of people (2).

By establishing a decent glisemic control on type 2 diabetes patients, developing diabetic microvascular and macrovascular complications can be kept under control. The gold standard of evaluating glisemic control among diabetes is HbA1c. However, especially postprandrial hiperglisemi peaks are accepted as the sign of cardiovascular risk increase. To provide a strict glisemic control, it is necessary to bring fasting and postprandial plasma glucose degrees to the condition of near-normal degrees. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Turkish Diabetes Foundation determined that, as a glisemic control aim, fasting blood sugar glucose should be 120 mg, HbA1c value should be less than 7%, young non-cardiovascular risk patients should be less than 6.5% and postpradial blood glucose should be less than 140mg/dL (3).

Nutritional theraphy and lifestyle modification including exercise are the bases of the treatment of type 2 diabetes disease. The importance of nutritional theraphy for diabetic patients has long been recognized for many years and has been in use since the 1550s. Although the nutritional treatments that have applied since the very beginning times have quite changed, the main aim is to keep the hyperglisemia of the patients under control. Besides, another aim is to provide optimal body weight, keep the hyperlipidemia under control and avoid akute and chronic complication development. Thanks to this review, it was observed that with the medical nutrition theraphy applied on type 2 diabetic patients, the development of mikro and makrovascular complications were regressed by means of decreasing HbA1c level. Different nutrition programs are being studied for optimal medical nutrition therapy for patients with type 2 diabetes (4). American Diabetic Association suggests that 45%-65% of the total energy comes from carbohydrates, 20%-35% from fat and 10%-20% from total protein when nutritional theraphy is planned in diabetic patients. Low carbonhydrate nutrition theraphy provides normaglisemia, but less than 130 grams of carbonhydrate intake is not suggested Daily (5). When the recommendations of guidelines are reviewed, it appears that the vitamin mineral requirements for diabetics are not very different from those of healthy individuals (6).

Oxidative stress is caused by the imbalanced in free radical production so that mitochondrial dysfunction increases and antioxidant defence decreases. According to the conducted researches, elevated blood glucose levels lead to vascular complications and lipid peroxidation. The experimental and clinical researches show that oxidative stress had a decisive role on the pathogenesis of diabetes. Free radicals are found more in diabetes patients (7,8). The amount of cytokine in their circulation increased because of the inflammation in type 2 diabetes patients. The increased cytokine level is the risk factor for atherosclerosis and cardiovascular diseases. Some of the cytokines are released from liver and some from the adipose tissue. CRP is produced in the liver and associated with diseases such as obesity, coronary heart disease and insulin resistance (9).

Chronic low level inflammation and increased oxidative stress are seen in Type 2 diabetes patients. Inflammation and oxidative stress can be reduced with the help of nutritional theraphy practiced on patients. In this study, it was aimed to evaluate the influence of on medical nutrition theraphy on oxidative stress, inflammation and providing glisemic control on type 2 diabetic patients.

Materials and Methods

This interventional study was carried on among 45 type 2 diabetic patients at the age of 20 and 65 who applied for Başkent University İstanbul Hospital the department of endocrinology between february and december 2015. All the patients participating in the study were given an informed consent form and all of them had written approval. Patients who want to leave at the beginning of the study or in any part of it have been removed without study. People who are under 20 and over

65 years old, smokers, pregnants and lactatings, those using antioxidant vitamins and mineral supplementations, having acute infections, using stomach pills and diuretics are not included in the research. Four of the patients who joined the research left the research because of not coming to the control meeting, and 6 of them left the research because of not practising the planned medical nutrition programme. The study was completed with 35 patients with type 2 diabetic patients. For this study, the ethic commitee approval was taken by Başkent University Clinical investigations ethic commitee the number for 15/25 and the date for 2015, february 18th.

At the beginning of the study, a general questionnaire consisting of 23 questions, an anthropometric measurement questionnaire, a three-day nutrition consumption registration form (three consecutive days which includes a weekend) and a physical activity assesment form were applied to patients. The height, weight, BMI, waist to hip ratio, neck circumference and body fat analyse of patiens were measured. At the end of the assessment, a medical nutrition treatment programme was prepared to protect their weights for normal weight patients, while to lose the 5%-7% of their initial weight for mildly obese and obese patients.

The evaluation of nutrition status

To identify the dietary habits of the patients, food consumption frequency form was applied. To determine the dietary status of the patients, a three-day food consumption form was taken at the beginning of the study and three months later nutritional education was given. 24-hour food consumption form was determined through the recordkeeping technique. By the researcher, the consumption forms were given to the patiens who were provided portion education and it was required to record the food and drinks they consumpted for three days, which includes a weekend and two weekdays, in the morning, afternoon and evening with the detail of the place and time they consumpted on the form. The portion education was provided to the people who joined this study by using food and nutrition photo catalog (10).

Determining the level of physical activity

To determine the level of the physical activity of the patients taking part in the study; in the beginning and after three months of the study, during 3 days it was needed to save the physical activities they did in details on the form. These activities were made by the daily physical activity level (PAL) (11).

Assessment of anthropometric measurements

The height measurement was done with the height meter, the brand of Seca-206 (Hamburg, Germany). While the height measurement was being done, the standing position and head at Frankfurt plane were paid attention. The body analyse of the patients was done with Tanita BC-418 analyzer (Tokyo, Japan). BMI can be measured with the weight/height equation (12). While evaluating the results of BMI, the BMI classification of WHO was used (13). The waist circumference of the first and last coming of the patients, the smallest waist circumference between bottom kosta and prosessus spina ilaca anterior superior were measured and saved with a measure parallel to the ground from navel by the researcher.

Biochemical measurements

Hemoglobin, HDL-C, LDL-C, TG, fasting plasma glucose, HbA1c, ALT, AST, CRP, and additionally MDA rates of the patients were practiced biochemical tests were done in Başkent University İstanbul Hospital the main labratory. The bloods were taken after 12-14 hours fasting in the morning. The insulin resistance was evaluated by HOMA-IR thanks to being practical. If the value calculated by HOMA-IR was over 2.5 mg, it is supported that the patient had an insulin resistance (14).

Statistical evaluation

The data of the research was evaluated by SPSS version 22.0 for Windows programme (SPSS Inc, Chicago, IL). The identifying statistics were denoted as average ± standard deviation, minimum and maximum, frequency distribution (n) and percent (%). The normal distribution suitability of the variables was analysed by using visual and analitical methods (Shapiro-Wilk Test). Paired Sample T Test was used for the normally-distributed variables between two dependent groups, and Student's T Test was used between two independent groups. Wilcoxon Signed Ranks Test was used for the non-normally-distributed variables between two dependent groups and Mann-Whitney

U Test between two independent groups as a statistical method. The relation between the variables were evaluated by the Spearman Test. The statistical significance level was accepted as $p<0.05$.

Results

The demographic characteristics of the study participants are shown in Table 1. The difference of the educational level between men and women is considered as something significant statistically. It was determined that the 80% of men and 35% of women work income-generating business. This difference between men and women was considered as something important statistically.

The biochemical finding of the patients who took part in the study is shown in Table 2 months after the beginning. With The blood samples which were taken in the beginning and at the end of the study, it was seen that there was a significant difference between serum hemoglobin, fasting plasma glucose, fasting insulin, HOMA-IR, HbA1c, CRP, TG and MDA values statistically. After practicing the nutrition programme for 3 months, it was determined that the values of hemoglobin, fasting plasma glucose, fasting insulin, HOMA-IR, HbA1c, CRP, TG and MDA of the patients reduced significantly compared to the beginning values. It was also determined that the values of HDL-C, LDL-C, ALT and AST were similar compared to the beginning and 3 months afterwards.

Table 1. The distribution of demographical qualities of the patients

Demographical Qualities	Male (n=15)		Female (n=20)		Total (n=35)	
	n	%	n	%	n	%
Age (years)						
≤50	6	40.0	4	20.0	10	28.6
51-60	4	26.7	6	30.0	10	28.6
>60	5	33.3	10	50.0	15	42.8
±SD **(Min-Max)**	**54.53±8.79**		**58.20±7.50**		**56.63±8.16 (37-65)**	
Marital Status						
Married	13	86.6	15	75.0	28	80.0
Single	1	6.7	2	10.0	3	8.6
Widow	1	6.7	3	15.0	4	11.4
Educational Status*						
Primary school	1	6.7	1	5.0	2	5.7
Secondary school	-	-	8	40.0	8	22.9
High school	2	13.3	5	25.0	7	20.0
University	12	80.0	6	30.0	18	51.4
Occupation						
Government official	3	20.0	-	-	3	8.6
Employee	2	13.3	4	20.0	6	17.1
Housewife	-	-	12	60.0	13	37.1
Retired	3	20.0	1	5.0	3	8.6
Self-employed	7	46.7	3	15.0	10	28.6
Income-Generating Business *						
Not-working	3	20.0	13	65.0	16	45.7
Working	12	80.0	7	35.0	19	54.3

* $p<0.05$

Table 2. The average of the biochemical values of the beginning and 3 months afterwards of the patients

Biochemical Values	Total (n=35)				p
	Beginning		Three months afterwards		
	±SD	Median (Min-Max)	±SD	Median (Min-Max)	
Hemoglobin (mg/dL)	14.1±1.6	14.2 (9.0-16.9)	13.8±1.3	13.8 (10-16.5)	0.011*
Fasting blood glucose (mg/dL)	144.8±39.5	137 (90-240)	134.2±49.8	120 (83-336)	0.013*
Fasting İnsülin (µU/mL)	18.8±17.8	12 (4-90)	17.4±17.9	10.2 (2.3-84.7)	0.010*
HOMA-IR	6.93±6.94	4.65 (1.38-28.89)	6.08±6.97	2.96 (1.09-29. 49)	0.007*
HbA1c (%)	7.0±1.6	6.5 (4.9-12.4)	6.7±2.1	6.2 (4.3-13.6)	0.001*
CRP (mg/L)	6.2±9.8	2.85 (0.20-43.12)	3.8±5.7	1.39 (0.20-23.54)	0.023*
HDL-C (mg/dL)	40.8±10.3	41 (21-66)	41.6±9.9	42 (24-73)	0.160
LDL-C (mg/dL)	134.7±40.1	130 (48-215)	125.9±32.4	126 (62-184)	0.124
TG (mg/dL)	218.1±231.9	178 (61-1420)	172.3±102.3	144 (60-605)	0.002*
MDA (ng/mL)	36.8±14.6	33.16 (16.05-69.53)	28.7±8.1	28.79 (16.47-50.58)	0.006*
ALT (U/L)	25.5±11.6	22 (14-65)	24.5±10.9	21 (13-65)	0.187
AST (U/L)	23.9±10.2	21 (8-60)	22.8±8.1	21 (8-44)	0.425

* $p<0.05$

The relation between the biochemical parameters and the nutrition programme practiced by the patients at the end of three months was shown in Table 3. There is a negative statistically significant relation between the energies that the patients took with their diets which they practiced at the end of threee months and MDA, and positive statistically significant relation between fasting plasma glucose, HbA1c, LDL-C, TG and CRP values. There is a positive nonsignificant relation between fasting plasma glucose, HbA1c and MDA with the percent that comes from carbonhydrates of the diets, and a negative nonsignificant relation between LDL-C, TG and CRP. It was determined that there is a negative statistically significant relation between fasting plasma glucose and the percent coming from the protein of the diet energy. It is also determined that there is a positive statistically nonsignificant relation between CRP and fasting plasma glucose with the percent coming from fat that is taken, and a negative statistically nonsignificant relation between HbA1c, MDA, LDL-C and TG. It was found that there is a positive statistically significant relation between polyunsaturated fatty acids and fasting plasma glucose.

Discussion

The medical nutrition therapy practiced on diabetic patients is a support treatment for the medical treatment. The aim of the nutrition programme suitable for the diabetics is to provide weight management, a better glisemic control and blood pressure. It is known that in diabetics, in the antioxidant protective mechanism the balance is damaged against the oxidant stress and cell damage is increased. In these patients, providing the control reduces the oxidative stress and inflammation. Therefore, the density of the microvascular and macrovascular complications of the diabet is reduced. In patients who cannot provide glisemic control for a long time, nonenzimatik glication, the metabolic stress caused by the changes in the energy metabolism, the activity of the sorbitol pathway, hipoksi and iskemia-reperfüzyon cause to increase the free radical production of tissue damage resulting from hipoksi and iskemi reperfüzyon and to change the antioxidant defence system, as a result cause to increase the density of diabetic complications in diabetics (15).

Lifesytle modification and associated weight loss in Type 2 diabetes patients are important in reducing insulin resistance, providing glycemic control, reducing lipidemia and blood pressure, reducing cardiovas-

Tablo 3. The relation between biochemical parameters and dietary factors at the end of 3 months

Dietary factors		Fasting blood glucose	HbA1c	MDA	LDL-C	TG	CRP
Energy (kkal)	r	0.218	0.229	-0.033	0.134	0.154	0.182
	p	0.209	0.186	0.849	0.442	0.379	0.296
Carbohydrate (total energy %)	r	0.104	0.123	0.173	-0.003	-0.110	-0.021
	p	0.553	0.482	0.321	0.988	0.528	0.904
Protein (total energy %)	r	-0.367	-0.276	0.067	0.179	0.197	-0.140
	p	0.030*	0.108	0.702	0.305	0.258	0.423
Fat (total energy %)	r	0.026	-0.050	-0.178	-0.144	-0.009	0.066
	p	0.882	0.774	0.305	0.409	0.958	0.707
Glucose (g)	r	0.060	0.266	0.013	0.050	-0.122	0.075
	p	0.732	0.123	0.940	0.774	0.486	0.667
Fructose (g)	r	0.117	0.312	0.090	0.073	-0.118	0.001
	p	0.503	0.068	0.605	0.677	0.499	0.994
Sucrose (g)	r	0.264	0.292	0.026	-0.052	-0.026	0.325
	p	0.125	0.088	0.882	0.766	0.881	0.056
Vitamin A (RE)	r	0.204	0.125	-0.050	-0.114	0.015	0.179
	p	0.240	0.473	0.776	0.515	0.930	0.304
Vitamin C (mg)	r	0.186	0.312	-0.019	0.037	0.012	0.180
	p	0.286	0.068	0.914	0.835	0.944	0.300
Vitamin E (mg)	r	0.345	0.205	-0.105	-0.109	0.290	0.158
	p	0.042	0.236	0.549	0.535	0.091	0.366
Protein (g)	r	-0.002	0.020	0.129	0.196	0.296	0.002
	p	0.993	0.910	0.461	0.259	0.085	0.989
Fiber (g)	r	-0.105	0.104	0.110	0.106	-0.150	-0.089
	p	0.549	0.551	0.531	0.545	0.390	0.612
Total cholesterol (mg)	r	0.265	0.099	-0.120	-0.113	0.142	0.265
	p	0.125	0.573	0.492	0.519	0.416	0.123
Saturated fatty acid (g)	r	0.169	0.174	-0.156	-0.025	0.046	0.171
	p	0.333	0.319	0.372	0.887	0.793	0.326
Monounsaturated fatty acid (g)	r	0.079	0.076	-0.244	-0.044	-0.055	0.049
	p	0.654	0.666	0.158	0.803	0.753	0.779
Polyunsaturated fatty acid (g)	r	0.336	0.267	-0.134	-0.010	0.234	0.126
	p	0.049*	0.122	0.444	0.956	0.176	0.472

* $p<0.05$

cular risk factor, inflammation and oxidative stress. In the look aheas study which was practiced with multicenter randomized conntrolled trial of 5.145 diabetics, the lifestyle intervention was made to the patients and in the end the patients lost the 8.6% of their initial weight. The levels of serum HbA1c reduced from 7.3% to 6.6%, and it was determined that there was a decrease in hypertension and hyperlipidemia, also a decrease in taking lipid lowering drugs (16). In another study, the nutrion treatment was practiced on the patients who had 9-year-diabet, not-provided a good glisemic control and a 7% HbA1c level, and at the end of 6 months it was seen that there was a 0.5% decrease in their HbA1c level (17). These studies are to show that which nutrition programme is useful to provide a glisemic control, and which is more useful for hiper-

lipidemia and hypertension control. In these studies the blinding factor is the loss of weight. It should be evaluated well that how much contribution a practiced nutrition programme type and loss weight provides to the change.

The medical nutrition theraphy practiced on Type 2 diabetes patients aims to control hyperglisemia and to provide loss weight in a long term. In the studies done, with the medical nutrition theraphy practiced on type 2 diabetes patients, it was seen that there was a 0.5%-2% decrease in the level of HbA1c and a regression of composing a micro and macrovascular complications (4). In the ukpds study which was done with over 5100 participants with the Type 2 diabetes, the effect of the glisemic control on micro and macrovascular complications provided on type 2 diabetes patients. It was seen that the 0.9% decrease in the level of HbA1c caused a significant decrease on micro and macrovascular complications ($p<0.05$) [18]. At the beginning of this study, the average of the HbA1c level was 7.0-1.6%, but at the end of the study after the individually planned medical nutrition programme for the patients, the average of the HbA1c level was determined as 6.7-2.1% and the difference between these values was considered as something important statistically ($p=0.001$).

Malondialdehid is the last product of the polyunsaturated lipid peroxidation used to determine the level of oxidative damage. MDA shows a significant correlation with the degree of lipid peroxidation. It can be looked in blood and urine (19). Its uprising causes an increase in lipid peroxidation. The MDA level in diabetics indicates the destruction of pancrease caused by oxidative stress. Soliman and et al. in a study thay they practiced with 80 diabetics, they determined that hyperglisemia increased oxidative stress and caused decreasing of antioxidant capacity in 2008 (20). In this study, the level of MDA in their blood was analyzed. The decrease happened on the MDA level was considered as statistically important ($p<0.05$).

In a prospective study, the levels of proinflammatory cytokines such as serum CRP are also elevated in type 2 diabetic individuals, but because of being economic, CRP is used more frequently. Serum CRP levels are identified as nonlipid cardiovascular risk indicator. It was found that people having more than 2.4 mg/L serum CRP level have a heart disease risk twice more than those having 1mg/L. In the Hoorn study, it was determined that it is a mortality indicator having a high serum CRP level after the 5-7 years of process for the type 2 diabetics (21).

Refined grains trigger proinflammatory sitokin production as they cause akut hyperglisemia. Instead of them, whole grain production usage causes a decrease of circulation of free radicals and proinflammatory sitokins. High CRP level, which is an indicator of systematic inflammation, can be reduced with lifestyle changes. These changes are loss weight, quitting smoke, doing exercise, reducing saturated fat intake, increasing the consumption of vegetable, and fruit and whole grain productions. In the woman health study practiced with type 2 diabetic women, it was seen that whole grain products and low glisemic index diet decrease CRP levels (22). In the meta-analysis study of Steckhan and et al. low fat (less than 30% of the amount of total energy coming from fat) and saturated fat reduction diets caused a decrease in serum CRP level, low carbonhydrated diets accelerated loss weight by causing a decrease in the insulin level, loss weight caused a significant decrease in proinflammatory sitokin release (23). At the end of this study, after 3 months period of time, it was determined that the decrease on CRP level was statistically important.

Compared to the healthy people, the balance between oxidant and antioxidant systems were impaired in Type 2 diabetes diabetics. In an oxidative stress parameters comparation study that 59 Type 2 diabetes diabetics and 48 healthy people were compared, there was a positive correlation between serum MDA levels and HbA1c levels of the participants, and it was determined that chronic hyperglisemia caused a significant increase in the oxidative stress indicators of the patients (24). At the end of this study, after 3 months diet, it was determined that there was a reduce in fasting plasma glucose, fasting insulin, HOMA-IR, HbA1c and MDA levels of patients compared to the initial study and this reduce was statistically significant.

Conclusion

Diabetes is accepted as a pandemi by WHO and United Nations, and its a disease that has a high mor-

tality and morbidity rate, which is rapidly increasing in the population. Every year 4.9 millions of people die because of diabet, and 50% of them have cardiovascular origins. Diabetes and the treatment of the diseases it causes are difficult and costly, so it is one of the diseases that are frequently observed in our country and in the world.

Diabetes is a chronic disease which can cause complications in a long term. Providing and maintaining a good glisemic control on patients can provide the development of the complication. At the beginning of the diabetes, a lifestyle change which will be practiced with a nutritional theraphy can reduce the possibility of diabetic complication, mortality and morbidity, also contributes to the economy of the country.

Altough many different studies about the nutrition treatments given to diabetics were done, the number of the studies identifiying the contribution of the inflammation and oxidative stress levels which cause the diabetes complications are limited. In the studies, in spite of seeing that different diet practices avail, it is known that individually prepared and practiced nutrition programme is effective by taking the nutrition habits and socioeconomic status of the patients into consideration. Therefore, a nutrition programme was prepared for the patients who took part in the study considering the individual features and suggestions of the guides.

The educations practiced on diabetics and these educations being put into practice by the patients in their daily lives have a siginificant place in the course of the disease. Educations being repeated in the suitable frequency and level for each patient by taking the suggestions of the guides into consideration, sparing time for the educations of patients as long as possible and planning these educations by using a comprehensible language suitable for everyone are quite important to establish a good glisemic control. There is a need to plan the studies that contain new methods and suggestions about the subject and to evaluate the contribution for the course of the disease.

Despite the fact that the time of the study and the number of the samples are limited, the results obtained emphasize the importance of the nutrition treatment for the diabetic patients. It is thought that it will be a significant source for the studies being done in a long time and with more samples.

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