Metabolic Syndrome and Cardiovascular Problems Associated with Different Types of Diet

Metabolik Sendrom ve Kardiyovasküler Problemlerin Farklı Diyet Türleri ile İlişkisi

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ABSTRACT

Metabolic syndrome (MS) is an important health issue all over the world. Diagnosis of the disease depends on the presence of obesity, dyslipidemia, hypertension, glucose intolerance and insulin resistance. These are the main risk factors for cardiovascular diseases. Because the most important reason of death is cardiovascular diseases, treatment of MS is essential. There are many types of diet for MS in literature. Not all types of diet can change all metabolic parameters. Cardiovascular disorders may not be seen depending on the diet type. For this reason, it is important for researchers to find appropriate diet type for their study. Present review includes effects of four frequently used diets on the cardiovascular system and metabolic parameters. High fat and high carbohydrate combinations were used in these diets. In this review, species, age and gender of the experimental animal; durations and ingredients of the diets were summarized. The largest increase in metabolic parameters and the abundant number of cardiovascular disorders was found out in high fructose diets. Loss of function in the aorta and the heart was detected similarly in all four diets. Our review which summarizes effects of four different types of diet may facilitate discovery of novel treatments on the metabolic syndrome and related cardiovascular diseases.

Keywords: Metabolic syndrome, Cardiovascular, Diet-Induced, Fructose, High Fat, Cafeteria

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ÖZET

Metabolik sendrom tüm dünyada geçerli önemli bir sağlık sorunudur. Hastalığın tanısı obezite, dislipidemi, hipertansiyon, glukoz intoleransı ve insülin direnci bulgularının bir arada bulunması ile konulur. Bu bulgular kardiyovasküler hastalıkların oluşmasında başlıca risk faktörüdür. Dünyadaki ölümlerin en önemli sebebinin kardiyovasküler hastalıklar olduğu düşünüldüğünde metabolik sendromun tedavisi önem arz etmektedir. Literatürde MS modeli oluşturmak için kullanılan çok sayıda diyet çeşidi bulunmaktadır. Farklı diyet türleri bütün metabolik parametrelerde aynı şekilde değişikliğe sebep olamayabilir. Kardiyovasküler bozukluklar diyete bağlı olarak her zaman ortaya çıkmayabilir. Bu yüzden araştırmacıların çalışmaları için uygun diyet tipini seçmeleri önemlidir. Sıklıkla kullanılan dört farklı diyet tipinin kardiyovasküler bozukluklar ve metabolik parametreler üzerindeki etkileri bu derleme çalışmasının konusunu oluşturmaktadır. Bu diyetlerde yüksek yağ ve yüksek karbonhidratın farklı kombinasyonları kullanılmıştır. Bu derlemede deney hayvanlarının türü, yaşı ve cinsiyeti; diyet süreleri ve içerikleri yer almaktadır. Metabolik parametreleri en fazla artıran ve en çok sayıda kardiyovasküler bozukluğa sebep olan diyet yüksek fruktozlu diyet olmuştur. Aorta ve kalpte normal fonksiyon kaybı dört farklı diyette de ortak olarak tespit edilmiştir. Dört farklı diyetin etkilerinin özetlendiği derleme çalışmamız, metabolik sendrom ve ilişkili kardiyovasküler sistem hastalıkları ile ilgili yeni tedavi yöntemlerini geliştirecek araştırmalar için yol gösterici olacaktır.

Anahtar Sözcükler: Metabolik Sendrom, Kardiyovasküler, Diyete bağlı, Fruktoz, Yüksek Yağlı, Kafeterya

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INTRODUCTION

Metabolic syndrome (MS) is a group of diseases in which obesity, dyslipidemia, hypertension, glucose intolerance and insulin resistance are seen together. Incidence of MS gradually increases because of the high calorie diet and physical inactivity. According to 'Adult Treatment Panel' (ATP) III criteria, prevalence of MS is 33,9% (men-28%, women-39,6%) in Turkiye (1). MS increases risk of cardiovascular diseases two fold (2). Coronary and peripheral artery diseases, myocardial infarction, congestive heart failure, arrhythmia and stroke are among the most seen cardiovascular diseases (3). Treatment of the MS is crucial because the leading cause of death is cardiovascular diseases in the world. Treatments for MS patients should correct disturbances of metabolic parameters and prevent cardiovascular diseases. For this reason, either efficacy of current treatments should be increased or new therapeutic approaches should be developed. It should be considered whether MS model in animal can reflect MS disease in human accurately. If the model of the disease in the animal can be generated and treatments can be done truly, these results can be adapted to clinical trials appropriately. Our review consists of the effect of different types of diet used for the MS model generation in rats on metabolic parameters and the cardiovascular system to clear up the confusion on this issue.

The Cafeteria Diet

Migration from village to city along with industrialization has brought health and nutrition problems. Industrial foods and their ingredients and lifestyle changing increase the risk of many diseases especially MS. Packed foods and beverages sold in the grocery are used to test cafeteria (C) diet type on experimental animals. In addition to standard chow diet, packed products are given to experimental animals by switching them daily or weekly. In studies examining how the C diet affects MS parameters and cardiovascular system, adult male wistar or spontaneously hypertensive rats were used generally, except one study (4) which they used three weeks old golden hamsters. Diet durations ranged from 10 to 19 weeks.

Body weight, serum insulin, fasting glucose, triglyceride and blood pressure which were used for the diagnosis of the MS were increased by *38%* (4–7), *398%* (4, 5, 7), *25%* (4, 5, 7), *98%* (4–8), *32%* (6–8) respectively by C diet as a mean. Aorta diameter and media thickness were increased (4), acetylcholine-induced vasodilation (7) and phenylephrine-induced vasoconstriction were decreased (8), cardiac contractility and isoproterenol-induced coronary vasodilation were decreased (6) by the C diet.

Depending on the C diet, it was revealed that atherosclerotic alterations on vessels and dysfunction of contraction-relaxation responses of vessels (4, 6–8).

The High Fat Diet

According to recommendations of the World Health Organization (WHO), total fat content of the healthy diet should not be more than %30 of the total energy intake. Furthermore, saturated fats should be less than %10 and trans fats should be less than %1 of the total energy intake. When the diet fat content increases, excess fat accumulates in the adipose tissue. For this reason, central obesity is observed in the MS. Studies that generate MS model with high fat (HF) diet take part in literature. In HF diet studies, 40-60% of the calories taken by the diet were provided from fats. There are also studies that used trans and saturated fats. If the consumption of the fat especially saturated fat increases, obesity and cardiometabolic diseases are seen more easily in the society (9).

4-12 weeks old experimental animals were used in HF diet studies in the present review. C57BL/6 mice were used in studies generally. However, Wistar Kyoto rats (10) and rabbits (11) were preferred as an experimental animal in relevant studies. Diet durations were changed from 6 to 24 weeks. In the one of these studies HF diet was applied for 16 months to determine the effect of the long term diet (12). Zhang L at al. pointed out that both male and female animals were used in their study, but they didn't mention it in results and discussion section (13). Other studies were performed with male experimental animals.

In HF diet groups compared with control groups, body weight, serum insulin, fasting glucose, triglyceride, total cholesterol and insulin resistance were increased by *39%* (12–14), *192%* (10, 12, 14), *26%* (10–12, 14), *63%* (10, 11, 14), *56%* (10, 12–15), *84%* (10, 14, 15) respectively as a mean.

Increase of the cardiomyocyte diameter, heart and left ventricle weight, (10, 12, 13), increase of the posterior wall thickness of the left ventricle (12–14), decrease of the capillary density in the heart (10, 13), increase of the interstitial collagen quantity (13, 14), increase of the myocardial oxidative stress and apoptotic cells (14), decrease of the acetylcholine induced vasodilation and increase of the norepinephrine induced vasoconstriction on thoracic aorta (11) and mesenteric artery (15), decrease of the contraction and relaxation responses in the heart (12); were discovered in HF diet groups.

Left ventricular hypertrophy, increase of the interstitial fibrosis, decrease of the angiogenesis, increase of the oxidative stress and apoptosis in the heart and dysfunction of vessels were found out in related studies depending on the HF diet (10–15).

The High Carbohydrate High Fat Diet

There has been a growing increase in the consumption of high-energy fast foods including more added sugars and fats in the society. This type of diet that contains saturated fats, refined carbohydrates and high sodium is called western type diet. Increasing preference of the western type diet with physical inactivity causes obesity, diabetes, MS and cardiovascular diseases. High carbohydrate high fat (HCHF) diet is used to investigate the effect of the diet on the cardiovascular system in the experimental animals. Diets used in these studies include sucrose or fructose and saturated fats from animal sources.

In this review, 8-9 weeks old adult male mice and rats were used in studies that applied HCHF diet. In one study, 22-26 weeks old male and female rabbits were chosen as an experimental animal (16). Diet durations ranged from 6 to 32 weeks.

In HCHF diet groups, body weight, serum insulin, fasting glucose, triglyceride, total cholesterol, blood pressure, insulin resistance and waist circumferences were increased by *16%* (16–21), *141%* (16–19, 21), *39%* (18–20), *54%* (16, 17, 19–21), *49%* (16, 18, 20, 21), *17%* (17, 19, 20), *195%* (17–20), *13%* (16, 21) respectively as a mean.

Increase of the left ventricular thickness and cardiomyocyte diameter (18–21), increase of the collagen quantity in the heart (18, 20, 21), decrease of the end-diastolic volume, stroke volume and ejection fraction (20), increase of the incidence and severity of reperfusion arrhythmias (17), increase of the arterial stiffness (16), decrease of both activity of nitric oxide and activity of Serca which related with nitric oxide in aorta, increase of free radicals production in aortic smooth muscle cells (22), increase of the phenylephrine-induced contraction and decrease of the acetylcholine-induced relaxation in aorta (21) were seen on the cardiovascular system related with HCHF diet.

Depending on the HCHF diet, left ventricular hypertrophy, cardiac fibrosis, systolic and diastolic dysfunction, arrhythmias, atherosclerosis and dysfunction of vessels (because of the migration of smooth muscle cells) were detected on the cardiovascular system. (16–22).

The High Fructose Diet

Sugars can be natural or added (refined, free) in foods and beverages. The main sources of added sugars in the diet are sugar-sweetened beverages and packed foods. According to WHO, percentage of the free sugar should be less than 10% in a healthy diet. Added sugars in foods and beverages are provided from sucrose (50% fructose – 50% glucose) or high fructose corn syrup (55% fructose – 45% glucose) (23).

Fructose is taken into the enterocyte by GLUT-5 located in the apical membrane. When the fructose enters the cell, it increases the GLUT-5 expressions on the cell membrane. After this stimulation, much more fructose can pass through the cell membrane. Fructose passes from portal vein into the hepatocyte by insulin-independent GLUT-2. Glucokinase is regulated by insulin and phosphofructokinase is rate limiting enzyme in the glucose metabolism. Unlike the glucose metabolism, fructokinase is insulin-independent and there is no any rate limiting enzyme in the fructose metabolism. Therefore, all fructose coming to the liver are metabolized without any control mechanisms. As a result, if the fructose intake is increased, lipogenesis increases at the same rate. Sangüesa at al. added glucose and fructose to rats' diet in their study. They have found that while the diet of the glucose group was high in calories, the fructose group had the worst metabolic and vascular outcomes (24). The model of the MS can be done by adding fructose to drinking water or food in experimental animals.

Adult rats and mice were used for doing MS model with high fructose (F) except one study which they used 21 days old weaned rats (25). The rate of the fructose added to the drinking water of experimental animals was ranged from 10% to 25%. Variously, Chou et al. used 60% fructose in the pellet food for animals (26). Diet durations of studies altered between 8 and 12 weeks.

In fructose used studies, body weight, serum insulin, fasting glucose, triglyceride, total cholesterol and blood pressure were increased by *33%* (27, 28), *160%* (26, 29–31), *74%* (26–31), *80%* (25, 26, 28–30), *67%* (25, 26, 28–30), *35%* (25, 27, 29–31) respectively as a mean.

In experimental animals which had added fructose in their diet, increase of the relative heart weight, left ventricular muscle mass and wall thickness, increase of the aorta tunica media thickness, prolongation of the isovolumetric relaxation period of the left ventricle (26, 27, 31), increase of the collagen accumulation in the aorta and the heart (28, 31), increase of the production of free radicals in the aorta, decrease of the total antioxidant capacity in the left ventricle (25, 26, 28), increase of the phenylephrine-induced contraction responses and decrease of the acetylcholine-induced relaxation responses in the aorta (26, 28), increase of the apoptotic cells in the left ventricle (29), increase of the mononuclear inflammatory cells in the cardiomyocytes (31), prolongation of the QT interval on the electrocardiography (30) were revealed via related studies.

Left ventricular hypertrophy, diastolic dysfunction, loss of the normal function of the aorta, fibrosis, oxidative stress, apoptosis and inflammation on the cardiovascular system, arrhythmias on the heart and the sudden death are significant cardiovascular problems, when the fructose diet was used (25–31).

Summary for Metabolic Parameters

Effects of different types of the diet on metabolic parameters and the cardiovascular system are also different when generating MS model. Changes in metabolic parameters are summarized on the Table 1 depending on the diet type. Body weight increased less by HCHF diet compared with other diets. Serum insulin values increased more by C diet. The most increase of glucose levels was seen in the F diet. Triglyceride increased more by C and F diet compared with others. While blood pressure results were not evaluated in the HF diet, it increased less by the HCHF diet. Total cholesterol values were not evaluated in the C diet. Insulin resistance calculations were performed only HCHF and HF diets. Other two diets' insulin resistance calculations were completed by us using homa-ir formula. After that, the most increase of the insulin resistance was occurred in the C diet and the lowest increase of the insulin resistance was occurred in the HF diet. Waist circumferences measurements were taken place in only HCHF diet.

In summary, the highest increase in metabolic parameters was seen in the F diet and the least increase in metabolic parameters was seen in the HF diet compared with others.

Table 1. Degree of increase in metabolic syndrome parameters depending on the diet.

Metabolic Parameters	Cafeteria (C) Diet	High Fat (HF) Diet	High Carbohydrate High Fat (HCHF) Diet	High Fructose (F) Diet
Body Weight	++	++	+	++
Insulin	++	+	+	+
Glucose	+	+	++	+++
Triglyceride	++	+	+	++
Blood Pressure	++		+	++
Total Cholesterol		+	+	+
Insulin Resistance	++++	+	++	+++
Waist Circumference			+	

The mean percentage increases of metabolic syndrome parameters in studies (references exist in the text) using the same diet type were calculated. These increases were scored as low (+), medium (++), high (+++) and very high (++++) separately for each metabolic syndrome parameter according to the diet type. (++++ > +++ > ++ > +)

Summary for Cardiovascular Disorders

When the effects of the diets on the cardiovascular system was analyzed (Table 2), it was revealed that the cafeteria diet caused loss of function in the aorta and the heart and increase of the aortic media thickness. Depending on the high fat diet, loss of function in the aorta and the heart, left ventricular hypertrophy, fibrosis, increase of the oxidative stress and apoptosis and decrease of the angiogenesis were seen on the cardiovascular system. Loss of function in the aorta and the heart, left ventricular hypertrophy, fibrosis, arrhythmias and atherosclerosis were found out when the high carbohydrate high fat diet was used. In high fructose diet used studies, loss of function in the aorta and the heart, left ventricular hypertrophy, increase of the aortic media thickness, fibrosis, increase of the oxidative stress, apoptosis and inflammation were detected.

Loss of function in the aorta and the heart is the common result for all four diets. While the high fructose diet contains the greatest number of cardiovascular disorders, the cafeteria diet contains the smallest number of cardiovascular disorders.

Table 2. Cardiovascular disorders which were seen depending on the diet

Cardiovascular Disorders	Cafeteria (C) Diet	High Fat (HF) Diet	High Carbohydrate High Fat (HCHF) Diet	High Fructose (F) Diet
Loss of Function in the Aorta and the Heart	+	+	+	+
Left Ventricular Hypertrophy		+	+	+
Increase of the Aortic Media Thickness	+			+
Fibrosis		+	+	+
Oxidative Stress		+		+
Apoptosis		+		+
Inflammation				+
Decrease of the Angiogenesis		+		
Arrhythmia			+	
Atherosclerosis			+	

Cardiovascular disorders which were given as a result in studies (references exist in the text) using the same diet type were grouped according to their similarities. They were marked with "+" according to the occurrence in the relevant diet group.

CONCLUSION

Results of different types of diet when generating MS model were evaluated in the present review. At the planning stage of these studies, it is important to answer questions such as "Which species, age and gender of the experimental animal will be used?", "Which ingredients and duration of the diet will be appropriate?", "Which parameters will be changed or unchanged at the end of the diet?". These questions should also be answered: "Which mechanism will be more effective for the treatment?" and "Which impaired metabolic parameter will cause cardiovascular disorder related to targeted treatment?". In this review, we have summarized that how four different types of diet affect metabolic syndrome parameters and cardiovascular disorders. We believe that our review will make a significant contribution to diet selection in preclinical studies researching effects of the metabolic syndrome on the cardiovascular system.

Conflict of interest

No conflict of interest was declared by the authors.

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