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Intermittent fasting - a diet to fight type 2 diabetes and obesity - current state of knowledge

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Abstract

Obesity is a chronic disease that requires diagnosis and treatment. Excess body fat and metabolic disorders, resulting from the disease, are associated with the risk of numerous complications. Among the most widespread are type 2 diabetes, hypertension, dyslipidemia, atherosclerosis, non-alcoholic fatty liver disease and sleep apnea syndrome. Weight reduction significantly improves prognosis, and can mitigate or even reverse complications. A dietary method gaining popularity recently is intermittent fasting. It involves alternating periods of eating and fasting according to a fixed time schedule. There are different types of diet, differing in the length of the fasting period. Intermittent fasting affects the human body by regulating the diurnal rhythm, inducing metabolic switching, that is switching from using glucose as an energy source to lipid oxidation, and by modulating the composition of the gut microbiota. The effects of the diet, proven in clinical trials, include weight loss, improved glucose tolerance, lowered hemoglobin A1c and insulin levels, and improved tissue sensitivity to insulin. However, there is no evidence supporting the superiority of intermittent fasting over continuous calorie restriction. Intermittent fasting also carries a risk of adverse effects, the most serious of which are hypoglycemic episodes. These occur especially in people with type 2 diabetes and taking diabetes medications.
Although intermittent fasting appears to be a promising strategy in the fight against obesity and type 2 diabetes, further research is needed to evaluate its long-term effects on the human body.

Keywords: intermittent fasting, obesity, type 2 diabetes

Introduction

Obesity is defined by the World Health Organization (WHO) as an abnormal, excessive accumulation of body fat in the human body, resulting from a long-term positive caloric balance. It is a chronic disease that does not resolve on its own and requires diagnosis and treatment. Obesity can be diagnosed when the BMI is greater than or equal to 30. It is determined by measuring weight and height, and then calculated using the formula: weight (kg)/height^2 (m^2).
According to the WHO, 890 million adults and 160 million children and adolescents under the age of 18 will be obese worldwide in 2022. Compared to 1990, this is a more than twofold increase in obesity in adults and a fourfold increase in those under 18 [1].
Excess body fat and metabolic disorders resulting from obesity are associated with the risk of associated diseases, such as insulin resistance and type 2 diabetes, hypertension, ischemic heart disease, dyslipidemia, atherosclerosis, stroke, Alzheimer's disease, dementia, obstructive sleep apnea, asthma, gastrointestinal disorders, kidney disease, reduced fertility, skeletal and immune system disorders [2].
It is estimated that more than 90% of diabetes cases worldwide are type 2 diabetes [3]. According to the International Diabetes Federation, 537 million adults worldwide will have diabetes in 2021. This number is expected to rise to as many as 783 million by 2045 [4].

Two main factors play an important role in the pathophysiology of type 2 diabetes. These include impaired insulin secretion by pancreatic β-cells and the inability of insulin-sensitive tissues to respond to the hormone, known as insulin resistance. Decreased insulin sensitivity of tissues occurs decades before the development of type 2 diabetes, and occurs as a result of reduced non-oxidative glucose metabolism associated with abnormal insulin-dependent storage of carbohydrates in the form of muscle glycogen. In the initial stages, blood glucose levels are normal, as impaired tissue sensitivity to insulin is compensated for by the ß-cells of the pancreas, which secrete greater amounts of insulin. However, after time, cell function deteriorates and insulin secretion decreases, which limits the body's ability to maintain physiological blood glucose levels [5].
A complex combination of interacting genetic, metabolic and environmental factors leads to the development of type 2 diabetes. Risk factors can be divided into non-modifiable ones, such as ethnicity and genetic predisposition, and modifiable ones, namely obesity, low physical activity and unhealthy diet [6].
Individual risk of type 2 diabetes is largely determined by genetic factors. The nature of the disease is multigene. Most loci increase the risk of the disease through a primary effect on insulin secretion, while fewer impair the action of the hormone. However, differences in known loci explain little of the observed heritability of type 2 diabetes [7]. Studies confirm that the missing heritability may be influenced by interactions between susceptibility loci and environmental factors that modulate a particular genetic variant [6]. Many cases of diabetes can therefore be prevented by improving modifiable risk factors. Obesity is considered the most important of these [8]. Lifestyle interventions underlie the treatment of both obesity and type 2 diabetes, and include increasing physical activity and reducing dietary caloric intake to affect fat loss. In recent years, the use of intermittent fasting for this purpose has gained popularity. This is a dietary regimen that involves alternating between eating meals without restriction (ad libitum) and fasting according to a fixed time schedule. It does not require changing eating habits, calculating the caloric value of the meals consumed, or excluding particular foods from the diet. There are different types of intermittent fasting. One model of the diet is the alternate day fasting (ADF) diet, which consists of a 24-hour period of complete fasting alternated with a 24-hour period of normal food consumption, repeated 2 to 3 times a week. Another version of this diet is mADF, or modified alternate day fasting, allowing the consumption of a meal on the fasting day. The amount of calories taken in on this day should not exceed 25% of the daily requirement. Another type of intermittent fasting is time - restricted feeding (TRF), consisting of daily extended night fasting. Eating is done only during a few hours per day. The most common version is eating for 8 hours and fasting for 16 hours. Fasting time can be extended or shortened [2]. The purpose of this work is to clarify the effects of intermittent fasting on weight loss and blood glucose regulation.

Methods

This systematic review was based on scientific papers searched on the PubMed platform and in the medical literature in March and April 2024. The search terms included "intermittent fasting," "time-restricted-feeding," "obesity," "diabetes mellitus" and "diabetes type 2." The focus was on results from 2017-2024. Some papers were rejected due to paid access. In addition, some articles were rejected because they were not related

to the topic of the paper. Articles written in English were used. A total of 34 articles were relied on.

Discussion

The main factor regulating human metabolism is the innate diurnal rhythm. It ensures that a balance is maintained between catabolic and anabolic reactions taking place in the body. To better understand the effects of intermittent fasting on the human organism, it is worth starting with metabolic processes involving glucose and lipids. For most tissues, the main source of energy is glucose, which is used immediately after a meal, and the excess is converted into glycogen. Fat is stored in the body in the form of triglycerides in adipose tissue. During periods of starvation or increased energy demands, triglycerides from adipose tissue are converted to glycerol and fatty acids, which are then oxidized to ketone bodies in the liver. These become an alternative energy substrate for tissues in a starvation situation, replacing glucose [9]. There are various hypotheses explaining the effect of intermittent fasting on human body processes.

Circadian rhythm theory

The theory of diurnal rhythm is based on the assumption that physiological processes should occur at evolutionarily determined times. The diurnal rhythm controls sleep and wake cycles, blood pressure, body temperature and the production and secretion of hormones. Disruption of diurnal rhythm regulation increases the risk of chronic diseases, including diabetes and obesity [10]. Studies conducted on shift workers show that irregular diurnal rhythm results in an increase in insulin and glucose levels, as well as a decrease in leptin, a hormone involved in regulating the sensation of hunger and satiety [11]. Time - restricted feeding, which reduces the time of eating to less than 10 hours per day, has a significant effect on the regulation of diurnal rhythm. Restricting the eating period to the time of day has been shown to have a beneficial effect on maintaining normal body weight. In contrast, nighttime eating may result in weight gain and increased susceptibility to metabolic disorders [12]. Nighttime eating contributes to an increased risk of insulin resistance and obesity, also as a result of impaired quality and quantity of sleep. An increase in insulin resistance occurs after just 3 days of diurnal rhythm disturbances. The impact of diurnal rhythm on metabolic processes in the body has been proven in studies. Individuals practicing time restricted - feeding at daylight hours achieved lower body weight and body fat, better blood glucose control and more favorable lipid levels. In contrast, deterioration in glucose and lipid control was observed in patients whose eating hours were shifted to later times and who consumed meals after 4 pm [10]. In an ongoing study in adult men with pre-diabetes who used time restricted - feeding for a period of 5 weeks and ate 6 hours a day, until 3:00 pm, there was an increase in insulin sensitivity and pancreatic ß-cell reactivity, regardless of the caloric value of the meals consumed [13]. Improvements in glycemic control occurred after just 4 days of restricting eating to 6 hours a day [14]. In contrast, studies do not demonstrate the validity of shortening the eating window to less than 6 hours per day, as this does not correlate with an adequate metabolic response. Obese individuals following a time-restricted-feeding regimen of 4 or

6 hours of eating for 8 weeks achieved similar weight reduction and improved insulin sensitivity [15].

Ketogenic state

Intermittent fasting also affects the human body through the induction of the ketogenic state. The theory of energy metabolism during periods of eating and fasting, known as the "glucosefatty acid cycle," was established as early as 1963. It assumes that glucose and fatty acids are competing substrates in the oxidation process [16]. The change from using glucose to using ketones derived from fatty acids for energy production is called metabolic switching. It usually occurs between 12 and 36 hours after finishing eating, depending on the liver's glycogen content and the fasting person's energy expenditure. Depletion of glycogen stores in hepatocytes induces lipolysis of adipose tissue and the production of fatty acids and glycerol. Free fatty acids in liver cells undergo β-oxidation with the formation of ketones: β-hydroxybutyric acid and acetoacetate. In cells with high metabolic activity, ketones are then converted to acetyl-coenzyme A, which is involved in the tricarboxylic acid cycle, leading to energy production [17]. Increased fat metabolism contributes to weight loss. In addition, ketone metabolism requires more energy, which also promotes weight loss [10]. Intermittent fasting generates especially a loss of visceral fat and trunk fat, due to the small caloric deficit. It affects the concentration and sensitivity to leptin and adiponectin, the hormones secreted by adipose tissue, and improves appetite control [18]. Using free fatty acids and ketones, derived from lipolysis, as an energy source, promotes favorable changes in body composition not only by losing body fat, but also by influencing the maintenance of muscle mass. In a study conducted on physically inactive overweight and obese adults, a group using time-restricted feeding and simultaneously performing resistance training achieved greater fat loss and greater lean mass than a control group with a standard diet [19]. The preservation of lean body mass during weight reduction is greater with intermittent fasting than with a diet that restricts caloric intake on a consistent basis [20].

Gut microbiota

The gut microbiota plays an important role in the development of metabolic diseases such as obesity and diabetes. Changes in the composition of the gut microbiota can both prevent and promote obesity by increasing energy absorption, increasing appetite and stimulating fat storage. Dysbiosis of the gut microbiota also results in the development of chronic inflammation and disruption of the diurnal rhythm. Intermittent fasting may promote weight loss by modulating the composition of the microflora present in the gut [21]. In a study of the effects of intermittent fasting on gut microflora, 72 normal-weight to obese subjects participated. They followed intermittent fasting for three weeks, fasting two days a week. On fasting days, they consumed a maximum of 25% of their daily caloric needs. After this time, participants' body weight decreased by an average of 3.67 kg. To assess the effect of the diet on microflora composition, patients were required to give a fecal sample before starting intermittent fasting and after the 3-week study. It was shown that the dietary intervention induced an increase in the relative abundance of bacterial species that are considered beneficial. There was an increase in Parabacteroides

distasonis and Bacteroides tetaiotaomikron, which can promote weight loss and improve metabolism [22].

Effects of intermittent fasting on obesity in clinical trials

The benefits of intermittent fasting in the treatment of obesity have been demonstrated in numerous studies conducted with humans. The research interventions involved various dietary regimens. In 2018, a study was published on the effects of intermittent fasting and continuous calorie restriction on body weight in overweight and obese individuals. Study participants were divided into three groups. The group practicing intermittent fasting fasted two days a week, and consumed 25% of their daily caloric needs on fasting days. The group practicing continuous calorie restriction maintained a daily deficit of 20% of caloric requirements. The control group consisted of patients with no dietary changes. After a period of 50 weeks, slightly greater weight loss was obtained in the intermittent fasting group than in the continuous calorie restriction group [23].
The effects of intermittent fasting and continuous calorie restriction on body weight were also compared in a study by Marguerite Conley involving 24 obese men. The continuous calorie restriction group consumed 500 kcal less than their requirements each day. The intermittent fasting group fasted two days a week and consumed 600 kcal on fasting days. After 6 months, however, there was no significant difference in weight loss between the groups. Those in the group restricting caloric intake each day lost an average of 5.5 ± 4.3 kg, while those in the intermittent fasting group lost an average of 5.3 ± 3.0 kg [24].
A study of the effect of fasting in a time-restricted-feeding regimen on body weight in obese subjects was published in 2022. Patients following the time-restricted-feeding regimen limited their food intake to 8 hours a day, between 7 a.m. and 3 p.m. The control group consisted of those taking in food for at least 12 hours a day, but limiting their daily energy intake to 500 kcal below requirements. Both groups experienced significant weight loss, averaging 6.3 kg for time-restricted-feeding subjects and 4 kg for those in the control group [25].
A study of 72 adults ranging in weight from normal weight to obesity also showed improvements in parameters. Intermittent fasting was implemented in a regimen of twice-daily fasting per week, with a maximum intake of 25% of caloric requirements on fasting days. The duration of the diet was 3 weeks. After this period, normal-weight study participants showed an average weight loss of 2.82 kg, overweight subjects lost 3.84 kg, while obese subjects lost
4.82 kg [22].

Effects of intermittent fasting on type 2 diabetes in clinical trials

Treatment of obesity and weight loss can delay the progression of the pre-diabetic state to type 2 diabetes and have a beneficial effect on the treatment of type 2 diabetes. Even modest weight loss improves glycemic control and insulin sensitivity. Intermittent fasting contributes to a decrease in insulin levels and an increase in insulin sensitivity by maintaining lower glycemic levels [26]. The diurnal rhythm makes glucose tolerance and insulin sensitivity highest in the morning. Diurnal changes in glucose tolerance are related

to the diurnal rhythm of pancreatic β-cells, insulin secretion and clearance. Pancreatic β-cell reactivity is higher in the morning, but maximum insulin secretion occurs in the afternoon. At night, insulin secretion is lowest. Creatinine clearance, on the other hand, is lowest in the morning and increases into the evening [27]. In a study of adults with a BMI between 25.0 kg/m² and 35.0 kg/m², lower mean 24-hour glucose levels were obtained in the time-restricted-feeding schedule group from 8:00 am to 2:00 pm than in the control group. In the control group, which consisted of those eating for 12 hours a day from 8:00 a.m. to 8:00 p.m., glucose levels remained elevated for almost half of the sleep episode. Time-restricted-feeding subjects also showed a reduction in fasting glucose and insulin in the morning, an increase in fasting insulin in the evening and a reduction in diurnal glycemic fluctuations [14].

In a 2018 study, diabetic subjects followed 24-hour fasting two days a week for 12 weeks. After this time, the subjects experienced a 1.1 mmol/L reduction in fasting glucose and a 0.7% reduction in hemoglobin A1c [28].

A case study of a 57-year-old normal-weight woman with type 2 diabetes for 15 years was also published in 2020. During treatment with metformin and a diabetic diet, the patient's HbA1c level was 9.3%. A ketogenic diet and intermittent fasting were introduced in the subject. Four weeks after the dietary changes, medications were discontinued, including metformin, a statin and an antihypertensive drug. During the first four months of the diet, the HbA1c value dropped from 9.3% to 6.4%, despite the discontinuation of medications [29]. In 2018, a study was published comparing the effects of intermittent fasting and continuous energy restricted diets on glycemic control in patients with type 2 diabetes. Study participants were divided into two groups, one of which consumed 1,200 to 1,500 kcal each day, while the other fasted twice a week, consuming only 500 to 600 kcal on those days. After 12 months, a reduction in mean hemoglobin A1c levels was obtained in both groups, with no significant differences between them. In the continuous energy restriction group, the average decrease in hemoglobin concentration was 0.5%, and in the intermittent energy restriction group it was 0.3% [30].

The effect of intermittent fasting on glycemic control in the time-restricted-feeding regimen was compared with continuous calorie restriction in a study published in 2023. Patients with a mean BMI of 39 kg/m² and a hemoglobin A1c of 8.1% were divided into three groups. One of them consumed meals in a time-restricted-feeding pattern. The other group did not restrict the time of eating, but reduced their daily caloric intake by 25%. The control group consisted of weight-maintaining subjects with their current diet and physical activity [31]. After 6 months of the study, better glycemic control results were obtained, with no significant differences between time restricted-feeding and continuous calorie restriction. There was a 0.91% reduction in mean hemoglobin A1c in the intermittent fasting group, and a 0.94% reduction in the continuous calorie restriction practice group.

Safety of intermittent fasting

No serious side effects of intermittent fasting were detected during clinical trials. In a study comparing the 4-hour and 6-hour time-restricted-feeding intervention, participants reported complaints such as nausea, dizziness, headache and diarrhea. However, the symptoms resolved before 3 weeks of the diet as patients became accustomed to the new diet and did not return later in the study [15]. Participants in a study evaluating the safety of 8-hour time-restricted-feeding also reported no negative psychological effects. No

overeating or use of laxatives was observed. Instead, patients reported improved perception of their body image [32]. Intermittent fasting increases the risk of hypoglycemic episodes, mainly in people with type 2 diabetes, requiring a reduction in the dose of diabetes medications during the diet and constant monitoring by a physician [33]. The most common symptoms reported by participants in studies of intermittent fasting are dizziness, weakness, difficulty concentrating, headache, feeling cold, sleep disturbances, and nausea and constipation [33] .

Conclusion

Modern medicine is grappling on a daily basis with the effects of the continued rise in obesity and type 2 diabetes worldwide. Dietary interventions are an extremely important tool in the fight against these diseases. Clinical studies to date have proven that intermittent fasting has numerous metabolic benefits. It affects the human body by regulating the diurnal rhythm, switching from the use of glucose as an energy source to the oxidation of fatty acids and modeling the composition of the gut microbiota. Intermittent fasting promotes weight loss and improves glycemic control, lowers hemoglobin A1c and insulin concentrations and results in increased insulin sensitivity. This diet may be particularly helpful for obese individuals who have repeatedly undergone attempts at continuous calorie restriction, but have failed to maintain an adequate deficit over a prolonged period of time. However, there is no evidence of an advantage of using intermittent fasting over continuous calorie restriction. It has also not been established which intermittent fasting regimen is the most effective. No serious adverse effects of this dietary strategy have been reported in studies to date. The most common complaints reported by patients include dizziness, weakness, difficulty concentrating, headache, feeling cold, sleep disturbances, nausea and constipation. However, intermittent fasting may promote hypoglycemic episodes, especially in people with type 2 diabetes taking antidiabetic medication. Intermittent fasting appears to be a promising strategy in the fight against obesity and type 2 diabetes, but requires further research to assess its long-term effects on the human body.

Disclosures

Authors do not report any disclosures.

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