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The Effect of Intermittent Fasting on Insulin Resistance and Lipid Metabolism

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Abstract. Dietary intervention with intermittent fasting can be a non-pharmacological management option in conditions of insulin resistance, dyslipidemia, and obesity. Intermittent fasting is an example of calorie restriction (not eating and drinking that contains calories) at predetermined times. This intermittent fasting protocol can be divided into time-restricted eating (TRE), alternative day fasting (ADF), or religious fasting. Intermittent fasting increases AMP activated protein kinase (AMPK) and triggers autophagy which has a favorable effect on glucose metabolism, namely lowering blood glucose, plasma insulin levels and homeostasis model assessment of insulin resistance (HOMA-IR). In addition, this fasting can reduce apolipoprotein B, increase apolipoprotein A, and reduce the hormone leptin which affects the decrease of LDL, increase of HDL and weight loss. Additional benefits of intermittent fasting are anti-aging, anti-inflammatory, and anticancer.

Keywords: intermittent fasting, insulin resistance, lipid metabolism, AMPK, autophagy, leptin.

INTRODUCTION

Insulin resistance is an important pathogenic mechanism of type 2 diabetes.[1] Insulin resistance often co-occurs with dyslipidemic conditions, especially in obese patients. Effective dietary intervention is a preventive measure that can accelerate weight loss, improve glucose and lipid metabolism, decrease insulin resistance, and prevent the occurrence and progression of diabetes, stroke and cardiovascular disease.[2]

The practice of this fasting has been common in ancient and modern societies for religious, spiritual and cultural reasons.[3] Intermittent fasting is one example of caloric restriction that is currently widely used, due to its low cost and proven potential to prevent diseases such as diabetes, cardiovascular disease, neurodegenerative diseases, and even cancer.[4] This article discusses the benefits of implementing intermittent fasting in improving insulin sensitivity and lipid metabolism.

Insulin Resistance

Insulin is a peptide hormone released by pancreatic beta cells in response to elevated plasma glucose and amino acid levels, thereby normalizing them back to physiological blood sugar levels.[5,6]

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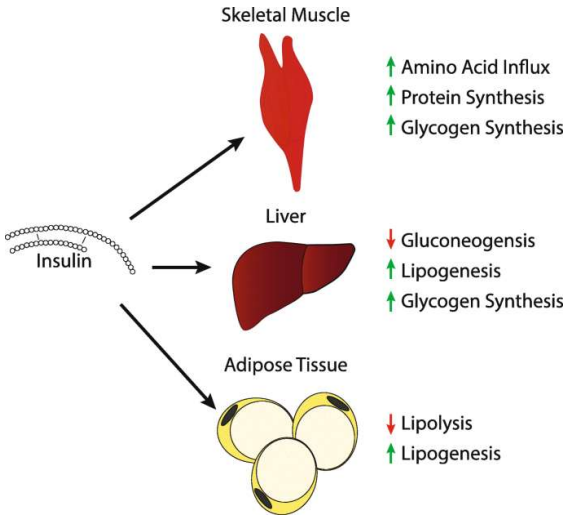

Figure 1. The Effects of Insulin on tissues[7]

Insulin resistance is a complex pathological state of inappropriate cellular responses to the hormone insulin. It is found in many metabolic disorders, such as obesity, dyslipidemia, metabolic syndrome, hypertension and atherosclerosis, non-alcoholic fatty liver disease (NAFLD), type 2 diabetes mellitus (DM), and some cases of type 1 DM.[8]

It inversely correlates with insulin sensitivity in insulin-dependent tissues and disables their ability to store and utilize glucose. This condition contains insulin-dependent cells, such as skeletal muscle and adipocytes fail to respond to normal circulating insulin levels.[8] Insulin has an important role in the entry of glucose into cells, so any disruption in insulin signal transduction is associated with hyperglycemia due to the inability of cells to take up and store glucose.[9]

Insulin signal transduction is complex involving many enzymes and modulatory proteins. Any defect in the expression/function of these agents can disrupt normal insulin signaling leading to insulin resistance in peripheral tissues. Insulin resistance in hepatocytes increases plasma glucose levels due to decreased glycogen synthesis. This effect is compounded by the inability of skeletal muscle and adipocytes to take up glucose. The exact pathophysiology of insulin resistance remains unclear, but defects in insulin signal transduction and activation of protein kinase C ε (PKCε) play an important role in the occurrence of insulin resistance.[8,9,10]

Lipid Metabolism

Lipids in the body consist of (1) neutral fats, also known as triglycerides; (2) phospholipids; (3) cholesterol; and (4) several other lipids. Triglycerides are used in the body

primarily to provide energy for various metabolic processes, a function similar to that of carbohydrates. However, some lipids, especially cholesterol, phospholipids and a small amount of triglycerides, are used to form cell membranes and to perform other cell functions.[11]

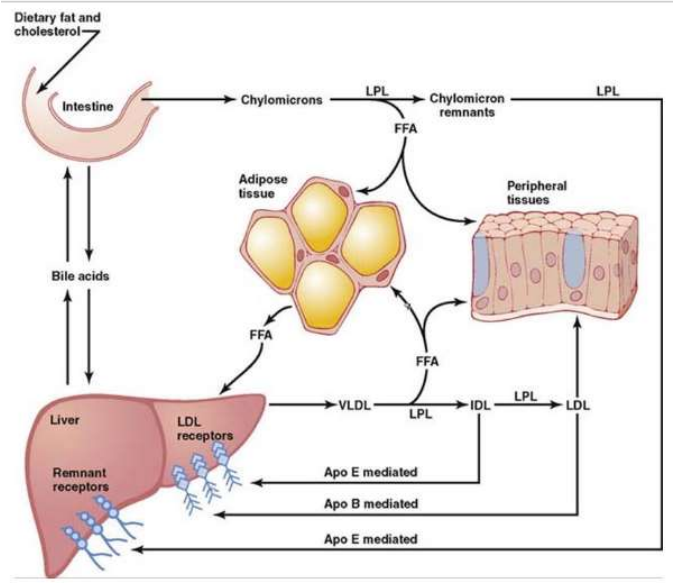

Figure 2. Lipid Metabolism[5]

Lipoprotein lipase converts very low-density lipoprotein (VLDL) into intermediate-density lipoprotein (IDL). This product, which has a relatively low triacylglycerol content, is absorbed by the liver through endocytosis and broken down by lysosomes. Intermediate-density lipoprotein can be converted into low-density lipoprotein (LDL).5 High-density lipoprotein (HDL) has an important role in the reverse transportation of cholesterol acting as a carrier of cholesterol back to the liver. HDL effectively functions in the homeostasis/balance of lipid metabolism. [12]

Dyslipidemia is defined as an abnormality of lipid metabolism characterized by increased or decreased levels of lipid fractions in plasma. The main lipid fraction abnormalities are increased levels of total cholesterol, LDL cholesterol and/or triglycerides, and decreased HDL cholesterol. Of the total serum cholesterol, LDL contributes 60-70% and has an apolipoprotein called apo B-100 (apo B). LDL cholesterol is the main atherogenic lipoprotein, and is the main target for management, contributing to 20-30% of total serum cholesterol, the main apolipoproteins are apo A-1 and apo A-II.13 While HDL is a lipoprotein that is anti-atherogenic. HDL plays a role in preventing the process of atherosclerosis not only through the reverse pathway of cholesterol transportation but also through anti-inflammatory and antioxidant effects in the blood vessel wall. [12]

Intermittent fasting

Intermittent fasting is an example of calorie restriction (not eating and drinking that contains calories) at predetermined times. Intermittent fasting protocols can be divided into intermittent fasting that promotes time-restricted eating (TRE) or alternative day fasting (ADF) with or without calorie restriction.[14] The practice of TRE is gaining popularity, with recent evidence supporting its use for patients with diabetes and weight management.[3]

TRE regimens have been shown to be well tolerated and lead to an average reduction in caloric intake of about 20%. Time-restricted eating involves short continuous periods of fasting, where food consumption is usually within an 8- to 10-hour window, such as a 16-hour fasting and 8-hour eating window (16:8) and the longer the eating window, the less it will be.[3,14] However, diabetic patients or first-timers can start with the 12:12 regimen, which is based on the fact that when the body is deprived of calories for 12 hours, it begins to break down triglycerides into fatty acids and glycerol.[15]

Another pattern is alternate day fasting (ADF), where on fasting days no food is consumed, which can be replaced by drinking water or juice, but on non-fasting days one can consume food as desired. However, ADF is not well tolerated and has recently been replaced with a modified ADF protocol (mADF) to allow individuals to be provided with up to 40% of the recommended daily calorie intake on fasting days.[3,14]

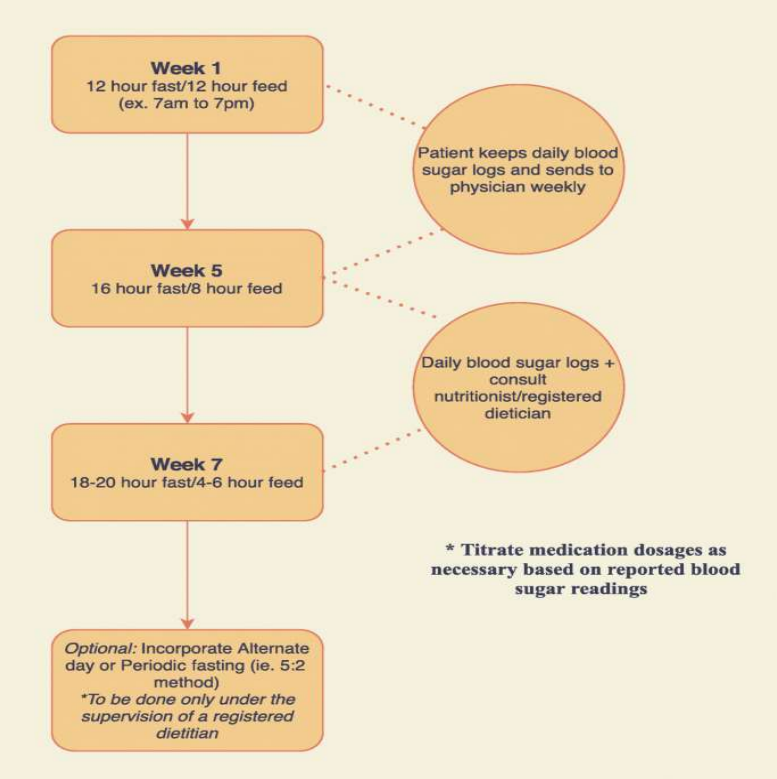

Figure 3. An example of an intermittent fasting regimen in patients with DM2[7]

Another implementation is religious intermittent fasting.[14] Indonesia, which is a Muslim-majority country, intermittent fasting can take the form of Monday- Thursday fasting. Or even in a certain month, namely the month of Ramadan, intermittent fasting with fasting patterns reaching 14 hours for 1 full month. In other religions, there are also other religious fasts, such as Upawasa, Musa, Uposatha, etc.

The Effect of Intermittent Fasting on Insulin Resistance

The implementation of intermittent fasting is believed to provide good results because it has been shown to reduce HbA1C levels in patients with T2DM. Halberg et al. showed that healthy men on an ADF diet experienced improved insulin sensitivity as assessed by a significant increase in glucose infusion rate, increased adiponectin, and inhibited insulin-mediated lipolysis.[16]

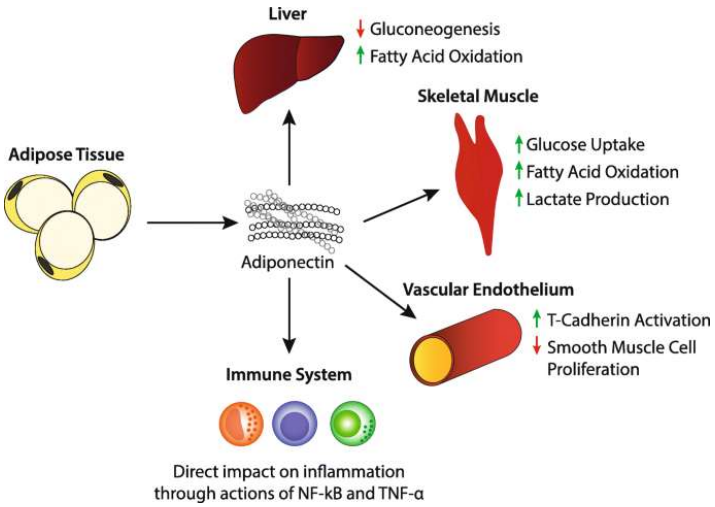

Figure 4. The Effect of adiponectin[7]

A case study with intermittent fasting 16 hours per day showed that HbA1c could drop to 5.8 % after they underwent 14 months of intermittent fasting program.[17] A systematic review and meta-analysis showed that intermittent fasting dietary intervention in terms of glucose metabolism reduced blood glucose, plasma insulin levels and homeostasis model assessment of insulin resistance (HOMA-IR).[18,19] The term "metabolic switch" was used by Anton et.al. to refer to the body's preference for using fatty acid-derived ketones and fatty acids over glucose during intermittent fasting.[20]

Intermittent fasting can reduce adiposity and insulin resistance through reduced caloric intake as well as metabolic reprogramming. In addition, energy/nutrient depletion (as achieved through reduced caloric intake) has been shown to improve healthier aging and chronic disease reduction through increased activation of AMP activated protein kinase (AMPK). AMPK

increases the AMP/ADP: ATP ratio which influences the endocrine signaling of hunger and satiety.[9]

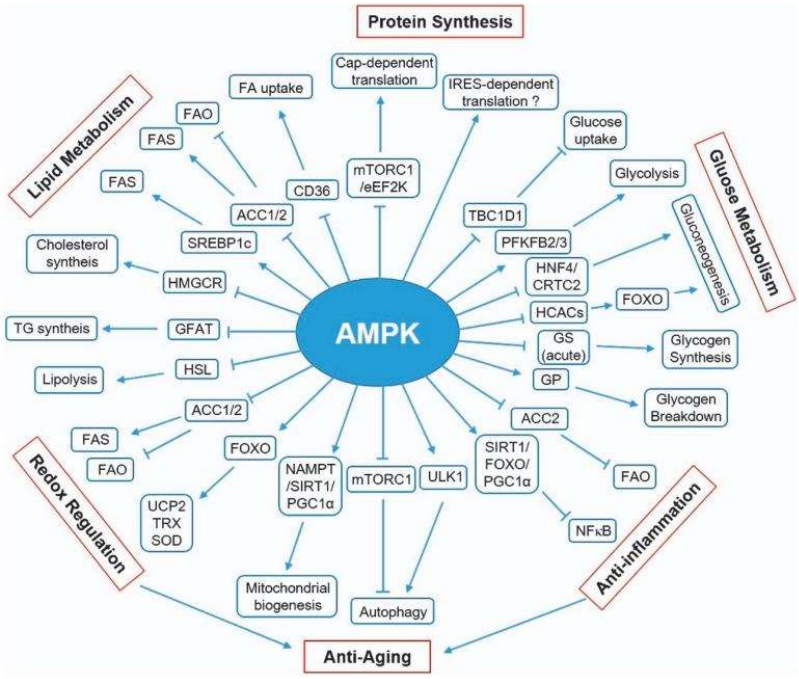

Figure 8. The Benefits of AMPK[28]

Increased insulin levels, either through increased energy intake or insulin resistance can lead to activation of downstream mediators that ultimately inhibit AMPK. The role of AMPK in improving insulin sensitivity is most evident through the positive effects of the biguanide namely metformin. Metformin is known to promote AMPK activation and has been shown to be highly effective in the treatment of DM2. In theory, a decrease in energy intake, such as that achieved through intermittent fasting, would lead to a prolonged decrease in insulin production levels and an increase in AMPK levels, which play a role in the improvement of insulin sensitivity and glucose homeostasis. [21,22,23]

Another benefit of fasting is that it induces autophagy. Autophagy is currently the talk of the world because of its benefits in repairing the body itself. Autophagy itself was discovered in 2016 by Yoshinori Ohsumi who won the Nobel Prize for the discovery.

Yamamoto et al. reported that in mice induced with a high-fat diet, there was Becn1-mediated hyperactivation of autophagy that improved insulin sensitivity by reducing endothelial reticulum stress and also reduced insulin secretion and storage through degradation of insulin granules in β-cells.[24]

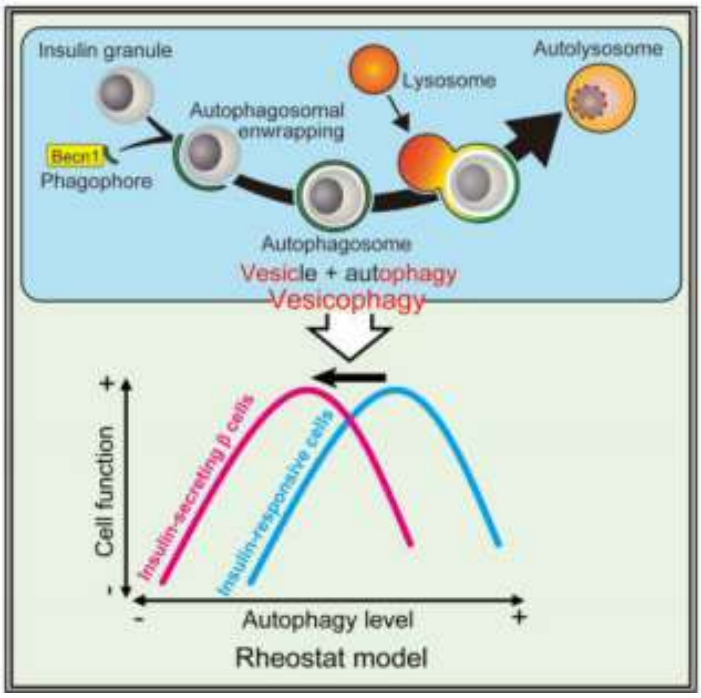

Figure 9. The Role of autophagy in insulin sensitivity[24]

The Effect of Intermittent Fasting on Lipid Metabolism

Glucose and fatty acids are the main sources of energy for cells. Glucose is used for energy after meals, and fat is stored in adipose tissue as triglycerides. During periods of fasting, triglycerides are broken down into fatty acids and glycerol. Then, they are used for energy. The liver converts fatty acids into ketone bodies that provide a major source of energy for many tissues, especially the brain during fasting. Blood levels of ketone bodies are low when a person eats and increase within 8-12 hours after fasting to reach levels of 2-5 mM within 24 hours.[15]

Intermittent fasting can cause our bodies to experience changes in lipid metabolism. Intermittent fasting decreases apo B, while serum apo AI increases compared to before fasting so that it will increase HDL and decrease LDL.[19,25,26] Changes in lipid metabolism have a good impact with a decrease in body weight (BW) and fat mass of about 8%. The resulting decrease in fat mass was also accompanied by a decrease in triglyceride levels. [27]

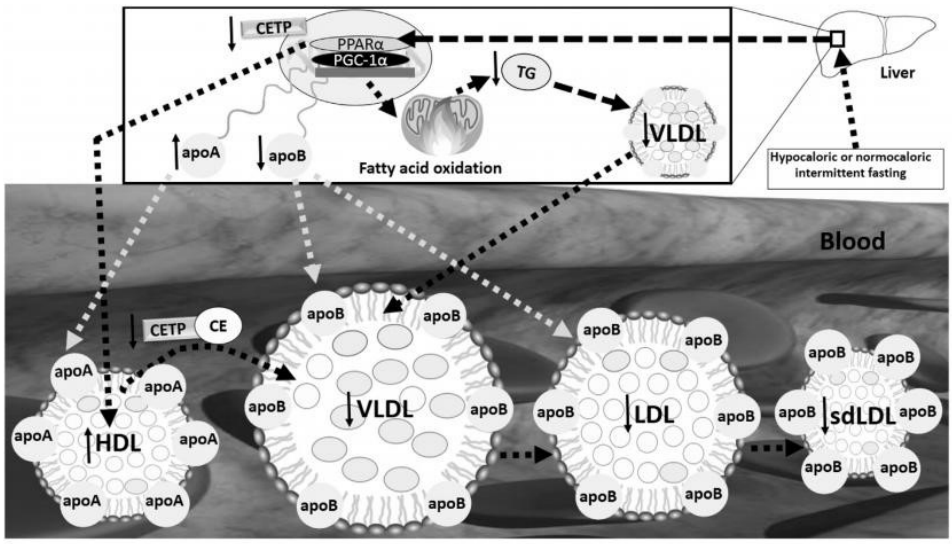

Figure 10. The Role of Intermittent Fasting on Lipid metabolism[27]

Adipocytes can secrete the hormone leptin which can affect a person's diet. Leptin levels can increase in those who are obese (leptin resistance), besides that leptin levels are also correlated with increased levels of total cholesterol, triglycerides, blood pressure (BP), and inflammatory effects on blood vessels. Intermittent fasting diets have been shown to suppress leptin concentrations and reset the leptin receptor in the hypothalamus which in turn also plays a role in lowering cholesterol levels and reducing the risk of metabolic diseases.[7]

CONCLUSION

Dietary interventions play an important role in the non-pharmacological management of DM2 or dyslipidemia conditions. Diet with intermittent fasting which is an easy, cheap, and safe fasting pattern is the consideration for this fasting. Intermittent fasting has been proven to increase insulin sensitivity, improve lipid metabolism, and at the same time obtain other benefits such as anti-aging, anti-cancer, and anti-inflammatory.

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