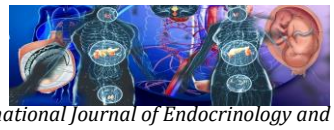

International Journal of Endocrinology and Disorders

www.alcrut.com

Review Article **International Journal of Endocrinology and Disorders** **Open Access**

Intermittent Fasting & Medications for Managing Insulin resistance among T2D Cases

Dr. Suresh Kishanrao
Public Health Consultant, Bengaluru, Karnataka, India.
***Corresponding Author**: Dr. Suresh Kishanrao Public Health Consultant, Bengaluru, Karnataka, India.
Received Date: January 16, 2023 ; **Accepted Date**: March 4, 2023 ; **Published Date**: March 10, 2023
Citation: Dr. Suresh Kishanrao, Intermittent Fasting & Medications for Managing Insulin resistance among T2D Cases, International Journal of Endocrinology and Disorders, 2(1).

Abstract
Diabetes mellitus (DM) is the most common endocrine disorder in humans, currently affecting over 170 million people world-wide with a potentially of affecting over 365 million by the year 2030. Clinically, the term "insulin resistance" implies that higher-than-normal concentrations of insulin are required to maintain normoglycemia. On a cellular level, it defines inadequate strength of insulin signalling from the insulin receptor downstream to the final substrates of insulin action involved in multiple metabolic and mitogenic aspects of cellular function. Insulin resistance is thought to precede the development of T2DM by 10 to 15 years. Insulin resistance is a complex condition in which our body does not respond as it should to insulin, essential for regulating blood sugar levels, resulting in continued hyperglycaemia, which causes symptoms, like Increased thirst, Frequent urination, Increased hunger, Blurred vision, Headaches, Vaginal and skin infections, Slow-healing cuts, and sores. If not identified early and treated, many complications like Several genetic and lifestyle factors can contribute to insulin resistance.
In this review, based on personal case, I have summarized current developments contributing to our understanding of insulin resistance, and to the pathogenesis of type 2 diabetes. Among the many molecules involved in the intracellular processing of the signal provided by insulin, malfunctioning of IRS-2, PKB, the Foxo protein and p85 regulatory subunit of PI-3 kinase results in insulin resistance. Addition contributing factors include, old age, excess body fat, especially around belly, a highly processed diet, high-carbohydrate and saturated fats foods, physical inactivity, and some Medicines.
The management approaches of insulin resistance include i) dietary management including Intermittent fasting, maintaining physical activity, keeping weight and stress under control, monitoring blood glucose levels, serum LDL Cholesterol and Blood Pressure, if required, insulin use via injections or pump.

Scientists so far, have identified several genes that make a person more or less likely to develop insulin resistance. By elucidating the cellular and molecular mechanisms responsible for insulin resistance, these studies provide potential new targets for the treatment and prevention of type 2 diabetes.
Materials & Methods:

This is a review of available literature and recent developments of Insulin Resistance and its management based on an autobiography, webinar and few studies across the globe.

Keywords: Hyperglycaemia; HbA1C; impaired fasting glucose (IFG); pre-diabetes; diabetes; insulin resistance; genetic biomarkers; pancreatic beta cells; cellular level function

Introduction

Diabetes mellitus (DM) is the most common endocrine disorder in humans, currently affecting over 170 million people world-wide and, potentially, over 365 million by the year 2030. Clinically, the term "insulin resistance" indicates that higher-than-normal concentrations of insulin is required to maintain normoglycemia. It is observed that over time, insulin resistance is worsening, among the pre-diabetics and diabetes type 2 patients. Insulin producing pancreatic beta cells start wearing out and may eventually, stop producing enough insulin to overcome the cells' resistance. The result is higher blood glucose levels.

"Prediabetes" is the term coined to refer to either "impaired fasting glucose (IFG)" or "impaired glucose tolerance (IGT)," both denoting levels of elevated glycemia that don't meet the thresholds for diabetes. It's a heterogeneous group overall, and despite its name, not everyone with prediabetes will progress to develop type 2 diabetes.

If someone has insulin resistance, but his/her pancreas can increase insulin production to keep their blood sugar levels in a normal range, they may not have any symptoms. However, over time, insulin resistance gets worse, and the cells in pancreas that make insulin can wear out. Eventually, the pancreas is no longer able to produce enough insulin to overcome the resistance, leading to elevated hyperglycaemia, which causes symptoms, like Increased thirst, Frequent urination, Increased hunger, Blurred vision, Headaches, Vaginal and skin infections, Slow-healing cuts, and sores.

Several factors and conditions can cause varying degrees of insulin resistance. Scientists so far, have identified several genes that make a person more or less likely to develop insulin resistance. In addition, old age, excess body fat- especially around belly, a highly processed or high-carbohydrate foods and saturated fats, physical inactivity and some Medicines are the main contributing factors to insulin resistance [1].

On a cellular level, it defines inadequate strength of insulin signalling from the insulin receptor downstream to the final substrates of insulin action involved in multiple metabolic and mitogenic aspects of cellular function [2]. Insulin resistance is a complex condition in which our body does not respond as it should to insulin, essential for regulating blood sugar levels. Insulin resistance is thought to precede the development of T2DM by 10 to 15 years.

People with diabetes experience damage to the small blood vessels in various organs, responsible for many complications and it has been known that good control of blood sugar levels reduces the risk of complications. The reasons for this are unclear yet.

Insulin resistance is associated with Obesity, Cardiovascular disease, Non-alcoholic fatty liver disease, Metabolic syndrome, and Polycystic ovary syndrome (PCOS) in addition to T2D.

Physiology- Normal Insulin Signalling:

The insulin receptor (IR) is a heterotetramer consisting of two α subunits and two β subunits that are linked by disulphide bonds. Insulin binds to the α subunit of the insulin receptor and activates the tyrosine kinase in the β subunit. Once the tyrosine kinase of insulin receptor is activated, it promotes autophosphorylation of the β subunit, where phosphorylation of three tyrosine residues (Tyr-1158, Tyr-1162, and Tyr-1163) is required for amplification of the kinase activity. Most of the metabolic and antiapoptotic effects of insulin are mediated by the signalling pathway involving the phosphorylation of the insulin receptor substrate (IRS) proteins, and

the activation of the phosphatidylinositol (PI) 3-kinase, Akt (protein kinase B), the molecular target of rapamycin (mTOR), and p70 S6 kinase. The insulin receptor tyrosine kinase phosphorylates the IRS proteins, and phosphotyrosine residues on IRS proteins become good targets for the p85 regulatory subunit of PI3-kinase. The activated PI3-kinase generates 3′-phosphoinositides [phosphatidyl-inositol-3,4-bisphosphate (PIP2) and phosphatidyl-inositol-3,4,5-trisphosphate (PIP3), which bind to the phosphoinositide dependent kinase 1 (PDK1). Known substrates of the PDKs are the protein kinase B (PKB) and atypical forms of the protein kinase C (PKC) [2].

Under normal circumstances, insulin functions in the following steps: i) Our body breaks down the food you eat into glucose, our body's main source of energy. ii)Glucose enters bloodstream, and signals to pancreas to release insulin. iii) Insulin helps glucose in our blood enter our muscle, fat, and liver cells which they use for energy or store it for later use. iv) When glucose enters cells, the level in our bloodstream decreases and signals to our pancreas to stop producing insulin [1].

The difference between insulin resistance and diabetes:

Everyone develops insulin resistance — temporarily or chronically. Over time, chronic insulin resistance can lead to prediabetes and then Type 2 diabetes if it's not treated.

Prediabetes happens when your blood glucose levels are higher than normal, but not high enough to be diagnosed as diabetes. Prediabetes usually occurs in people who already have some insulin resistance. Prediabetes can lead to Type 2 diabetes, the commonest diabetes.

Type 2 diabetes (T2D): happens when pancreas doesn't make enough insulin or body doesn't use insulin well (insulin resistance), resulting in high blood glucose levels.

Type 1 diabetes (T1D) happens when our body's immune system attacks and destroys the insulin-producing cells in our pancreas for unknown reasons. People with T1D must inject synthetic insulin to live and be healthy. T1D is not caused by insulin resistance, but patients can experience insulin resistance as their cells don't respond well to injected insulin [1].

Gestational diabetes mellitus (GDM) is a temporary form of diabetes that can happen during pregnancy. It's caused by insulin resistance that's due to the hormones the placenta makes. Gestational diabetes goes away once you deliver your baby. In India, GDM is defined as 2-h Oral Glucose Tolerance Test [OGTT] > 140 mg/dL the National Guidelines. The reported prevalence of gestational diabetes in India, vary from 7% to nearly 16%. Healthcare providers prefer using glycated haemoglobin (A1c) to diagnose [6].

Prediabetes at an HbA1c level between 5.7% and 6.4% and type 2 diabetes if an HbA1c level of 6.5% or higher on two separate tests [3].

Case Studies:

1. My case study: I was diagnosed as T2D in 1990 for the first time. I maintained my Blood sugar and Hb1Ac under good control until 2015. My public health consultancy jobs after retirement in 2006, disrupted my diet and exercise particularly since 2015. In my annual check-up of 2018, my endocrinologist was unhappy as Hb1Ac had gone up to 7.4. He added Empagliflozin (Gibtulio- SGLT 2) 10 mg before lunch in addition to Glimepiride (Amaryl) 3 mg 30-45 minutes before lunch & dinner, Metformin 500mg after breakfast, lunch & dinner, Acarbose (Glucobay) 50 mg before breakfast and evening snacks. After moving to Bengaluru in April 2018, I decided to reduce my weight and strengthen my muscles using the Gym in out apartment complex. I started a sort of intermittent fasting-

i) delaying Breakfast till 1030-1100 and eating only Papaya Fruit 10G/Kg body weight,

ii) Lunch around 13330-1400 having only 2 Chapati's or Jowar Roti's, a small cup of rice and lots of vegetables, Dal (Sambar with vegetable/GLV) and Curds (100g each time)

iii) evening (1800-1830) light snacks of dry fruits, seasonal fresh fruits and lightly fired Puffed (Murmura) or flattened rice (Poha) with pea nuts and roasted Bengal grams) and iv) Dinner (2030-2100) only one Chapati or Roti and small cup of rice along with lots of vegetables, Dal (Sambar with vegetable/GLV) and Curds (100g each time).

By late 2018 I started noticing reduction in my weight and by end 2019 I reduced my weight by 5 kg (from 65 to 60). In early 2020 monitoring Fasting Blood sugar and Hb1Ac quarterly I started reducing my oral antidiabetic drugs by 1/3 (stopped Glaucoma 50 mg before main meals and reduced, Amaryl from 3 mg to 2 mg before each meal and Glycomet SR from 3 to 2 only after main meals. (Not after breakfast too as did earlier). In the last 2 years I have reduced my weight further by 2Kgs (60 to 58 Kg) and Hb1Ac remains around 7. However, an ALRI episode in November 2022 disrupted my exercise and diet pattern for nearly 4 weeks and my fasting BS has gone up to 150, pointing to relaxation in disciplined lifestyle disrupts tackling Insulin resistance.

2.*My Patient:* A patient of mine 36 years old male diagnosed with Type 2 diabetes in March 2019. He chose not to take any medications. Influenced by an article of 2017 [10] I advised him to change his diet and lifestyle. For the first 6 weeks I put him on a low carb high fat diet, LCHF. He did not eat more than 20 grams of carbs a day. That lowered his blood sugar to the normal range. Then I adjusted that diet for him, allowing not more than 50 grams of carbs a day and low to moderate fat. NO sugar, NO sugary drinks, NO fruit juices, NO sweet fruits, No refined flour, no potatoes, or potato products. As he had witnessed his father, who had Type 2 diabetes, injecting insulin every day and dying of diabetes complications imagery helped him to be disciplined. Also, I introduced him to a specific mindfulness meditation to reduce stress that raised his blood sugar levels. After 9 months, his blood sugar is perfect was every day. Now he eats a lot of salads with olive oil and vinegar. Fish, chicken, eggs, veggies, nuts. He makes his own sugar free BBQ sauce and salsas. If he wants something sweet, he eats chocolate or green gram Laddu made using jaggery to sweeten on empty stomach. Still no sugar, no sweet fruits like Mango, Chicco etc. but eats apples, all types of berries. He walks every day at least 4km and more on the day he eats a high carb meal like a south Indian festive meal. So far, his blood glucose and HbA1c stays perfect [10].

Discussions:

Pathogenesis: The pathogenesis of type 2 diabetes involves abnormalities in both insulin action and secretion. Recent studies have contributed to a deeper understanding of the underlying molecular mechanisms i.e., Free fatty acids are known to play a key role in promoting loss of insulin sensitivity in type 2 diabetes mellitus, though the underlying mechanism is still unclear. It has been postulated that an increase in the intracellular concentration of fatty acid metabolites activates a serine kinase cascade, which leads to defects in insulin signalling downstream to the insulin receptor. The complex network of adipokines released from adipose tissue also modulates the response of tissues to insulin. Among the many molecules involved in the intracellular processing of the signal provided by insulin, dysfunction of the proteins like the insulin receptor substrate 2, the protein kinase B and the fork head transcription factor Foxo 1a result in insulin resistance in vivo. Recently, studies have revealed that phosphor-inositide-dependent kinase 1-independent phosphorylation of protein kinase Cε causes a reduction in insulin receptor gene expression. Mitochondrial dysfunction triggers activation of several serine kinases and weakens insulin signal transduction [2,3].

Mutations In Irs Proteins

Disruption of the IRS-1 gene in mice results in insulin resistance, mainly of muscle and fat. Interesting results are obtained by studying IRs in knockout mice. Heterozygous knockout mice lacking a single allele of IRS-1 gene lack any significant phenotype, whereas homozygous disruption of the IRS-1 gene results in a mild form of insulin resistance. IRS-1 homozygous null mice (IRS-1-/-) do not show a clear diabetic phenotypic expression, presumably because of pancreatic β cell compensation. IRS-2-/- mice, on the other hand, developed diabetes because of severe insulin resistance paired with β cell failure. Recent studies have made it apparent that serine phosphorylation of IRS proteins can reduce the ability of IRS proteins to attract PI3-kinase, thereby minimizing its activation, and can also lead to an accelerated degradation of the IRS-1 protein. This serine phosphorylation in turn decreases IRS-1 tyrosine phosphorylation, impairing downstream effectors. Serine phosphorylation of IRS proteins can occur in response to several intracellular serine kinases. In humans, rare mutations of the IRS-1 protein are observed with insulin resistance [3].

OTHER CAUSES OF INSULIN RESISTANCE

i) Mitochondrial dysfunction

It has been known for many years that severe mitochondrial dysfunction can result in diabetes. In a study using 13C/31P MRS, it was found that in healthy lean elderly volunteers with severe muscle insulin resistance, there is ∼40% reduction in the rates of oxidative phosphorylation activity associated with increased intramyocellular and intrahepatic lipid content. This study suggests that an acquired loss of mitochondrial function associated with aging predisposes elderly subjects to intramyocellular lipid accumulation, which results in insulin resistance. Further, it was found that mitochondrial density was reduced by 38%, intramyocellular lipid content was increased by 60% and serine phosphorylation of IRS-1 was increased by 50% in

the young insulin-resistant offspring of type 2 diabetes parents [3].

ii) Adipokines

Insulin has three major target tissues-skeletal muscle, adipose tissue, and the liver. Not only is IR overexpressed in the cells of these tissues, but these are also the three places where glucose is deposited and stored; no other tissue can store glucose. About 75% of insulin-dependent postprandial glucose disposal occurs into the skeletal muscle; it is therefore the major target organ. Patients suffering from insulin resistance and type 2 diabetes frequently display signs of abnormal lipid metabolism, increased circulatory concentration and elevated deposition of lipids in the skeletal muscle. Increase in plasma FFA reduces insulin-stimulated glucose uptake, whereas a decrease in plasma lipid content improves insulin activity in the skeletal muscle cells, adipocytes and liver. Studies have shown that raising plasma fatty acids in both rodents and humans abolishes insulin activation of IRS-1-associated PI3-kinase activity in skeletal muscle where IRS-1 is most prevalent. Lipid-associated insulin resistance has also been shown to be linked to GLUT4 translocation defects.

Adipose tissue also acts as an endocrine organ producing adipokines which modulate glucose homeostasis. Currently, those most intensely discussed are TNF-α, leptin, adiponectin and resistin. At a molecular level, TNF-α increases serine phosphorylation of IRS-1 and down-regulates GLUT4 expression, thereby contributing to insulin resistance. Furthermore, mice lacking functional TNF-α were protected from obesity-induced insulin resistance. Humans with leptin deficiency or leptin receptor mutations are severely obese. In addition, it has direct effects on insulin sensitivity. Adiponectin has insulin-sensitizing effects, as it enhances inhibition of hepatic glucose output as well as glucose uptake and utilization in fat and muscle. The expression of adiponectin is decreased in obese humans. Thus, in humans, adiponectin levels correlate with insulin sensitivity. Because of its insulin-antagonistic effects, the adipokine resistin has attracted a lot of primarily preclinical research interest. Resistin decreases insulin-dependent glucose transport in vitro and increases fasting blood glucose concentrations and hepatic glucose production in vivo [2,3].

iii) Epigenetic markers:

A new study from Lund University supports the notion that patients with type 2 diabetes can be divided into subgroups as it demonstrated distinct epigenetic differences between these two different groups. The epigenetic markers are also associated with different risks of developing common complications in type 2 diabetes, such as stroke, heart attack and kidney disease and be given individualized treatment. In November 2021, the authors published a new study which highlighted genetic differences between the four subgroups of type 2 diabetes, suggesting different causes of the disease [4].

This study looked at 533 individuals recently diagnosed with type 2 diabetes from two population-based cohorts in Sweden. The authors measured DNA methylations in the blood at 800,000 sites in the genome of all participants. DNA methylation is a chemical process through which methyl groups attach to the DNA molecule, affecting the function of genes. The researchers found that the four subgroups had different levels of DNA methylation at 4.465 sites. The findings were used to develop epigenetic risk scores to predict common complications of type 2 diabetes. Epigenetic markers associated with two of the subgroups could predict an increased risk of developing heart attack, stroke, and kidney disease. "Heart attack and stroke are responsible for most deaths among patients with type 2 diabetes. Kidney disease causes a lot of suffering and is very costly for society, as many patients need dialysis treatment. An epigenetic biomarker that can predict complications at an early stage would make preventive actions possible [4,5].

The authors will need to verify their results in other population-based cohorts. They are also planning to study DNA methylation in tissues from, for example, muscle, adipose tissue, liver, and the pancreas of the four subgroups with type 2 diabetes [5].

Diagnostic tool:

Insulin resistance is characterized by an impaired response to either endogenous or exogenous insulin. While some Insulin resistance is a common feature of type 2 diabetes, cases of severe insulin resistance remain relatively uncommon but are likely to increase as the prevalence of diabetes, duration of illness over 3o years and obesity surges. The degree of insulin resistance can be measured using the euglycemic insulin clamp technique, but this is not a clinically useful method. The most widely reported and clinically useful definitions of insulin resistance are based on exogenous insulin requirements. The methods use either the number of units per kilogram of body weight per day or the total daily dose. Patients who require >1 unit/kg/day are considered to have insulin resistance, and those requiring >2 units/kg/day have severe resistance. Alternatively, a total daily insulin dose of more than 100 units /day and that of >200 units is considered as severe insulin resistance. Large total daily dose requirements create practical problems about insulin delivery as 1) a large volume of standard U-100 insulin can be painful to administer and 2) the onset and duration of insulin activity can be altered with high-volume doses.

The levels of long-term blood sugar, HbA1c, can be used to accurately determine the risk of a person with type 1 diabetes developing eye- and kidney complications. One of the recent studies inferred that around 2/3 of patients would have diabetic kidney disease, 20 (18%) non-diabetic kidney diseases like IgA nephropathy, glomerular disease, focal segmental glomerulosclerosis, minimal change disease, amyloidosis (n=1), membranous nephropathy, membranous-proliferative glomerulonephritis, tubule-interstitial disease, acute tubular necrosis and vascular disease, and hypertensive arteriosclerosis and another ~16% patients would have mixed kidney disease with characteristics of both diabetic and non-diabetic kidney disease[13]. The blood sugar level in a healthy person is very closely controlled, with a maximum HbA1c level of 42 mmol/mol (6.0%). A study from Linköping University, Sweden, has shown that this level should be lower than 53 mmol/mol (7%). The study has followed individuals for more than 30 years after the onset of type 1 diabetes [5].

Insulin Resistance Management:

The therapeutic approach includes monitoring blood glucose levels, dietary management, maintaining physical activity, keeping weight and stress under control, monitoring oral medications and, if required, insulin use via injections or pump. Blood pressure medication, Statins to lower LDL cholesterol need to be supplemented [8,9].

The Diabetes Prevention Program and its Outcomes Study (DPP & DPPOS) demonstrated that lifestyle intervention was both a significant and cost-effective intervention for diabetes prevention in high-risk adults. Intensive Lifestyle intervention that includes dietary interventions and therapy, Promoting and executing physical activity, both aimed at weight reduction, represents the cornerstone of treatment for insulin resistance too. Medications for hyperglycaemia management monitoring HbA1c compliments the lifestyle intervention [9].

A) Intensive Lifestyle Intervention:

O Dietary intervention should include a combination of calorie restriction and reduction of high glycaemic index carbohydrates.

O A dietary therapy with sodium reduction, fat reduction, calorie restriction, and attention to the glycaemic index of foods

O Physical activity improves both calorie expenditure and insulin sensitivity in muscle tissue.

B) *Education, support, and personalized programs*

O A 10% (7% weight loss reduced the onset of T2DM by 58%) weight reduction

O Metformin and other oral antidiabetics arm which reduce/ maintain Blood sugar levels

Intensive Lifestyle intervention:

Intermittent fasting (IF) diets have become popular in recent years as an effective weight losing method and metabolic health. IF helps lower blood pressure, blood sugar, and blood fat levels. For some people, it also works as part of a healthy long-term diet pattern.

Definition: Intermittent fasting is an eating pattern during which you refrain from consuming any calories for an extended period of 12 and 40 hours. Water, coffee, and other calorie-free beverages are allowed during the fast, but no solid foods or calorie-containing drinks are permitted.

IF can produce weight loss at a rate of approximately 0.25–0.75 kg per week. People also experience a 4–7% reduction in waist circumference, indicating that they lost belly fat. In, intermittent fasting, the client eats only during a specific window of time. Fasting for a certain number of hours each day or eating just one meal a couple of days a week can help body burn fat. Research shows intermittent fasting can lower risk of diabetes, insulin resistance and heart disease and can help in complete diabetes remission, defined as

an HbA1c level of less than 6.5% at least one year after stopping [7,8]. The previous follow-up by the research group was conducted 20 years after the onset of disease. Now after 30 years, the results show that damage has arisen at lower blood sugar levels than was the case after 20 years. More patients have experienced damage, despite having blood sugar levels that are not higher than those they have previously had. It seems that the threshold for developing complications falls gradually with time [8].

For example, observing Ekadashi an age-old Indian Practice of finishing dinner at 9 p.m. on Dashami (twice a month) and don't eat again until 9 AM on Dwadashi. We complete a 36-hour fast. A full 24-hour fast every other day can seem extreme and may be difficult for many people to maintain, so it's not recommended for beginners. Some people choose to fast from breakfast to breakfast or lunch to lunch based on the time frame works best depends on the individual routine. However, you don't have to go all-in right away, and many intermittent fasting routines start with shorter fasting periods. Here are 5 of the most popular eating patterns for adding intermittent fasting to your diet:

1. *Time-restricted eating*. Involves fasting every day for 12 hours or longer and eating in the remaining hours.
    a. *Fast for 12 hours a day:* The easiest way to do the 12-hour fast is to include the period of sleep in the fasting window. For example, a person could choose to fast between 9 p.m. and 9 a.m. is easy, as will be asleep for much of the time. Finish dinner before 9 p.m. and wait until 9 a.m. to eat breakfast
    b. *More popular example is the 16/8 method*. It features a daily 16-hour fast for men and 14 hrs for women and an 8-10 hour eating window wherein one can fit in 2, 3, or more meals.
2. *The 5:2 diet*: The 5:2 diet involves eating as you normally do 5 days of the week and restricting your calorie intake to 500–600 on the remaining 2 days.
3. *Eat Stop Eat*: Eat Stop Eat involves a 24-hour fast once or twice per week.
4. *Alternate day fasting*: the goal is to fast every other day.

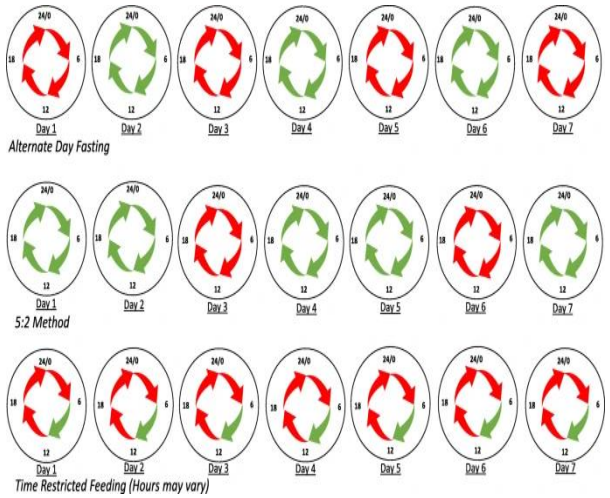


Figure-1

1. *Meal skipping:* This flexible approach to intermittent fasting may be good for beginners. It involves occasionally skipping meals, People can decide which meals to skip according to their level of hunger or time restraints. but it is important to eat healthful foods at each meal. Meal skipping is likely to be most successful when individuals monitor and respond to their body's hunger signals. Essentially, people using this style of intermittent fasting will eat when they are hungry and skip meals when they are not, feeling more natural rather than the other fasting methods.
2. *The Warrior Diet:* The Warrior Diet is among the first popular diets. It involves eating very little, usually just a few servings of raw fruit and vegetables, during a 20-hour fasting window, then eating one large meal at night. The eating window is usually only around 4 hours, during which, people must make sure that they consume plenty of vegetables, proteins, and healthful fats and some carbohydrates.

Cellular and Molecular Level Interactions during IF and Calorie Restriction (CR):

A variety of molecular and cellular signalling pathways and the ratio of bioenergetic sensors are activated and oscillated by the amount of energy consumed, the content of meals, and the length of fasting. This impact is mediated by higher activated protein kinase (AMP) and a decrease in cellular adenosine triphosphate (ATP), which results in AMPK activation, which inhibits various anabolic pathways & boosts catabolic processes. Exertion & energy deprivation activate AMPK, a critical regulator of energy metabolism. Nicotinamide adenine dinucleotide (NAD+) deacetylase activity of sirtuins (SIRTs) and AMPK deacetylation of LKB1 and SIRT1 trigger a feedback loop. Many downstream proteins govern cell function and resistance to stress are activated by these intermediate energy carriers, like forkhead box Os (FOXOs), peroxisome proliferator-activated receptor coactivator 1 (PGC-1), and nuclear factor erythroid 2–related factor 2 (NRF2). There are numerous metabolic health concerns that can be improved by the combination of these pathways. For a better understanding a schematic representation is depicted in Figure 2 [1, 9].

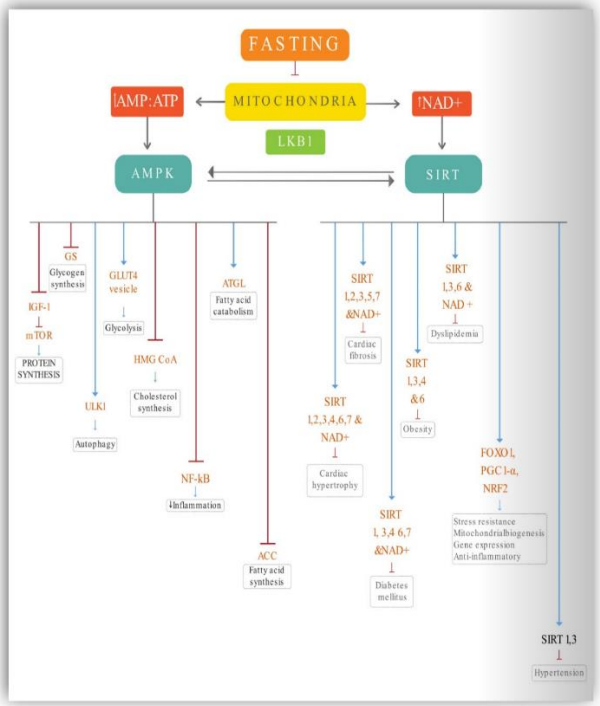


Figure 2. Molecular mechanism of action of fasting.
Blue lines—activating action, Red lines—inhibiting action.

Effect of a short IF diet intervention: A 3-month intermittent fasting diet intervention among 36 people with diabetes and found almost 90% of participants, including those who took blood sugar-lowering agents and insulin, reduced their diabetes medication intake after intermittent fasting. Sixty-five percent of the study participants who achieved diabetes remission had a diabetes duration of more than 6 years (6-11 years). Fifty-five percent of these people experienced diabetes remission, discontinued their diabetes medication, and maintained it for at least one year, negating the view that diabetes remission can only be achieved in those with a shorter diabetes duration (0-6 years). The study also showed that medication costs decreased by 77% in people with diabetes after intermittent fasting [7].

VISS Study: Researchers in a Vascular Diabetic Complications in Southeast Sweden (VISS), followed the patients' HbA1c values, which reflect their average blood sugar levels during a longer period, The study subjects were all children and adults younger than 35 years who developed type 1 diabetes during the period 1983-1987, and who received care in the South-East Healthcare Region of Sweden. All 447 newly diagnosed were monitored for the development of eye- and kidney damage for a period of between 32 and 36 years after diagnosis. The small blood vessels in the eye are particularly susceptible to damage in type 1 diabetes. Nearly all patients experience small haemorrhages

in the eye that do not affect their vision. In some cases, new blood vessels develop in the retina. The latter is known as 'proliferative retinopathy' and can lead to blindness. Another effect of diabetes concerns the area known as the 'macula' of the retina, where high-focus vision is located. Damage here leads to blurred vision [8].

Benefits of IF:

1.Supports weight loss and improve metabolic health: Metabolic health is a marker of how well the body processes, or metabolizes, energy, measured by blood pressure, blood sugar, and blood fat levels. Fasting or abstaining from food can create a calorie deficit, the hallmark of most weight loss diets. Research shows that some types of IFs can be as effective for weight loss, if not more effective as other diets, that rely on limiting your daily calorie intake. Time-restricted eating routines like the 16/8 method, alternate day fasting and the 5:2 diet are effective for weight loss. IFs support weight loss by regulating appetite to increase feelings of fullness while suppressing feelings of hunger. Ifs have also been linked with a) lowering blood pressure b) improving blood sugar c) repairing damaged cells and d) protecting brain health.

2. Can be a sustainable lifestyle change: Fasting helps in simplifying our day since we need to plan fewer meals. It doesn't typically require calorie counting, watching your macros, eating certain foods that you might not be used to eating, or eliminating certain foods that you otherwise enjoy. For example, having an early dinner followed by a late breakfast the next day is one way to fast intermittently, that I practice. I finish my last meal at 9 p.m. and don't eat until noon the next day, thus technically fasted for 16 hours. A variant of this for *people who get hungry in the morning and like to eat breakfast, could eat some fruits like Papaya around 1000-1100. For those who can't eat until later in the evening due to work schedules/ other obligations, this method may be hard to practice.*

3. Works well with a nutritious, whole foods diet: Because intermittent fasting is *focused more on when rather than what you eat*, it's generally easy to implement in conjunction with your current diet. You won't necessarily need to buy any special foods or diverge much from what you typically eat. For those already content with their current diet but are looking for other ways to continue to boost overall health, fasting might help.

Cons of intermittent fasting:

1. **Might go against intuition:** Intermittent fasting requires discipline, restraint, and planning. For people, comfortable with calorie intake within a designated time frame there is no problem, but for some others, it might feel unnatural at first. For those prefer not to follow a strict schedule, intermittent fasting may be frustrating. If an individual's schedule tends to vary from day to day because of work, family, or other obligations, keeping calorie intake to a designated time frame could be challenging.
2. **You'll feel hungry:** An 8- or 12-hour fast might feel like a long time when you're not used to fasting. May feel going to bed hungry or being hungry early in the morning and feel unpleasant and unsustainable in the long term. At times, it might be necessary to override your natural hunger and fullness cues to not break your fast earlier than planned. However, once you've adjusted to intermittent fasting, you might feel less hungry and enjoy it after a few months.
3. **The side effects could affect your mood:** When you first try intermittent fasting, one of the first things you may notice besides feeling hungry is ups and downs in your mood. initially increasing hunger levels, fasting can have side effects, like headaches, constipation, fatigue, sleep disturbances etc. One may have irritability and anxiety, symptoms of low blood sugar levels, a common body response to restricting calories

Once one had time to adjust, intermittent fasting brings a sense of pride [1,2].

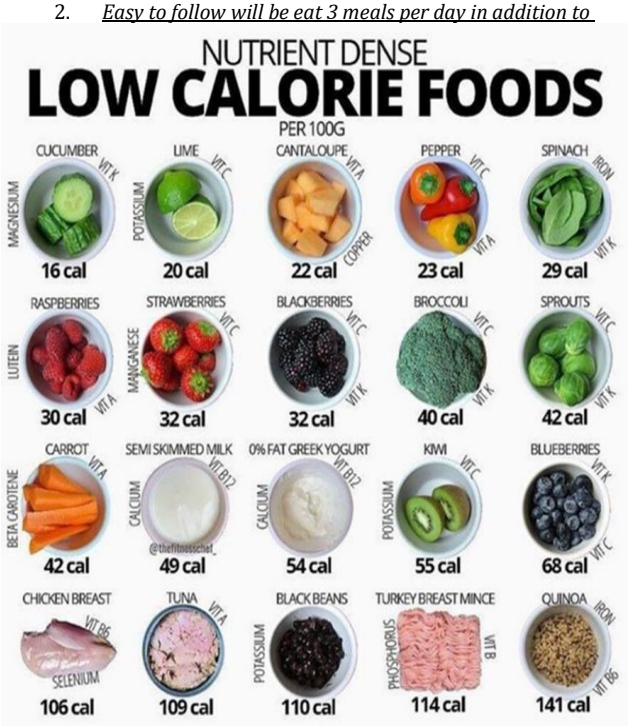
Tips to stay on track and maximize the benefits of intermittent fasting:

1. *Staying hydrated*. Drink lots of water and calorie-free drinks, such as herbal teas, throughout the day.
2. *Avoiding obsessing over food*. Plan plenty of distractions on fasting days to avoid thinking about food, such as catching up on paperwork or going to see a movie.
3. *Resting and relaxing.* Avoid strenuous activities on fasting days, although light exercise such as yoga may be beneficial.
4. Making every calorie count: If the chosen plan allows some calories during fasting periods, select nutrient-dense foods that are rich in protein, fiber, and healthful fats. Examples include beans, lentils, eggs, fish, nuts, and avocado.
5. *Eating high-volume foods*. Select filling yet low-calorie foods, which include popcorn, raw vegetables, and fruits with high water content, such as grapes and melon.
6. *Increasing the taste without the calories*. Season meals generously with garlic, herbs, spices, or vinegar. These foods are extremely low in calories yet are full of flavour, that help to reduce feelings of hunger.
7. *Choosing nutrient-dense foods after the fasting period.* Eating foods that are high in fiber, vitamins, minerals, and other nutrients helps to keep blood sugar levels steady and prevent nutrient deficiencies. A balanced diet will also contribute to weight loss and overall health.

Prescribing Intermittent Fasting:

Clinicians and dieticians are obliged to prescribe IF by individual requirement.

1. *Alternate day fasting,* and *periodic fasting* have demonstrated efficacy in improving metabolic risk factors, but it will be difficult to convince patients to give up or severely restrict calories for an entire 24 h period.
2. *Easy to follow will be eat 3 meals per day in addition to*



3. *frequent snacking* concentrating on low calorie foods. Diet: Diet has a big impact on your blood sugar and insulin
4. levels. Highly processed, high-carbohydrate and high-fat foods require more insulin. In general, eating foods that have a low to medium glycaemic index and limiting foods that have a high glycaemic index can help you reverse and/or manage insulin resistance. Eating foods with fiber also helps regulate blood sugar levels because it takes your body longer to digest fiber, meaning your blood sugar levels don't spike as much.

The glycaemic index (GI) is a measurement that ranks foods containing carbohydrates according to how much they affect your blood sugar levels. The Glycaemic Index Foundation (GIF) classifies the GI of foods as either low, medium, or high, with pure glucose generally as a reference at 100:

Low GI: 55 or less., Medium GI: 56–69., High GI: 70 or greater

High-GI foods generally have a lot of carbohydrates and low to no fiber content. Low-GI foods have low and high amounts of carbohydrates & fiber respectively

Examples of foods with a high GI include White bread, Potatoes, Breakfast cereals. Cakes and cookies, Fruits such as watermelon and dates.

Foods with a low GI include Beans and legumes, Fruits-Papaya, apples and berries, non-starchy vegetables,

asparagus, cauliflower and leafy greens, Nuts. Dairy, fish, and meat.

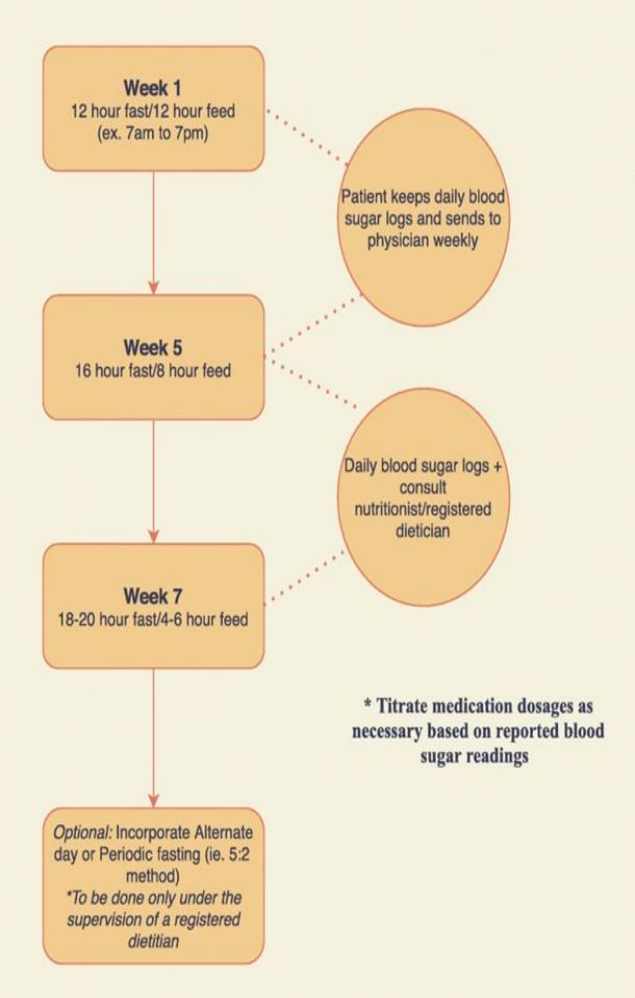


Fig.5. Medications to be titrated

3.**Clinicians may consider recommending:**

i) First patients restrict their intake to a daily 12 h period, typically an overnight fast (for example, 9 pm to 9 am). As patients become more comfortable with this pattern

ii) the feeding window can be restricted further (16 h fast followed by an 8-hr feed)

iii) 20 hrs. fast followed by a 4 hrs feeding window: This allows the patient some daily flexibility in choosing when to consume calories, thus increasing the likelihood of compliance.

Lastly, patients who have become adapted to time restricted feeding may choose to switch to alternate day or periodic fasting with the supervision and guidance of a registered dietician

Caution: Intermittent fasting is generally considered safe. However, it is best to use caution when beginning or following the eating routine. Restricting calorie intake for an extended period could be dangerous for children and adolescents, people who are pregnant or nursing/ breastfeeding, people who have diabetes, people taking certain medications, people with a history of eating disorders. Therefore, before embarking on intermittent fasting or making any other drastic changes to diet, consult a trusted healthcare professional to help you get started safely.

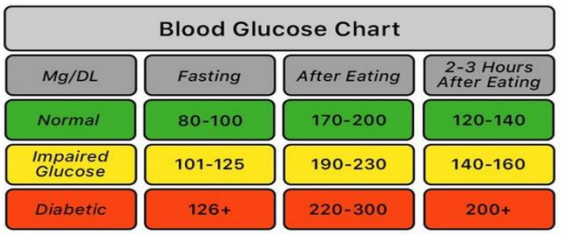


Fig.6. Blood sugar guide for adjusting medicines

Medical Management:

Concentrated Insulin Products

1. *Concentrated insulin products* help improve the delivery of insulin when very large doses. U-500 insulin is five times more concentrated than standard U-100 insulin and is considered the cornerstone of therapy for most patients with severe insulin resistance. Two new concentrated insulin pen products are now available in the United States—U-200 insulin lispro and U-300 insulin glargine.

2. *Metformin:* Metformin as the initial pharmacological option for most people with type 2 diabetes. It has a strong record of safety and efficacy, as well as a favourable effect on weight. Although it is common practice to combine metformin with insulin, it's use has not been specifically evaluated in the setting of severe insulin resistance.

3. *Glucagon-Like Peptide 1 Receptor Agonists:* Glucagon-like peptide 1 (GLP-1) receptor agonists stimulate the GLP-1 receptors in the pancreas and thereby increase insulin release and inhibit glucagon secretion, but only in the presence of elevated blood glucose. A recent meta-analysis of 15 studies showed that a GLP-1 receptor agonist combined with basal insulin was superior to basal-bolus insulin combinations in patients with type 2 diabetes. GLP-1 agonists are generally taken by injection given daily or weekly and include: Dulaglutide (weekly), Exenatide extended release (Bydureon bcise) (weekly), Exenatide (Byetta) (twice daily), Semaglutide (Ozempic) (weekly), Liraglutide (Victoza, Saxenda) (daily) and recently introduced E.g., Oral Semaglutide. oral dosage form (tablets): Adults—At first, 3 milligrams (mg) once a day for 30 days.

4. *Sodium-Glucose Cotransporter 2 Inhibitors*: Sodium-glucose cotransporter 2 (SGLT2) inhibitors increase the excretion of urinary glucose, thereby reducing plasma glucose concentrations independent of the presence of insulin (36). These medications have been shown to reduce body weight. E.g., Canagliflozin (Invokana), Dapagliflozin (Farxiga), Empagliflozin (Jardiance, GIBTULIO 20 mg), Ertugliflozin (Steglatro). SGLT2 inhibitors are known to increase the risk of urinary tract and genital mycotic infections, particularly in women with a history of these infections

5. *Dipeptidyl Peptidase-4 Inhibitors*: Dipeptidyl peptidase-4 (DPP-4) inhibitors prolong the activity of endogenous GLP-1 and glucose insulinotropic polypeptide by preventing their breakdown and potentiating their actions. Taken orally, would appear to be an attractive alternative to GLP-1 receptor agonists for the management of patients with severe insulin resistance

6. Pramlintide: Pramlintide is a synthetic analog of amylin, a neuroendocrine hormone that is cosecreted with insulin from pancreatic β-cells. It is effective as an adjunct to insulin therapy in patients with type 1 or type 2 diabetes by reducing postprandial glucose excursions. Severe hypoglycaemia requiring assistance may occur during the first 4 weeks of treatment with pramlintide.

Conclusion

In this review, I have summarized current developments contributing to our understanding of insulin resistance, and the pathogenesis of type 2 diabetes. Among the many molecules involved in the intracellular processing of the signal provided by insulin, IRS-2, PKB, the Foxo protein and p85 regulatory subunit of PI-3 kinase have attracted particular interest, because their dysfunction results in insulin resistance in vivo. The identification of signalling defects and an understanding of the complex relationship of the different factors modulating insulin sensitivity is an important prerequisite for the development of novel and more specific anti-diabetic compounds. By elucidating the cellular and molecular mechanisms responsible for insulin resistance, these studies provide potential new targets for the treatment and prevention of type 2 diabetes.

References:

1. https://repositorio-aberto.up.pt/bitstream/10216/144976/2/589971.pdf
2. Molecular mechanisms of insulin resistance in type 2 diabetes mellitus, Vandana Saini, World J Diabetes. 2010 Jul 15; 1(3): 68–75. doi: 10.4239/wjd. v1.i3.68
3. https://repositorio.udd.cl/bitstreams/8304ad73-2bbd-4115-a4ca-b3ab6cd5a5c6/download
4. Novel Subgroups of Type 2 Diabetes Display Different Epigenetic Patterns, which Associate with Future Diabetic Complications. Diabetes Care, 2022; DOI: 10.2337/dc21-2489
5. "Epigenetic markers predict complications in patients with type 2 diabetes." Lund University, ScienceDaily. ScienceDaily, 25 May 2022.
6. https://bmcpregnancychildbirth.biomedcentral.com/articles/10.1186/s12884-022-04389-5
7. i)Time-restricted Eating for the Prevention and Management of Metabolic Diseases. Emily N C Manoogian, et.al, Endocrine Reviews, 2022; 43 (2): 405 DOI: 10.1210/endrev/bnab027
8. ii)www.sciencedaily.com/releases/2022/12/221214092433.htm>.
9. Recommended blood sugar levels to avoid diabetes-related damage, Linköping University,Sweden,
10. Treatment Approach to Patients with Severe Insulin Resistance, Timothy J. Church, et al, Clin Diabetes. 2016 Apr; 34(2): 97–104, doi: 10.2337/diaclin.34.2.97
11. Which are the foods to avoid for diabetics? Jon Shore, Type 2 Diabetic, Psychotherapist dietingmindfully.com
12. Impact of Intermittent Fasting on Metabolic Syndrome and Periodontal Disease, Sameena Parveen et.al, Int. J. Environ. Res. Public Health 2022, https://doi.org/10.3390/ijerph192114536
13. Intermittent fasting: is there a role in the treatment of diabetes? Michael Abosta et.al, Clinical Diabetes and Endocrinology volume 7, Article number: 3 (2021) https://clindiabetesendo.biomedcentral.com/articles/10.1186/s40842-020-00116-1
14. Basu M, et al. Prevalence of non-diabetic kidney disease and inability of clinical predictors to differentiate it from diabetic kidney disease: results from a prospectively performed renal biopsy study. BMJ Open Diabetes Res Care. 2022 Dec;10(6): e003058. Doi: 10.1136/bmjdrc-2022-003058..