Review

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Low-Carbohydrate Diets and Type 1 Diabetes

Düşük Karbonhidratlı Diyetler ve Tip 1 Diyabet

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Abstract

Despite the significant medical and technological advances, the management of Type 1 diabetes remains unsatisfactory. The most significant challenge herein is the difficulty in controlling post-prandial glycemia. The type and amount of carbohydrates consumed have a greater influence on the post-prandial hyperglycemia and glycemic variability than other dietary factors, which consequently generates interest in carbohydrate-modified diets for the management of Type 1 diabetes. Individuals with Type 1 and Type 2 diabetes prefer low-carbohydrate diet regimens in order to maintain glycemic control. Few studies have examined the effects of a low-carbohydrate diets on the course of glycemic control in individuals with Type 1 diabetes. Low-carbohydrate diets may reduce glycemic fluctuation, hemoglobin A1c levels, and insulin requirement in adults with Type 1 diabetes. The long-term effects of a low-carbohydrate diets are not well documented, although it is believed to alter the lipid profile and cause nutrient deficiencies and cardiac complications in the long term. In children and adolescents with Type 1 diabetes, it may improve glucose levels in the short term, although it may lead to growth retardation, deficiency in the intake of vitamin, minerals, and fiber, increase in blood lipids, fatigue, anxiety, and social isolation. This review discusses the effects of low-carbohydrate diets on Type 1 diabetes.

Keywords: Low-carbohydrate diets; Type 1 diabetes; glycemic control

Özet

Önemli medikal ve teknolojik ilerlemelere rağmen Tip 1 yönetimi yetersiz kalmaktadır. Bu konudaki en önemli zorluk postprandiyal glisemiyi kontrol etmedeki güçlüktür. Tüketilen karbonhidratın türü ve miktarı postprandiyal hipeglisemiyi ve glisemik değişkenliği diğer diyetsel faktörlerden daha fazla etkilemekte, bu durum da Tip 1 diyabette karbonhidratı modifiye edilmiş diyetlere ilgiyi artırmaktadır. Tip 1 ve tip 2 diyabetli bireyler, glisemik kontrollerini sağlamak için düşük karbonhidratlı diyet uygulamalarını tercih etmektedir. Düşük karbonhidratlı diyetlerin tip 1 diyabetli bireylerde glisemik seyir üzerine etkisini inceleyen sınırlı sayıda çalışma bulunmaktadır. Erişkin Tip 1 diyabetli bireylerde düşük karbonhidratlı diyetler glisemik dalgalanmayı, hemoglobin A1c seviyelerini ve insülin ihtiyacını azaltabilmektedir. Düşük karbonhidratlı diyetin uzun dönem etkileri tam olarak kanıtlanamamakla birlikte, uzun dönemde lipit profilinde değişikliğe, besin ögesi yetersizliği ve kardiyak komplikasyonlara neden olabilmektedir. Tip 1 diyabetli çocuk ve adolesanlarda kısa dönemde glukoz seviyelerini iyileştirebilmekte, ancak uzun dönemde büyüme geriliğine, vitamin-mineral ve posa alımında yetersizliğe, kan lipitlerinde artışa, yorgunluk, anksiyete ve sosyal izolasyona yol açabilmektedir. Bu çalışmada, düşük karbonhidratlı diyetlerin Tip 1 diyabet üzerindeki etkilerinin tartışılması amaçlanmıştır.

Anahtar kelimeler: Düşük karbonhidratlı diyetler; Tip 1 diyabet; glisemik kontrol

Introduction

Type 1 diabetes is characterized by an absolute insulin deficiency, which is caused by T-cell-mediated autoimmune destruction of pancreatic β-cells (1). Type 1 diabetes accounts for 5-10% of all global cases of diabetes mellitus and 90% of the juvenile and adolescent diabetes cases (2, 3). According to the data obtained from the Diabetes Atlas by the International Diabetes Federation (IDF) (2017), the number of children and adolescents (0-19 years) with type 1 diabetes is estimated to be 1,106,500 worldwide. Furthermore, it is reported that the annual number of newly diagnosed cases is 132,600 (4).

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The management of type 1 diabetes requires both effort and attention (5). The overall purpose of the treatment is to achieve a metabolic balance and thus minimize the short-term (hypoglycemia, diabetic ketoacidosis) and long-term complications (retinopathy, nephropathy, neuropathy), and to ensure and maintain normal growth, development, and emotional maturation (6). Measurement of the glycated hemoglobin (HbA1c), which is considered to be the gold standard of glycemic control, is the most significant indicator of successful treatment (7). It is possible to reduce the microvascular and macrovascular complications of diabetes by lowering HbA1c levels by approximately 7% and lower (8). According to the Journal of the International Society for Pediatric and Adolescent Diabetes (ISPAD), the HbA1c cut-off in the treatment of type 1 diabetes should be <7.0%, without significant episodes of hypoglycemia (9). According to the American Diabetes Association (ADA), the HbA1c threshold should be <7.5% for all the younger age-groups and <7% for adults (1). However, current studies have shown that only a few individuals have achieved these targets (10-12). In a multicenter incidence study called SEARCH for Diabetes, which investigated diabetes in youth in America, it was observed that 17% of 3947 individuals with type 1 diabetes had HbA1c levels higher than 9.5% (13).

Despite recent advances in the treatment of diabetes, including novel insulin analogs, intensive insulin therapies, and new therapeutic technologies such as continuous glucose monitoring system (CGMS), a substantial number of patients fail to either achieve or maintain the target HbA1c levels (14). Therefore, it is stated that the existing treatments are insufficient and additional strategies should be considered. Medical nutrition therapy (MNT) is one of the most important strategies in the prevention and treatment of diabetes (15). Deviations in blood glucose levels are a function of the input of glucose from food, mainly carbohydrates (16, 17). Therefore, individuals with type 1 and type 2 diabetes prefer low-carbohydrate diets to maintain glycemic control, which is also recommended by various media forums (18).

Although some evidence shows that low-carbohydrate diets may be effective for weight loss in obese adults (19, 20), maintenance of glycemic control and HbA1c in adults with type 2 diabetes, and reduction of the postprandial blood glucose and insulin requirements (21, 22), scientific research supporting these findings in individuals with type 1 diabetes is scarce (16, 23, 24). Compliance with these diets may be difficult and may pose a health risk to the patient (25). It is reported that such diets can cause hypo or hyperglycemia, increase the risks of ketosis, and may lead to an increased risk of cardiac complications in the long term (26, 27). Thus, the role of low-carbohydrate diets in patients with diabetes remains unclear (1). To address this gap in the literature, this review will discuss the effectiveness of low-carbohydrate diets on the treatment of type 1 diabetes.

Definition of a Low-Carbohydrate Diet

Post-prandial glycemia is the main factor affecting the levels of blood glucose and glycated hemoglobin in type 1 diabetes (28). MNT plays an important role in maintaining glycemic control (15). Dietary carbohydrates represent the most important factor in determining post-prandial blood glucose and pre-prandial insulin dose. It is the amount of glucose that is digested, absorbed, and then circulated in the blood that determines the post-prandial blood glucose levels (16). According to the classification by the American Diabetes Association (ADA), a diet with a carbohydrate intake of less than 130 g/day or 26% of the total energy intake is defined as a low-carbohydrate diet (1), while a diet with a carbohydrate intake of 21-70 g/day is defined as a very low-carbohydrate diet (29).

Effects of Low-Carbohydrate Diets on Glycemic Control in Individuals with Type 1 Diabetes

Before the discovery of insulin, low-carbohydrate diets were used as the only treatment for type 1 diabetes. The subsequent discovery of insulin and development of flexible insulin-treatment methods led to the replacement of low-carbohydrate diets by methods that ensured the delivery of insulin in proportion to the carbohydrate intake in

meals and current blood sugar levels (17). The carbohydrate counting method, which enables the matching of short-acting insulin boluses with carbohydrate uptake, allows for significant flexibility in carbohydrate consumption (30). However, errors in predicting the carbohydrate content and insulin dose, especially in high-carbohydrate meals, results in the inappropriate use of this method by individuals with type 1 diabetes (16). The estimated amount of carbohydrates in the meal is subject to an error of up to 50% (31), while absorption of insulin may vary by up to 30% (32). Therefore, incompatibilities and miscalculations in the carbohydrate to insulin ratio may lead to unpredictable glucose fluctuations after meals. High insulin doses, especially in response to high amounts of carbohydrates, can cause unpredictable fluctuations in blood glucose levels. It may be possible to minimize these fluctuations and the risk of hypoglycemia by reducing the number of carbohydrates and insulin doses. It may also be possible to provide a better and more predictable absorption rate and facilitate more effective use of insulin by reducing the amount of insulin taken by individuals (33, 34). This leads to some individuals with type 1 diabetes, who use flexible insulin therapy, to substantially limit the amount of carbohydrates consumed.

Some studies have stated that low-carbohydrate diet regimens cause a reduction in the post-prandial blood glucose levels, insulin dose, and body mass index (BMI) in individuals with type 1 diabetes (16, 23, 24, 30, 34). A study examining the effects of a diet containing 30 g/day carbohydrate on glycemic control in adults with type 1 and type 2 diabetes reported a more significant improvement in the HbA1c values (8.4% to 5.8%) of individuals with type 2 diabetes, compared to the HbA1c values of individuals with type 1 diabetes (6.8% to 5.5%). In addition, a significant decrease in the amount of insulin administered daily by individuals with type 1 diabetes (from 47 to 30 units), compared to the amount of insulin administered daily by individuals with type 2 diabetes (22.3 to 21.2 units), was observed. Furthermore, no incidence of severe hypoglycemia was observed during the study period of 22 months (34). In another study, it was stated that the carbohydrate quantities of less than 40 g/day were not realistic in the general diabetic population and that such a radical decrease in carbohydrate amounts could limit the number of individuals wanting to try the method and also possibly increase the risk of ketoacidosis. In this study, 24 patients with type 1 diabetes were given 70-90 g of carbohydrate per day (20% of the total energy requirement) for 12 months, by the end of which, it was observed that the reduction in the amounts of carbohydrates and corresponding insulin doses led to a decrease in mean blood glucose as well as fluctuations, improved the HbA1c values, and significantly decreased in the incidences of hypoglycemic episodes (nearly 6-fold reduction) (23). Similarly, Krebs et al. (2016) compared the effects of low-carbohydrate diet (50-75 g/day) and standard diet on glycemic control, the course of glucose and daily insulin use, and found that the low-carbohydrate diet reduced the total daily insulin requirement, improved the glycemic control, and reduced the BMI. However, in this study, three of the participants with a carbohydrate-restricted diet reported that their insulin doses, given in proportion to the number of carbohydrates consumed, were not sufficient to control the post-prandial blood glucose concentrations. It was suggested that such a change may occur due to the fact that gluconeogenesis from proteins was an important source of glucose. It was recommended that patients who wished to reduce carbohydrate intake should consider their protein intake while determining insulin doses and set a protein/insulin ratio (30). In a study conducted by Ranjan et al. (2017) that involved the application of isocaloric high-carbohydrate (≥250 g/day) and low-carbohydrate (≤50 g/day) diets for one week in individuals with type 1 diabetes, it was observed that the glycemic times of the individuals on a low-carbohydrate diet increased, while their glycemic fluctuations, total insulin, and bolus insulin doses decreased. Although fasting ketone levels have been reported to increase in low-carbohydrate diets, no episode of diabetic ketoacidosis was recorded (24). In another study, the long-term (four years) effects of low-carbohy-

drate diets (≤75 g/day) on the body weight, lipid profile, and HbA1c were investigated. At the end of study, a significant increase in the HDL cholesterol levels and a decrease in the HbA1c levels were observed in individuals with type 1 diabetes (16). Leow et al. (2018) reported that although ketogenic diets (<55 g/day) provided better HbA1c levels and lower glycemic variability, they were associated with dyslipidemia and more episodes of hypoglycemia (26). Recently, Eiswirth et al. (2018) studied the impact of a very low-carbohydrate diet (30-50 g/day) on the mean blood glucose, daily glycemic variability, and HbA1c values in a patient over a 6-month period. They observed a near normalization of glycemic indices (HbA1c=5.3%; average daily blood glucose=6.1 mmol/L) with no significant hypoglycemic episodes and minimal impact on the circulating lipids (35). In a systematic review by Turton et al. (2018), it was reported that the overall effect of low-carbohydrate diets could not be determined due to significant heterogeneity of the studies involved. According to this review, some studies reported that low-carbohydrate diets effected a significant decrease in the HbA1c levels and total daily insulin dose, while other studies observed non-significant changes in these parameters. The authors also suggested that the intake of low-carbohydrate diets may result in reducing or preventing hyperinsulinemia in type 1 diabetes by decreasing the amount of insulin required for tight glycemic control (17).

In addition to direct interventional studies, observational data also demonstrate the beneficial effects of low-carbohydrate diets on the glycemic control in individuals with type 1 diabetes. A large observational study of 1020 European outpatients with type 1 diabetes showed that low carbohydrate intake was associated with reduced HbA1c levels (36). An online study examining children and adults with type 1 diabetes, which followed a very low-carbohydrate diet, was carried out by Lenners et al. (2018). In this study, it was observed that the participants (both adults and children) took a very low-carbohydrate diet (average daily carbohydrate intake of 36±14 g) over an average of 2.2±3.9 years (1.4±1.2 years for the pediatric age group) and their HbA1c values after this diet were 5.67±0.66% (5.71±0.58% in the pediatric age group). It was observed that a very low-carbohydrate diet provided good glycemic control in children as well as adults, and only 2% of the participants experienced ketoacidosis and hypoglycemia, although a decrease in the height of the children was observed after the diagnosis was made (37). This study did have several limitations, including an inability to confirm all the medical data. In addition, this study was conducted through an online social media group that increased the risk of selection bias, as the online community did not represent a general type 1 diabetic community (38). Apart from this study, only case studies reporting on low-carbohydrate diets in children and adolescents with type 1 diabetes are available. In one such case study, the long-term effects of a ketogenic diet on a 3.5-year-old girl with type 1 diabetes and epilepsy were investigated. During the 15-month observation period, no severe hypoglycemia or ketoacidosis occurred, the HbA1c levels (6.2%) remained within the desired range and no epileptic seizures were recorded. However, the patient refused to follow the ketogenic diet after 15 months (39). Similarly, in another case study, it was reported that a 2-year-old epileptic patient was given a ketogenic diet after the diagnosis of type 1 diabetes, and no epileptic seizures and episodes of diabetic ketoacidosis occurred during the 10-month period when the ketogenic diet and insulin therapy were administered together (40).

It has been reported that low-carbohydrate diets may help maintain and increase the amount of insulin produced by certain people with diabetes, in addition to providing normal glycemic control. This effect can be even more beneficial for individuals with type 2 diabetes who produce some amount of insulin, as well as in patients with type 1 diabetes who are in temporary remission and honeymoon phase (34). The symptoms of diabetes occur when approximately 80% of a person's islet cells are destroyed (41). It has been reported that high-carbohydrate diets can accelerate the death of the remaining islet cells in diabetic patients and

lead to a process called β-cell depletion (34). It has been shown that high levels of blood glucose reduce the ability of islet cells to produce insulin by inhibiting gene expression and binding to critical insulin transcription factors (42).

It is suggested that these effects, together with the depletion of β-cells, may accelerate the destruction of islet cells, increase the requirement of insulin, and lead to poorer glycemic control. Therefore, it is proposed that low-carbohydrate diets may help in the maintenance of the remaining islet cells, reducing the need for insulin in individuals with type 2 diabetes by preventing the over-activity of islet cells, and helping individuals with newly-diagnosed type 1 diabetes to maintain the "honeymoon phase" (34). Toth and Clemens, in two case studies, examined the effects of paleolithic ketogenic diets on the management of diabetes in 19- and 9-year-old male patients with type 1 diabetes. After starting a paleolithic ketogenic diet, the glucose levels of the patients returned to normal and insulin treatments were stopped (after 6.5 months in the 19-year-old patient and 19 months in the 9-year-old patient). Furthermore, the C-peptide level of the 19-year-old patient increased significantly (more than 3-fold) within two months. The researchers reported that a low-carbohydrate diet may halt or reverse the autoimmune process leading to the destruction of pancreatic β-cells. However, they emphasized that the paleolithic ketogenic diet could only be used in patients with residual insulin secretion as a single treatment option (42, 43).

Pediatric endocrinologists and dieticians in Australia and New Zealand reported a series of cases examining the effects of low-carbohydrate diets on the endocrine and metabolic outcomes in children with type 1 diabetes. Accordingly, it was shown that the carbohydrate-restricted diets, which were applied to reduce the course of glycemia and insulin in children, decreased the energy intake (if the amount of energy from carbohydrates is not sufficiently obtained from fat and proteins), led to suboptimal growth, caused vitamin and mineral deficiencies, increased the metabolic profile causing cardiovascular risk, and increased the risk of disrupted eating behaviors. In addition, this study reported that the release of growth hormone was suppressed, response to the growth hormone decreased as dietary fat became the main source of energy, high amount of fat and protein consumption caused glycemic fluctuations, and the low-carbohydrate diet led to fatigue, anxiety, and social isolation in individuals (18). Similarly, The Diabetes Control and Complications Trial (DCCT) examined the associations of nutritional intake, physiological parameters, and daily activities on the average HbA1c. It was found that lower carbohydrate and higher fat intake were associated with higher HbA1c levels (44). This could be attributed to the fact that patients only took insulin for the intake of carbohydrates, but did not take into account the fat and protein content of the diet, thus creating an incompatibility with the dose of insulin. The results of clinical trials in children and adults with type 1 diabetes are summarized in Table 1 and Table 2.

Conclusion

A limited number of studies have examined the effects of low-carbohydrate diets on the course of glycemia in individuals with type 1 diabetes. The evidence examining the effects of low-carbohydrate diets on type 1 diabetes is controversial and contradictory. A significant body of research from diverse study types shows that in the short- to medium-term, low-carbohydrate diets have the potential to reduce the average HbA1c, stabilize the blood glucose levels, and decrease the insulin requirement in patients with type 1 diabetes. Although the long-term effects of low-carbohydrate diets are not well documented, the possible complications may include alterations in the lipid profiles, micronutrient deficiencies, and cardiac complications. Adhering to these diets can be difficult or restrictive for some patients, and they may even pose health risks such as hypoglycemia and ketosis for the patients. In addition, low-carbohydrate diets may be more expensive. Carbohydrate-rich foods (e.g., potato, rice, bread) are cheaper than protein-rich ones (e.g., meat, fish, and dairy foods). Low-carbohydrate diets have a higher content of fat and protein, which can also influence the pattern of post-prandial

Table 1. Summary of clinical trials in child and adolescents with type 1 diabetes and primary finding.

Authors/year	Duration	Subjects	Diet	Primary findings
Dressler et al., 2010[39]	15 months	A three-and-half-year-old girl	1200 kcal 3:1 (fat:protein+ carbohydrate) ratio ketogenic diet	- No severe hypoglycemia or ketoacidosis - No clinically overt seizures - Improved HbA1c levels Improved activity levels and achievements
Castaneda et al., 2012[40]	10 months	A two-year-old girl	4:1 (fat:protein +carbohydrate) ratio ketogenic diet	- No epileptic seizure and ketoacidosis - Few mild episodes of hypoglycemia - No change in linear growth
Toth and Clemens, 20144[2]	6.5 months	A 19-year old boy	2:1 (fat:protein +carbohydrate) ratio ketogenic diet	- Improved glucose levels - Insulin therapy discontinued - More than threefold increase in C-peptide within two months
Toth and Clemens, 2015[43]	19 months	A 9-year old boy	2:1 (fat:protein +carbohydrate) ratio ketogenic diet	- Improved glucose levels - No hypoglycemic episodes - Insulin therapy discontinued - Improved physical fitness
Lenners et al., 2016[37]	1.4±1.2 years	316 participants (42% child) Aged 9±4 years in the pediatric group	Low carbohydrate diet (36±14 g/d)	- Significant reduction in HbA1c (11%±2% to5.71%±0.58%) - Decrease in height SDS since diabetes diagnosis
de Bock et al., 2017[18]	1.5-4 years	Case series (6 children) 3.5-12 years	Low carbohydrate diet 40-75 g/d carbohydrate	- Deficient total energy intake - Deficient anthropometric measurements. Increased lipid profile - A poor growth hormone response - Fatigue and low enjoyment for sports

Table 2. Summary of clinical trials in adults with type 1 diabetes and primary findings.

Authors/year	Duration	Subjects	Diet	Primary findings
O'Neill et al., 2003[34]	21.4 months	30 participants (20 participants with type 2, 10 participants with type 1)	Very low carbohydrate diet (30 g/d)	Both type 1 and type 2 diabetics, there was a significant improvement in glycemic control and mean fasting lipid profile
Nielsen et al., 2005[23]	12 months	22 participant Aged 51±10 years	70-90 g/d	-The HbAlc level was significantly lowered -The meal insulin requirements were reduced -Triglyceride level was significantly lowered -Rate of hypoglycemia was significantly lowered.
Nielsen et al., 2012[16]	4 years	48 participants (31 women) Aged 52±11.5 years	Carbohydrate-restricted diet (75 g/d or less)	-Mean HbA1c for all attainders was at the start, at 3 months and 4 years 7.6%±1.0%, 6.3±0.7%, 6.9±1.0%, respectively. -Significant rise in HDL cholesterol levels
Krebs et al., 2016[30]	12 weeks	10 participants (3 women) Aged 44.6±8.9	Standard diet vs. Low carbohydrate diet (75 g/d)	-Significant reduction in HbA1c and daily insulin use in carbohydrate-restricted group
Ranjan et al., 2017[24]	1 week	10 participant (4 women) Aged 48±10 years	Isocaloric Low carbohydrate diet (≤50 g/d) vs. High carbohydrate diet (≥250 g/d)	-Low carbohydrate diet resulted in more time in euglycemia, less time in hypoglycemia and less glucose variability than the high carbohydrate diet
Leow et al., 2018[26]	1.5 years	11 participant 36.1±6.8 years	Ketogenic diet <55 g/d carbohydrate	-Participants spent 74±20% and 3±8% of their time in the euglycemic and hyperglycemic range, respectively with little daily glycemic variability -A median (range) of 0.9 (0.0-2.0) daily episodes of hypoglycemia -Increased total LDL cholesterol, total/HDL cholesterol ratio, and triglycerides
Eiswirth et al.,2018[35]	6 months	1 participant	30-50 g/d carbohydrate	-Reduction in HbA1c and daily blood glucose levels -Reduction in insulin dose (from 50.0 to 30.0 units) -Reduction in glycemic variability -No change in lipid profile, no significant hypoglycemic events

glycemic homeostasis. A low-carbohydrate diet may also cause hyperglycemic effects due to fat and protein metabolism to form glucose.

Low-carbohydrate diets are not recommended for children and adolescents with type 1 diabetes, as they may hinder their growth and development. Low-carbohydrate diets may cause growth retardation; increase blood lipids; deficiency of vitamin, minerals, and fiber; increase social isolation, and increase the risk of improper eating behaviors in children and adolescents. International clinical guidelines for the management of type 1 diabetes offer a healthy and balanced diet program that consists of a variety of nutrients. The recommendations on nutrition for individuals with diabetes, as well as their families, should be based on scientific evidence and not on testimonials. Individuals with diabetes and their families that adopt a restrictive nutrition program to improve their glycemic control should be carefully monitored and consulted on the physical and psychosocial effects of a low-carbohydrate diet by their diabetes team. In order to reduce glycemic fluctuations, individuals with type 1 diabetes should be trained to consume foods with low glycemic index and low glycemic load, prepare the appropriate dose of insulin before meals while consuming food containing carbohydrates, create meal-time routines, minimize the frequency of snacking, and calculate the appropriate insulin dose based on the high amount of fat and proteins consumed. In individuals with type 1 diabetes, fulfilling the total energy requirement from balanced macronutrient sources and increasing the quality of diet by consumption of fruits and vegetables, whole-wheat bread, legumes, and whole grain products can improve the metabolic profile.

There are some limitations to this review. In the evaluated studies, small sample sizes, short follow-up periods, multiple study designs, and inadequate dietary reports yielded different and contradictory results on the effect of low-carbohydrate diets on glycemic control. In conclusion, more randomized controlled trials and evidence on the long-term effects of low-carbohydrate diets on the treatment of type 1 diabetes are needed.

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Conflict of Interest

The authors declare no conflict of interest.

Authorship Contributions

Idea/Concept: Rukiye Bozbulut, Esra Döğer Design: Rukiye Bozbulut, Esra Döğer, Aysun Bideci, Orhun Çamurdan, Peyami Cinaz, Control/Supervision: Rukiye Bozbulut, Esra Döğer, Orhun Çamurdan Data Collection and/or Processing: Rukiye Bozbulut, Esra Döğer, Analysis and/or Interpretation: Rukiye Bozbulut, Esra Döğer, Aysun Bideci, Orhun Çamurdan, Peyami Cinaz, Literature Review: Rukiye Bozbulut Writing the article: Rukiye Bozbulut, Esra Döğer, Critical Review: Rukiye Bozbulut, Esra Döğer, Aysun Bideci, Orhun Çamurdan, Peyami Cinaz, References and Funding: Rukiye Bozbulut, Esra Döğer Materials: Rukiye Bozbulut, Esra Döğer, Aysun Bideci, Orhun Çamurdan, Peyami Cinaz.

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