Intermittent fasting: a dietary intervention for prevention of diabetes and cardiovascular disease?

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Abbreviations and Acronyms

IFG – Impaired fasting glucose
IGT – Impaired glucose tolerance
IL-6 – Interleukin-6
LDL-C – Low density lipoprotein cholesterol
TAG - Triacylglyceride
TDEE – Total daily energy expenditure
TNF-α – Tumour necrosis factor alpha

Abstract

Intermittent fasting, in which individuals fast on consecutive or alternate days, has been reported to facilitate weight loss and improve cardiovascular risk. This review evaluates the various approaches to intermittent fasting examines the advantages and limitations for use of this approach in the treatment of obesity and type 2 diabetes.

Key words diet, fasting, intermittent fasting, obesity, type 2 diabetes, weight loss

Introduction

The increasing prevalence of obesity and type 2 diabetes in recent decades has been associated with increased comorbidities including atherosclerotic macrovascular disease and premature mortality (1-3). Individuals with sub-diabetic degrees of hyperglycaemia, such as IGT and IFG are also at increased risk of premature cardiovascular disease, emphasising the importance of interventions to improve glucose homeostasis in pre-diabetic, as well as diabetic individuals (4 -5).

Several large studies have identified pre-diabetic individuals as subjects in whom to investigate lifestyle changes to prevent the progression to a fulminant diabetic state (6-10). However, there is considerable debate regarding the most effective manner in which lifestyle changes such as diet and/or exercise should be implemented (11). The approach of intermittent fasting is currently generating particular interest.

Intermittent Fasting

Extensive evidence suggests that imposing fasting periods upon experimental laboratory animals increases longevity, improves health and reduces disease, including such diverse morbidities as cancer (12, 13), neurological disorders (14-17) and disorders of circadian rhythm (18, 19). The specific benefit of intermittent fasting as a health giving therapeutic approach has been recognised since the 1940's (20).

Intermittent fasting can be undertaken in several ways but the basic format alternates days of 'normal' calorie consumption with days when calorie consumption is severely restricted. This can either be done on an alternating day basis, or more recently a 5:2 strategy has been developed (Figure 1), where 2 days each week are classed as 'fasting days' (with <600 calories consumed for men, <500 for women). Importantly, this type of intermittent fasting has been shown to be similarly effective or more effective than continuous modest calorie restriction with regard to weight loss, improved insulin sensitivity and other health biomarkers (1, 21).

Fasting has been used in religion for centuries. For example, the Daniel fast is a biblical partial fast that is typically undertaken for 3 weeks, and during Ramadan, the ninth month of the Muslim calendar, there is a month of fasting during daylight hours, during which some observers also refrain from fluid consumption (22). Such periods of fasting can limit inflammation (23), improve circulating glucose and lipid levels (24-27) and reduce blood pressure (28), even when total calorie intake per day does not change, or is only slightly reduced. Ethical and logistical constraints have restricted most caloric deprivation studies to 6 months, although some have assessed the effects for longer (29-31). The majority of studies show positive effects on markers of metabolic health and body composition, in part due to the demonstrated effects intermittent fasting has on metabolic tissues (Figure 2). In addition caloric restriction studies undertaken in animals and humans have suggested that fuel selection is altered and efficiency of metabolism is improved (32, 33) while oxidative stress is reduced (34). It is possible that short periods of fasting mobilise ectopic TAG in non-adipose depots, reducing the detrimental effects of intra-myocellular and intra-hepatic TAG deposition (19, 35) and redistributing TAG into adipose tissue.

Intermittent Fasting and Obesity

Obesity comprises multiple genetic, metabolic and behavioural abnormalities that complicate treatment. Most pharmaceutical therapies that promote weight loss have been discontinued, and at the time of writing the only licensed anti-obesity drug on the UK market is orlistat (1). Increasing numbers of obese individuals are undergoing bariatric surgery, but this remains a restricted minority treatment (36). The mainstay of treatment for obesity therefore remains lifestyle intervention based around dietary changes (37-40) which generally form the first step in any weight loss programme.

Intermittent fasting is known to be useful in the treatment of intractable obesity (41), and morbidly obese individuals (42). Original treatment regimens were based upon intermittent starving as opposed to restricting calories (43, 44) a harsh regime that must have challenged adherence. Despite the seemingly strict nature of the fasting days intermittent fasting has a generally good adherence record and can cause significant reductions in body weight in individuals with obesity (45-46), suggesting that this is a clinically relevant therapeutic approach.

Intermittent Fasting and Type 2 Diabetes

Since obesity commonly coexists with type 2 diabetes (1) patients are usually initially assigned lifestyle interventions aimed at reducing body weight (46). Most obese type 2 diabetes patients however will progress onto drug based therapies, some of which can exacerbate their existing obesity (1). Intermittent fasting can reduce the incidence of diabetes in experimental animals (47-49) and there is evidence that this type of fasting may also slow the progression of type 2 diabetes in obese individuals.

Indeed, a recent study confirmed earlier reports of a reversal of type 2 diabetes through daily calorie restriction, with improvement of pancreatic function and a reduction of occult triglyceride deposition (50). The particular diet employed a maximum of 600 calories every day, which may prove too severe for many type 2 diabetes patients, but an intermittent fasting strategy may be more acceptable and still improve metabolic parameters, insulin levels and insulin sensitivity (51, 52) and prevent the development of diabetic complications (53). Indeed, intermittent fasting might achieve much of the benefit seen with bariatric surgery (65), but without the costs, restriction on numbers and risks associated with surgery.

Whether intermittent fasting can be used as a tool to prevent diabetes in those with IGT or IFG, or to prevent progression in those recently diagnosed with type 2 diabetes remains a tantalising notion.

Intermittent Fasting and Cardiovascular Disease

Although with up to 80% of obese type 2 diabetes patients die from cardiovascular complications (54,55) and the benefits of weight loss well recognised (56) it is also known to be more difficult for individuals with type 2 diabetes to lose weight (57,58).

Intermittent represents a potential therapy for those at high cardiovascular risk. Intermittent fasting in animal models can reproduce some of the cardiovascular benefits such as improvements in blood pressure and heart rate that are seen with physical exercise (59). Caloric restriction studies have shown improvements in circulating cholesterol, triglycerides, improved blood pressure, and reduced carotid intima-media thickness (28, 60). Also, improvements in physiological cardiovascular parameters are associated with intermittent fasting and survival from l myocardial ischaemia (61) through pro-angiogenic, anti-apoptotic and anti-remodelling effects.

Intermittent fasting also appears to be cardioprotective, providing experimental animals with resistance to ischaemic injury (62), in a manner possibly associated with increases in levels of the adipokine adiponectin (63). Adiponectin is a unique adipokine that appears to have beneficial effects but has circulating levels that are negatively correlated with body composition (64, 65). However, intermittent fasting modulates the levels of visceral fat and several additional adipokines, including leptin, IL-6, TNF-α and IGF-1 (66). These changes are responsible for a reduction in LDL-C and total cholesterol, consistent with a potentially beneficial effect on cardiovascular risk. Although most fasting is generally regarded to reduce cardiovascular risk, over-zealous fasting for protracted periods is not without risks of reducing myocardial mass alongside reductions in other components of reduced lean body mass.

Conclusion

The use of intermittent fasting offers the potential to improve weight loss and enhance the cardiovascular health of overweight and obese individuals with type 2 diabetes and reduces cardiovascular risk. This type of intervention is cost-effective and associated with a low risk of adverse events.

Key messages

- Intermittent fasting promotes weight loss in obese individuals
- Limiting calories in this way can reverse diabetes
- Intermittent fasting is potentially cardioprotective

Figure Legends

Figure 1. Diagrammatic representation of a typical intermittent fasting plan. Subjects who undertake this form of diet are required to limit their calorie intake for two days, consecutively or otherwise each week. The calorie limit for fasting days is approximately 25% of TDEE or 600 calories for men and 500 for women. On non-fasting days subjects can eat normally to their TDEE calorie level (approximately 2500 for men and 2000 for women).

Figure 2. Tissue-specific effects of intermittent fasting and calorie restriction. Research has identified several biological effects of intermittent fasting and/or calorie restriction on tissues that are central to metabolic and cardiovascular health. Key: NO = nitric oxide, TAG = triacylglycerides.

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