A NARRATIVE REVIEW ON THE POSSIBLE CAUSES OF INSULIN RESISTANCE

By

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A thesis submitted to School of Pharmacy in partial fulfillment of the requirements for the degree of
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Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at BRAC University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I/We have acknowledged all main sources of help.

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Approval

The thesis/project titled "A NARRATIVE REVIEW ON THE POSSIBLE CAUSES OF INSULIN RESISTANCE" submitted by Zobair Mohaimin Sabbib (21146060) of Spring 25, 2025 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy on 23.09.25

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Ethics Statement

No animals or humans were harmed during this project. This was based on evidence-based review on the possible causes of Insulin Resistance with existing data and information from scholarly articles.

Abstract

Insulin resistance is a multifactorial condition that significantly contributes to the development of type 2 diabetes, obesity and cardiovascular diseases. While traditionally linked to obesity and sedentary lifestyles, recent research reveals a more complex etiology involving behavioral, nutritional, endocrine, genetic, environmental, and cellular factors. This review explores both established and emerging contributors to insulin resistance including poor dietary habits, physical inactivity, chronic stress, circadian rhythm disruption and micronutrient deficiencies. Hormonal imbalances particularly involving cortisol, thyroid and sex hormones are examined for their impact on insulin signaling. Additionally, chronic inflammation, oxidative stress, mitochondrial dysfunction and endoplasmic reticulum stress are highlighted as key intracellular mechanisms reducing insulin sensitivity. The review also considers fewer known influences such as alterations in gut microbiota, exposure to endocrine disrupting chemicals, early developmental conditions and epigenetic changes. By integrating these diverse factors this paper aims to provide a comprehensive understanding of insulin resistance and its multifaceted origins.

Keywords: Insulin Resistance; causes; genetic factors; obesity; endocrinology;

Dedication

While pursuing my degree, there have been moments I found myself in situations I didn't see a way out of. I dedicate this to each and every one who stood by me. Had the faith in me that I am capable. Loved me unconditionally. To the best parents in the world who never lost hope in me. To the friends we found and lost on the way. Lastly, to the person who chose to stay with me through thick and thin, Anushka Alam Nabila.

Lastly, if you ask me what kept me going? The promise made by Allah to every one of us.

فَإِنَّ مَعَ ٱلْعُسْرِ يُسْرًا ۝٥

So, surely with hardship comes ease.

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List of Acronyms

IR	Insulin Resistance
T2DM	Type 2 Diabetes Mellitus
PCOS	Polycystic Ovary Syndrome
HPA	Hypothalamic–Pituitary–Adrenal (Axis)
IGF-1	Insulin-like Growth Factor 1
GH	Growth Hormone
TNF-α	Tumor Necrosis Factor Alpha
IL-6	Interleukin-6
IL-1β	Interleukin-1 Beta
Th1	T Helper 1 (Cell)
Tregs	Regulatory T Cells
NLRP3	NOD-like Receptor Family Pyrin Domain Containing 3
CRP	C-Reactive Protein
IRS-1	Insulin Receptor Substrate-1
PPARG	Peroxisome Proliferator-Activated Receptor Gamma
FTO	Fat Mass and Obesity-Associated (Gene)
TCF7L2	Transcription Factor 7-like 2
GLUT4	Glucose Transporter Type 4
AKT2	Protein Kinase B Beta (also known as AKT2)
GCKR	Glucokinase Regulatory Protein
MTNR1B	Melatonin Receptor 1B
EDCs	Endocrine Disrupting Chemicals
BPA	Bisphenol A
SLE	Systemic Lupus Erythematosus
NAFLD	Non-Alcoholic Fatty Liver Disease

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Chapter 1

Introduction

Insulin resistance (IR) is being considered one of the most urgent health issues of the modern time and the future. Simply explained, insulin resistance is a physiological condition where body tissues that use the hormone insulin such as the skeletal muscle, liver and adipose tissues do not respond well to the hormone insulin properly anymore. As insulin plays a vital role in balancing glucose levels in the blood by facilitating glucose uptake and storage, this impaired effectiveness and response causes the pancreas to release more insulin in order to maintain normal glucose levels. This compensation of high insulin levels cannot be sustained in the long run and eventually results in the emergence of type 2 diabetes mellitus (T2DM). Yet diabetes is small compared to the significance of insulin resistance. The metabolic syndrome is related to obesity, dyslipidemia, hypertension, non-alcoholic fatty liver disease (NAFLD), cardiovascular disease and polycystic ovary syndrome (PCOS). In another aspect, insulin resistance is not the precursor of diabetes but a factor working behind a wide variety of metabolic and endocrine conditions that has a larger influence and impact on the human health.

Traditionally, overweight and physical inactivity was considered to be the main reason behind insulin resistance. Though being overweight and the accumulated fat particularly visceral fat are thought with the loss of insulin sensitivity, recent scientific studies show that the pathophysiology of insulin resistance is much more complicated and multi-factorial. Many studies now show a complex of interacting factors including diet, sleeping pattern, stress, endocrine imbalances, inflammation, genetics and even environmental pollutants work together and are the leading cause of Insulin Resistance. It is this complexity that is making insulin resistance not only biomedical but also a state which is created by both modern lifestyle and environmental factors meaning that a different approach must be taken to understand the causes of insulin resistance.

The epidemiological effect of insulin resistance cannot be ignored. The International Diabetes Federation estimates a total of more than 537 million adults in the world suffer from diabetes and most of them are suffering from insulin resistance and it is the key determinant of diabetes. Besides, hundreds of millions of people are prediabetic or at least suffer from a metabolic disorder and both of them are linked to insulin resistance which is not pathological. The numbers shown on the statistics are not normal. Along with this an increase in healthcare costs, reduced productivity, reduced quality of life and more deaths are being reported. Knowledge of what causes insulin resistance is not only an academic research, but it indicates towards a greater global health crisis.

Cellular and molecular insulin resistance are a result of the stop signal in the insulin signaling pathway. Under normal conditions, insulin binds to receptors on cell membranes and activates glucose uptake, glycogen synthesis and lipid metabolism. In many cases, this mechanism gets disrupted in a patient suffering from insulin-resistance due to serine phosphorylation of insulin receptor substrate (IRS) proteins, inhibition of glucose transporter type 4 (GLUT4), dysfunction of mitochondria, oxidative stress and endoplasmic reticulum (ER) stress. The presence of chronic inflammation also referred to as metaflammation facilitate the process further by producing inflammatory mediators like cytokines that disrupt the signal of insulin. These pathophysiological modifications demonstrate how varying stimuli such as diet and stress can work together and overlap each other and be combinedly reduce the effects of insulin.

Lifestyle and behavioral factors are which are the most commonly considered mainly responsible in insulin resistance. Repeatedly eating high-carbohydrate, saturated and trans-fat and added sugar have been shown to have a negative influence on insulin sensitivity and dietary habits such as the Mediterranean diet actually have positive influence. The other part is sedentary lifestyle in which a person has a decreased physical activity which reduces absorption of glucose in skeletal muscle as the muscles are not used much. Mitochondrial density also

reduces as a result and ultimately causes lipid deposition in the body. Sleep deprivation, circadian rhythm disruption and chronic stress are becoming newly accepted factors of Insulin Resistance. These lifestyle factors are not necessarily cause and effect but they interact and work together causing an imbalance in the metabolic functions in the body.

Endocrine and hormonal issues can cause drastic changes to insulin sensitivity. A study showed that disruption in the insulin and thyroid function is reduced by high levels of cortisol as seen in the the case of chronic stress or Cushing syndrome and the function of using glucose effectively by the body also reduces because of this. An hyperandrogenic PCOS heightens the insulin resistance in women and in men, low testosterone levels are seen which are found responsible for impotence to as the body focuses more to metabolize glucose. Insulin sensitivity is also regulated by the secretion of adipokines such as leptin and adiponectin in the blood by the adipose tissue and this is the relationship between hormones, fat buildup and metabolism.

A person is also likely to acquire insulin resistance because of genetic and epigenetic factors as well. Polymorphic mutations in IRS1, PPARG, FTO and TCF7L2 genes have been linked to gene defects associated with defective insulin signaling and precursor to develop diabetes. Changes in the environment (diet, exposure to new surroundings during childhood, etc.) can cause epigenetic changes that will alter gene expression. These findings show that not all insulin resistance is acquired and some development and inheritance can be coded.

Also, there are emerging and environmental factors which are gaining popularity in recent studies. Insulin signaling pathways have been reported to be disturbed by exposure to endocrine-disrupting chemicals, phthalates and organic pollutants (POPs) including bisphenol A (BPA). Air pollution is also another concerning factor coming up is environmental risk factors which leads to oxidative stress and systemic inflammation.

Together these studies contribute to the fact that the insulin resistance cannot be seen from a single perspective. Rather, it occurs due to a combination of lifestyle, hormonal, inflammatory, genetic and environmental factors.

Chapter 2

Material and Methodology

This review article aims to harmonize current knowledge regarding the causes of insulin resistance by analyzing existing literature from various scientific databases. A systematic approach was used to gather relevant studies ensuring a comprehensive understanding of all the relevant reasons behind insulin resistance.

Extensive searches were conducted across PubMed, Scopus, and Google Scholar to gather relevant literature. The search parameters included key terms like "insulin resistance," "causes," "pathophysiology," "metabolic syndrome," and "inflammation". Both clinical and theoretical studies were prioritized alongside reviews and research papers to capture different perspectives on the topic. Research papers focusing on the causes of obesity, modern day stress factors, insulin resistance were primarily taken as the key source of information.

Chapter 3

The Causes of Insulin Resistance

3.1 Lifestyle and Behavioral Factors

Insulin resistance development is predominantly influenced by lifestyle and behavioral factors on a global scale. Key factors found to prominently influence insulin resistance encompass poor dietary habits, reduced physical activity, poor circadian rhythm, increased stress levels and substance abuse.

Dietary habits, particularly the consumption of energy dense but poor nutrient value have been strongly associated with insulin resistance. Consuming diets abundant in refined carbohydrates, saturated fats, and added sugars stimulate increased insulin release by the beta cells of pancreas. Over time, sustained high insulin concentrations can impair the body's ability to effectively respond to insulin and hence glucose intolerance (Ludwig et al., 2018). A high intake of trans fats coupled with insufficient dietary fiber has been associated to inflammation and imbalance of the gut microbiome and both of which worsens insulin resistance (Ley et al., 2006). On the other hand, a diet consisting of high intake of fibrous food items, lean proteins and unsaturated fats have been found to show protective effects against risk of insulin resistance and the development of type 2 diabetes mellitus (Esposito et al., 2004).

Physical inactivity is a big factor determinant in the onset of impaired insulin sensitivity. Humans have evolved from agriculture-based lifestyles to modern sedentary ones. Thus, decreasing the amount of physical movement by a great margin. Lack of movement prolongs the time sugar stays in the body. Therefore, increasing the amount of insulin. Sedentary behavior hampers the efficiency of glucose transport into skeletal muscle cells, a major pathway for insulin-mediated glucose disposal, thereby leading to reduced insulin sensitivity. Prolonged inactivity reduces mitochondrial density and function further impairing metabolic flexibility (Hawley & Lessard, 2008). In easier words, lack of mitochondria rich muscle fibers due to inactivity impairs metabolic flexibility.

Sleep duration and quality are increasingly recognized as important determinants of insulin sensitivity. Sleep deprivation, poor sleep quality and circadian rhythm disruptions have been shown to adversely affect the metabolism of glucose, thereby increasing the risk of insulin resistance (Spiegel et al., 2009). Mechanistically, insufficient sleep elevates evening cortisol secretion, activates the sympathetic nervous system and disrupts the balance between appetite-regulating hormones reducing leptin and increasing ghrelin all of which collectively promote

increased appetite, weight gain, and metabolic dysfunction (Taheri et al., 2004). Moreover, shift work and irregular sleep-wake cycles are associated with higher rates of metabolic syndrome and type 2 diabetes (Knutson et al., 2007).

Psychological stress represents another behavioral factor with substantial metabolic consequences. Chronic activation of the HPA axis due to stress leads to prolonged cortisol elevation, which antagonizes insulin's effects. Cortisol plays a great role in Insulin resistance by increasing glucose output from the liver, decreased glucose uptake and fat deposition in the visceral region of the human body (Rosmond, 2005). Besides, constantly being stressed results in stress eating, lack of physical movement, sleep disturbances, etc. which increases the impact of stress on the metabolic health by many times.

Uses of substances like drugs, tobacco and alcohol are found to influence the Insulin Resistance process by a great margin. Nicotine helps in developing insulin resistance by increasing lipolysis and the rise free fatty acids in blood stream (Eliasson, 2003).

These lifestyle factors are interrelated and together work and develop Insulin Resistance. For example, stress can lead to over eating, completely shatter the sleep pattern and timing and reduced physical activity may create a cycle that promotes insulin resistance.

3.2 Dietary and Nutritional Factors

Dietary and nutritional factors are considered to be the core concept though which Insulin Resistance develops, progresses and we can also reverse this condition by fixing the dietary habits. Nutrition is central in modulating glucose metabolism, hormonal regulation and inflammatory pathways. The quality, quantity and composition of the diet all contribute to metabolic health with specific dietary patterns promoting or impairing insulin sensitivity.

Excessive intake of refined carbohydrates and added sugars is among the most well-established dietary contributors to insulin resistance. Diets rich in high glycemic index foods like white bread, sweetened breakfast cereals, soft drinks, and sugary desserts causes swift elevations in blood glucose, prompting a compensatory insulin surge. Chronic high insulin levels promote cellular desensitization to insulin leading to insulin resistance (Ludwig et al., 2018). Furthermore, commonly found in processed foods, high-fructose corn syrup can drive hepatic insulin resistance by enhancing liver fat synthesis and leading to increased intrahepatic fat deposition (Tappy & Lê, 2010).

Dietary fat quality also influences insulin action. Saturated fats, especially from animal sources, impair insulin signaling pathways and promote fat accumulation in muscle and liver (ectopic fat). This intramyocellular lipid accumulation disrupts insulin signaling and impairs the muscle's ability to uptake glucose in response to insulin (Sparks et al., 2005). Conversely, monounsaturated and polyunsaturated fats, particularly omega-3 fatty acids exert anti-inflammatory effects and are linked to improved insulin sensitivity. Trans fats which often found in fried and processed foods are particularly harmful as they not only impair insulin signaling but also exacerbate systemic inflammation.

Dietary fiber, particularly soluble fiber, plays a protective role against insulin resistance. Fiber slows glucose absorption, blunts postprandial glucose spikes and supports a healthy gut microbiome. High intake of fiber-rich foods including whole grains, legumes, fruits, and vegetables is consistently linked with lower odds of insulin resistance and type 2 diabetes (Weickert & Pfeiffer, 2008). A fiber rich diet fosters microbial diversity and the production of short-chain fatty acids, especially butyrate which strengthen the intestinal barrier and suppress systemic inflammation.

Micronutrient deficiencies are another important, often overlooked, dietary factor. Low levels of magnesium, vitamin D, chromium and zinc have been linked to impaired insulin action. As a vital cofactor in glucose-processing enzymes, magnesium supports normal glucose metabolism, while inadequate intake or deficiency is associated with increased insulin resistance (Hruby et al., 2014). Vitamin D is essential for maintaining pancreatic β-cell health and inflammation. Chromium and zinc have been found to decrease the chances of insulin resistance.

Dietary patterns provide a broader picture of metabolic influence on insulin resistance. A diet prevalent in Western countries rich in red and processed meats, refined grains, and sugary foods, while low in fruits and vegetables has long been linked to higher rates of insulin resistance (et al., 2005). On the other hand, the Mediterranean diet, characterized by high consumption of whole grains, fruits, vegetables, legumes, nuts, olive oil, and fish, has been linked to improvements in insulin sensitivity and overall metabolic function (Esposito et al., 2004). Moving to a plant-based diet which focuses on the intake of whole plant foods and limits animal sources of proteins have been found to improve insulin sensitivity as there is a lower dietary fat, high fiber and low inflammatory agents in the diet.

Time of the day a meal is taken and the frequency of meals taken influence how insulin is released and used in the body. Irregular eating without a fixed routine, unnecessary snacking and late-night munching can disrupt circadian regulation of insulin secretion and sensitivity.

Consistently eating in excess irrespective of the remains a key driver of insulin resistance. Chronic energy surplus leads to adipocyte hypertrophy, inflammation and ectopic fat deposition, all of which impair insulin signaling (Hotamisligil, 2006). Even in the absence of obesity, excess caloric intake, particularly from low-nutrient foods, promotes metabolic dysfunction.

On the other hand, caloric restriction without malnutrition improves insulin sensitivity, reduces oxidative stress and enhances mitochondrial biogenesis. Evidence from both anima land human studies suggests that modest caloric restriction can delay the onset of insulin resistance and type 2 diabetes (Redman & Ravussin, 2011). Nutritional interventions that combine moderate caloric restriction with high nutrient density are particularly effective.

The connection between the gut microbiome and dietary impacts on insulin resistance is becoming more evident, as research continues to explore this relationship. Diet directly affects the growth function of the gut microbiome. Diets high in fiber content and polyphenols positively affect the growth of beneficial microbes that produce anti-inflammatory metabolites. On the other hand, high-fat, low-fiber diets have been shown to decrease microbiome diversity and compromise intestinal barrier function, resulting in metabolic endotoxemia that drives systemic inflammation and insulin resistance (Cani et al., 2007).

In summary, dietary and nutritional factors are central to both the cause and potential reversal of insulin resistance. The type, quality and timing of food consumed can either exacerbate or mitigate insulin resistance through mechanisms involving inflammation, oxidative stress, gut health and hormonal regulation. Public health interventions and clinical strategies focused on dietary education, food environment improvement and personalized nutrition hold promise in addressing the growing burden of insulin resistance and related metabolic disorders.

3.3 Hormonal and Endocrine Imbalances

Endocrine and hormonal imbalances contribute to insulin resistance by altering metabolic and inflammatory pathways that maintain glucose and lipid homeostasis. The human endocrine system consists of multiple glands and hormone each interacting with insulin pathways directly or indirectly. When these hormonal balances are dysregulated, insulin sensitivity can be compromised. One of the most prominent hormonal contributors is **cortisol**, the primary stress

hormone produced by the adrenal glands. Chronic psychological or physiological stress activates the hypothalamic pituitary adrenal (HPA) axis which leads to elevated cortisol levels. Cortisol promotes hepatic gluconeogenesis and lipolysis while antagonizing the action of insulin in peripheral tissues (Rosmond, 2005). Prolonged hypercortisolemia as seen in Cushing's syndrome or chronic stress conditions has been strongly associated with fat deposition in the visceral region, central obesity and insulin resistance.

T3 and T4, the primary thyroid hormones, are essential regulators of basal metabolic rate, glucose homeostasis, and mitochondrial function. hen thyroid function is reduced, as in hypothyroidism, glucose uptake by muscles and fat cells declines, often resulting in weight gain and abnormal lipid profiles, which promote insulin resistance. Even mild thyroid dysfunction, such as subclinical hypothyroidism, has been associated with a greater risk of insulin resistance and type 2 diabetes.

Sex hormones also modulate insulin action. In women, conditions like polycystic ovary syndrome (PCOS) characterized by elevated androgens and menstrual irregularities are frequently associated with significant insulin resistance (Dunaif, 1997). Androgens interfere with insulin receptor signaling and many women with PCOS exhibit hyperinsulinemia even in the absence of obesity. Low testosterone in men has been correlated with increased adiposity and impaired insulin responsiveness. Testosterone replacement in hypogonadal men has shown improvements in insulin resistance markers (Grossmann et al., 2008). Both growth hormone and insulin-like growth factor 1 act as key modulators within the endocrine network, influencing growth and metabolism. GH antagonizes insulin action in adipose tissue and the liver, especially when present in excess, as in acromegaly (On the other hand, Since IGF-1 mimics some functions of insulin, decreased levels of this hormone are linked to impaired insulin sensitivity in both diabetic and non-diabetic populations. Furthermore, Changes in the

levels of adipose-derived hormones such as leptin, adiponectin, and resistin are known to impact the body's sensitivity to insulin. Leptin resistance is common in obesity and can impair the central regulation of energy balance. Adiponectin which enhances insulin sensitivity is usually decreased in individuals with insulin resistance, whereas resistin levels tend to increase and contribute to inflammation and glucose dysregulation (Kadowaki & Yamauchi, 2005).

3.4 Inflammatory and Immune Mechanisms

Persistent low-level inflammation is now recognized as a key feature in the development and progression of insulin resistance. The inflammatory response typically predates the development of type 2 diabetes and is heavily influenced by obesity, nutritional choices, and other external factors. The immune system, particularly innate immune responses, interacts with metabolic pathways in a phenomenon termed "metaflammation" which is a chronic, sterile inflammatory state driven by metabolic excess (Hotamisligil, 2006). Visceral fat, a type of adipose tissue, has a key role in driving this mechanism. In obesity, expanding adipose tissue becomes hypoxic and stressed, which triggers the attraction and activation of immune cells, with macrophages being notably involved. Macrophages in adipose tissue switch from the anti-inflammatory M2 type to the pro-inflammatory M1 type, releasing cytokines like TNF-α, IL-6, and IL-1β (Weisberg et al., 2003). The action of these cytokines impairs insulin receptor function, resulting in lower glucose absorption by cells and enhanced hepatic glucose production.

As an early-identified cytokine in insulin resistance, TNF-α interferes with insulin action by increasing serine phosphorylation on IRS proteins, hindering the signaling cascade required for proper glucose absorption (Hotamisligil et al., 1996). IL-6and IL-1β similarly contribute to systemic insulin resistance by activating inflammatory cascades promoting hepatic

gluconeogenesis and inhibiting insulin stimulated glucose uptake in peripheral tissues (Donath & Shoelson, 2011).

Other than macrophages, other immune cells including T lymphocytes, B cells, mast cells and neutrophils contribute to the inflammatory response in metabolic tissues. T helper 1 (Th1) cells and cytotoxic CD8+ T cells increase inflammation in the body while regulatory T cells (Tregs) help to reduce the inflammation (Winer et al., 2009).

3.5 Inflammation and Decreased Effectiveness of Insulin

Inflammation plays a major role in the development of Insulin Resistance through the NLRP3 which is an inflammasome. When there is too much nutrition, lipids and oxidative stress in the body, inflammasomes get activated in the body which results in increased inflammation in the body. Activation of NLRP3 induces the release of interleukin-1β (IL-1β). This is a pro-inflammatory cytokine that interferes with the process of insulin signaling and damages the pancreatic β-cells of the body (Stienstra et al., 2010).

Higher levels of inflammation can be seen in people who are suffering from Insulin Resistance. It can be seen that levels of C-reactive protein (CRP) and fibrinogen are high and it helps in predicting the future risk of type 2 diabetes and heart disease (Pradhan et al., 2001).

3.6 Genetic Factors Behind Insulin Resistance

Insulin resistance is strongly influenced by genetics and IRS1 gene is the most studied. This gene encodes the protein IRS-1 which plays the role of conducting signals of Insulin from cell to cell. This gene has been associated with mutations and polymorphisms that may disrupt insulin signaling and make a a patient prone to type 2 diabetes (Ruchat et al., 2009). Glucose and lipid metabolism are regulated by a crucial gene known as PPARG. One of the most

common genetic variants Pro12Ala has been found to be relevant to insulin sensitivity and individuals with the Ala version are at lower risk of insulin resistance (Barroso et al., 1999). FTO gene which is often linked to obesity has been seen to have an influence on the progression of insulin resistance. The rs7903146 variant is also closely linked to the risk of type 2 diabetes and insulin resistance as it affects the insulin release and the way glucose is processed in the human body (Grant et al., 2006). Insulin signaling pathway components like AKT2 and GLUT4, whose gene products are glucose carrier (transporter) and essential part of the insulin pathway, can directly modulate cellular insulin responses when mutated (Taniguchi et al., 2006). Research has demonstrated that other genes such as IRS2, GCKR and MTNR1B which contribute to insulin resistance via modulation of different metabolic signals including liver glucose synthesis and circadian rhythms (Dupuis et al., 2010). In addition, insulin sensitivity can be altered by epigenetic modifications of DNA and histone protein structure and altered gene activity in response to lifestyle and environmental conditions (Ling and Rönn, 2019).

3.7 Emerging and Rare Causes of Insulin Resistance

A few rare and emerging causes have been identified behind insulin resistance but the most established are obesity and type 2 diabetes. Lipodystrophies is a genetic disorder in which fats are deposited in places they should not. For example, the liver, abdomen, cardiovascular system etc. AGPAT2, BSCL2 and LMNA genetic mutations are known to play a role in the development of the conditions (Garg, 2004). Due to the mutations in the INSR gene encoding the production of insulin receptor, there may be extreme cases of insulin resistance. The mutations cause disorders such as Donohue syndrome and Rabson-Mendenhall syndrome and its symptoms include severe hyperinsulinemia and growth problems (Musso et al., 2004). Certain endocrine disorders may pose as an influence on insulin sensitivity such as Cushing's syndrome which involves elevated cortisol levels present in the bloodstream for prolonged

time. It works by increasing glucose production in the liver and hence increased levels of insulin in the bloodstream to reduce the sugar level back to normal. Similarly, acromegaly caused by an overproduction of growth hormone can interfere with insulin action (Kreze et al., 2001).

Polycystic Ovary Syndrome (PCOS) is another important condition related with insulin resistance though it has become very common among the female. The presence of high androgen levels in PCOS disrupts insulin signaling in muscle and fat tissue (Goodarzi et al., 2011).

Chemicals like BPA, phthalates, and persistent organic pollutants, known as endocrine disruptors, interfere with insulin pathways and act as obesogens by encouraging obesity which subsequently leads to impaired insulin sensitivity (Heindel et al., 2017). These chemicals have been found to inhibit some receptors and function as antagonists that lead to disrupted hormonal activity. In addition to these, constant exposure to air pollution has been found to generate a systemic inflammatory response and reduced insulin sensitivity (Brook et al., 2013). Different hormonal receptors have also been found to also be antagonized by pollutants which eventually lead to insulin resistance. Insulin resistance can also occur due to autoimmune and chronic inflammatory diseases that interfere with normal insulin functions via inflammatory cytokines. (González-Gay et al., 2010).

Chapter 4

Prevention of Impaired Insulin Sensitivity

At the current rate at which people are being insulin resistant, it will be a leading cause behind the low quality of life and decreased life expectancy of humans. Therefore, controlling, identifying and acting on the solvable causes of insulin resistance have become a dire need. Finding new ways to cope up the modern lifestyle and staying healthy is the new challenge of modern age and necessary steps must be taken to ensure we can prevent Insulin Resistance. The possible solutions that we may adopt in our day to day life to prevent insulin resistance are-

4.1 Maintaining a Healthy Diet

A Nutrient rich diet can prevent insulin resistance and the risks associated with this disease.

Reducing Refined Carbohydrates and Sugars: Frequent consumption of refined carbs and added sugars leads to sharp spikes in blood sugar and insulin, fostering decreased insulin effectiveness. Replacing these with whole grains such as oats, quinoa, and brown rice, which digest more slowly and have a lower glycemic response, supports better insulin sensitivity (Ludwig, 2002).

- **Boost Fiber Consumption**: Soluble fiber found in foods like legumes, vegetables, fruits, and whole grains helps enhance insulin sensitivity by slowing glucose absorption and minimizing blood sugar spikes after meals. Research has demonstrated that high-fiber diets are linked to a reduced risk of insulin resistance and type 2 diabetes (Weickert & Pfeiffer, 2018).
- **Healthy Fats**: Eating unsaturated fats found in foods like olive oil, avocados, nuts, and fatty fish has been shown to enhance the body's sensitivity to insulin. In contrast, trans

fats and excessive saturated fat intake can impair insulin action (Salas-Salvadó et al., 2011).

- **Adequate Protein**: Incorporating lean protein from sources like tofu, beans, poultry, and fish helps balance blood glucose and limit sugar cravings, while excessive red or processed meat intake may negatively affect metabolic health.
- Anti-inflammatory medications, adopting healthy habits like exercising regularly and losing excess weight, combined with dietary supplements like omega-3 fatty acids and polyphenols, may significantly boost insulin sensitivity.

4.2 Maintain an Active Lifestyle

Staying physically active is crucial in lowering the chances of developing insulin resistance and in managing existing cases. By boosting glucose uptake in muscle tissue and reducing central fat, exercise plays a significant role in enhancing insulin sensitivity and combating IR.

- **Endurance training:** Engaging in activities such as walking, jogging, cycling, and swimming improves both heart health and insulin sensitivity. Studies indicate that 30 minutes of moderate exercise five times a week can significantly decrease the chances of developing insulin resistance (Colberg et al., 2010).
- **Resistance Training:** By increasing muscle mass, strength training boosts the body's capacity to store and utilize glucose. The best outcomes for insulin sensitivity come from combining aerobic exercise with resistance training.
- **Stay Active Throughout the Day**: Reducing prolonged periods of sitting is crucial. Incorporating small bursts of activity, such as stretching, walking, or standing, can prevent the negative effects of sedentary behavior on insulin action.

4.3 Achieve and Sustain an Ideal Weight

Abdominal fat, or visceral fat, along with overall excess body weight, plays a major role in the development of insulin resistance. Even a modest weight loss of 5-10% can lead to substantial improvements in insulin sensitivity and help reduce the likelihood of type 2 diabetes (Knowler et al., 2002). A healthy weight, supported by a well-rounded diet and regular exercise, is essential for preventing insulin resistance in the long run.

4.4 Minimize Stress

Persistent stress raises cortisol, a hormone that boosts glucose production in the liver and reduces insulin sensitivity. Stress-relief practices such as meditation, yoga, deep breathing, and getting enough sleep can help lower cortisol and enhance metabolic function (Lasselin et al., 2016).

4.5 Prioritize Sleep

Inadequate sleep and poor sleep quality raise the likelihood of developing insulin resistance by disrupting hormonal balance, leading to greater appetite, weight gain, and difficulties with glucose metabolism. To promote healthy insulin activity, adults are advised to get between 7 and 9 hours of quality sleep each night (Buxton & Marcelli, 2010).

Time restricted eating and intermittent fasting can improve the sensitivity to insulin, reduced inflammation and better blood sugar control (Patterson & Sears, 2017). These benefits may be mediated through reduced hepatic fat accumulation and improved mitochondrial function.

4.6 Avoid Smoking and Limit Alcohol Consumption

Smoking has been linked to increased inflammation and oxidative stress, which impair insulin signaling and contribute to IR. Quitting smoking significantly improves insulin sensitivity over time (Chiolero et al., 2008). Similarly, excessive alcohol consumption can worsen insulin resistance, particularly when it contributes to fat accumulation in the liver. Moderate alcohol intake, particularly red wine, may have protective effects, but it should be consumed cautiously.

4.7 Minimize Exposure to Environmental Toxins

Emerging research points to endocrine-disrupting chemicals, EDCs such as BPA and phthalates as potential contributors to insulin resistance, as they can disrupt hormonal and metabolic functions. Using BPA-free items and steering clear of plastic food storage containers can help minimize this exposure and reduce risk (Heindel et al., 2017).

4.8 Monitor and Address any Pre-existing Health Conditions

PCOS, metabolic syndrome, and sleep apnea are medical conditions that increase the likelihood of insulin resistance. Early diagnosis and management of the conditions including appropriate medical treatment and lifestyle modifications are a must for preventing Insulin Resistance.

Chapter 5

A Comparison

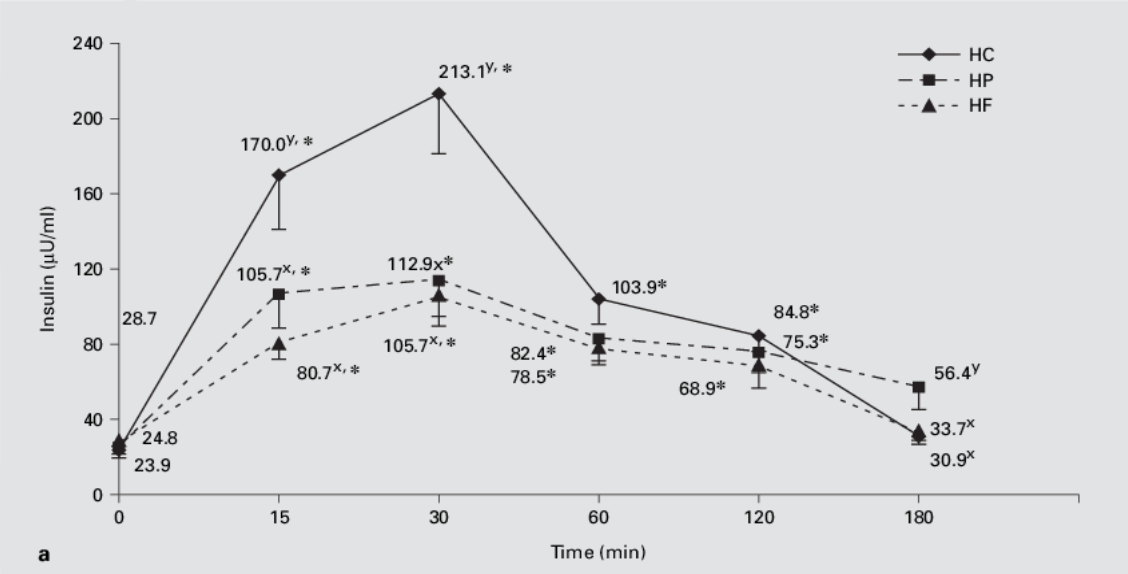

Fig 1- Comparison between insulin concentration after taking meals containing high carbohydrate, fat and protein (Khoury, 2006)

The diagram shows the difference in peak insulin levels after having meals containing high carbohydrate, fat and protein. The comparative data show that highest peak of insulin was found after having a meal of High carbohydrates whereas high protein and fats give a lower insulin spike. A: The serum insulin response after consuming high-carbohydrate (HC), high-fat (HF), and high-protein (HP) meals in adult males was analyzed. B: Changes in serum insulin levels from baseline were measured following HC, HF, and HP meals in adult males.

This is an indication that, meals of higher protein and fat content instead of carbohydrates are more effective at minimizing insulin spikes. Reduced amount and duration of insulin spikes prevents the body from getting desensitized to insulin and improves blood sugar management in the body.

Chapter 6

Conclusion

Insulin resistance (IR) develops by combination with many underlying factors. These include genetic, environmental and also physiological factors. Common causes like obesity, lack of physical activity and high-calorie diets are well established and the impact of these diseases increase by many folds due to chronic inflammation, abnormal fat deposition in the body and problems in insulin signaling due to genetic, environmental or habitual development. Modern research shows us that Insulin Resistance cannot be analyzed and viewed from a single perspective only. There are rare genetic disorders as well as common pollutions and habits of a person which causes the cellular and molecular defects and eventually damaging the way the body uses insulin. Pollution and use of chemicals in all the possible areas of our life is growing at an alarming pace that is also a contributing factor to the worsening of metabolic health of all ages and races. In some endocrine disorders, autoimmune disorders and rare metabolic disorders, insulin resistance may be a condition that is observed to affect a broad part of the body. It is impossible certainty say that Insulin Resistance is a result of just one factor. These multi-dimensional causes require an individual approach in order to prevent, diagnose and treat this condition. A deeper study will help us in knowing the effects of insulin resistance on our health. Research in this area may help us to develop a more personalized treatment, patient care and may help prevent complications such as diabetes type 2 and heart diseases frequently observed to develop with an insulin resistant patient. It can also be taken as precautions which help us in self-regulation and maintenance where we might check on ourselves and come up with a personalized guideline to follow so that we may not develop Insulin resistance and be a healthy person.

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