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A Review Study on the Effects of Insulin Resistance on Various Body Tissues

Research project

Submitted to the department of (Biology) in partial fulfillment of the requirements for the degree of BSc. in Biology

By

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DECLARATION

I declare that the research entitled **A Review Study on the Effects of Insulin Resistance on Various Body Tissues** is my own original work, and hereby certify that unless stated, all work contained within this research is my own independent research and has not been submitted for the award of any other degree at any institution, except where due acknowledgement is made in the text.

Signature:

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Date: /04/2023

SUPERVISION CERTIFICATE

This research has been written under my supervision and has been submitted for the award of the degree of bachelors of Science in Biology with my approval as a supervisor

Signature:

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Date:/04/2023

DEDICATION

I dedicate this work to:

- My dear parent who always pray for me and support me in everything, andmy sisters and brothers who are beside me.
- My supervisor
- Best friends who helped me.

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First of all, I wish to express my thanks to the most gracious "ALLAH", the facilitator in every step of my life and work.

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Abstract

The aims of our study are to provide information about the impacts of insulin resistance (IR) on many tissues of human body and to identify the main symptoms, causes and methods for treatment of this condition. It is a complex condition in which the body does not respond adequately to insulin which is, a hormone secreted by the pancreas with an essential role in the regulation of blood sugar levels. it is one of the major factors in the pathology of cardio metabolic diseases, which are commonly associated with peripheral IR consists of an impaired biologic response to insulin stimulation of peripheral target tissues, namely the liver, muscle and fat tissue. Generalized IR occurs primarily as a result of obesity, a consequence of caloric excess, physical inactivity, genetics, and age. It is associated with many serious medical conditions, such as type 2 diabetes mellitus hyper-tension, atherosclerosis, and metabolic syndrome. Four types of insulin resistance are present: type A, B, C, and secondary causes. Type A is associated with dysfunction or decreased number of insulin receptors; type B refers to antibodies against insulin receptors (e.g., leprechaunism with insulin-receptor mutations), and type C is characterized by post-receptor defects (lipodystrophies). There is pharmacological treatment for IR alone without obesity or other concomitant diseases.

Key words: Insulin resistance, Insulin, Pancreas, Obesity, Diabetes.

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1. Introduction

Insulin resistance (IR) is a state of decreased cellular sensitivity to insulin despite an elevated or normal serum insulin concentration, which is an expression of their dysfunction. The reduction in insulin utilization prompts pancreatic beta cells to produce and release increasing amounts of insulin in order to break down cellular resistance and correct the relative insulin deficiency (Yazıcı and Seze, 2017).

Insulin is a peptide hormone synthesized and secreted by the beta cells of the pancreas. Glucose is the main regulator of insulin secretion; as the glucose concentration increases, it stimulates insulin secretion. Some of the glucoregulatory effects of insulin are inhibition of glycogenolysis and gluconeogenesis, increased transportation of glucose into adipose tissue and muscle, stimulation of glycogen synthesis, as well as a playing a major role in lipid and protein metabolism (Edgerton *et al*., 2006)

New studies have shown that liver and fat cells may also develop IR in subjects with the metabolic syndrome, like hyperglycemic. Abdominal adiposity may cause IR in subjects with the metabolic syndrome by intracellular accumulation of acyl CoA and triglyceride, an increased production of peptides from the adipose tissue, such as tumor necrotic factor (TNF) alpha and reduced production of adiponectin may also play a role. The mechanism by which free fatty acid (FFA) and triglyceride, together with the peptides, may induce IR at a cellular level, resulting in reduced glucose transport (Beck-Nielsen, 2002).

Insulin resistance can be treated as a symptom or consequence of obesity, the main causal treatment seems to be anti-obesity management, which consists of three main steps: lifestyle changes (nutritional treatment, exercise), pharmacotherapy and metabolic (bariatric) surgery (Golacki *et al*., 2022)

Since obesity and insulin resistance are widely distributed in our society, therefore, we have made this review study in order to:

1-Provide information about the impacts of IR on many tissues of human body.

2- Identify the main symptoms, causes and methods for treatment of IR.

2. REVIEW OF LITERATURE:

2.1. Structure and Function of Pancreas

The pancreas is a secondary retroperitoneal organ located in the upper part of the abdomen. Macroscopically, it has conventionally been divided into three main parts: the head, the body, and the tail that act is a key organ in overall body homeostasis; it is responsible for regulating macronutrient digestion and releasing hormones that control digestive processes and the blood glucose level. It has two distinct components: the exocrine pancreas and the endocrine islets (walkowska *et al.,* 2022).

Exocrine pancreas the portion of the pancreas that makes and secretes digestive enzymes into the duodenum. This includes acinar and duct cells with associated connective tissue, vessels, and nerves. The exocrine components comprise more than 95% of the pancreatic mass. Endocrine pancreas, the portions of the pancreas (the islets) that make and secrete insulin, glucagon, somatostatin and pancreatic polypeptide into the blood. Islets comprise 1-2% of pancreatic mass (Daniel, 2021).

Additionally, exocrine pancreatic acinar cells constitute most of the pancreatic tissue; these cells produce digestive enzymes which are transported via the pancreatic ducts. The endocrine pancreas is illustrated with all cell types; 1; Beta cells 2; Alpha cells 3; Epsilon cell 4; Pancreatic polypeptide 5; Delta cells (Fig 2.1). The cells are arranged in compact islets and secrete a number of classical and 'no classical' peptides, as depicted (English and Irwin, 2019.)

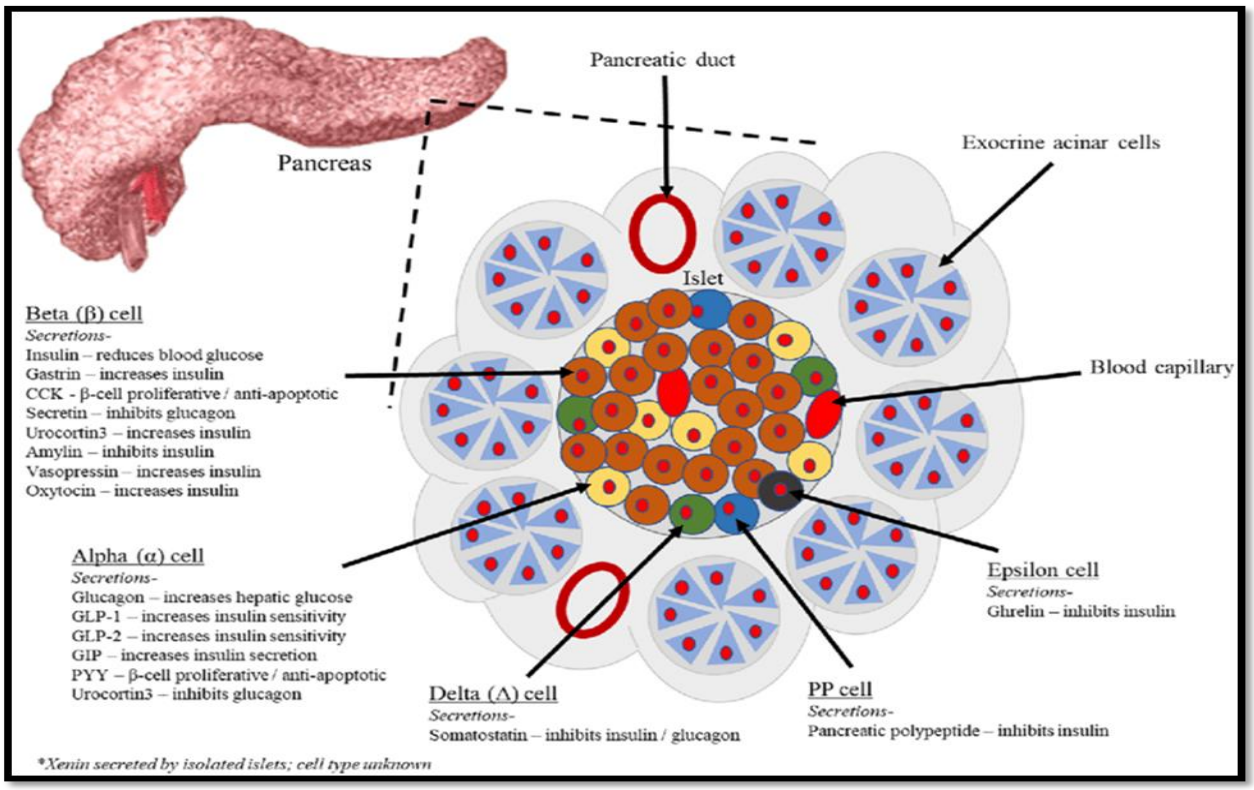

Figure 2.1: Types and functions of pancreatic cells. (English and Irwin, 2019).

1- Beta Cells and Insulin

Pancreatic beta cells are endocrine cells that synthetize, store, and release insulin, the anti-hyperglycemic hormone that antagonizes glucagon, growth hormone, glucocorticosteroids, and epinephrine, to maintain circulating glucose concentrations. In an adult human being, beta cells release ~30–70 U insulin per day (mainly depending on body weight), half of which is secreted after meals and the rest under basal conditions (Marchetti *et al.*, 2017).

The main hormone produced from beta cells is insulin. It is derived from a precursor peptide, proinsulin. Proinsulin is cleaved to form two products, insulin and C-peptide. While insulin is known for its effects in glucose metabolism, C-peptide has no known metabolic effects. C-peptide has a 1:1 stoichiometry with insulin and due to having a longer half-life than insulin; it is often used in the insulin treatment. Its

measurement also plays a role in distinguishing between Type1 and 2 diabetes (Xavier, 2018).

2-Alpha Cells and Glucagon

Alpha cells comprise 15 - 20% of islet cells in humans and produce the hormone glucagon .Glucagon is released from pancreatic α-cells as a response to hypoglycemia. Glucagon then serves as a signal to mobilize glucose from the liver to restore blood glucose levels back to normal. The discovery of glucagon occurred only two years after Banting and Bests discovery of insulin. The first notion of glucagon came when Murlin and coworkers detected that pancreas extracts contain a second hormone with the ability to increase blood glucose. They gave this hormone the name "glucagon" from its function as a glucose agonist (Wendt and Eliasson, 2020).

3-Epsilon Cells and Ghrelin

Epsilon cells represent less than 1% of islet cells in humans. They secrete ghrelin, which was first identified as a ligand leading to the secretion of various growth hormones. It also plays a role in modulating appetite. Ghrelin is produced by numerous tissues throughout the body including the GI system and its levels are increased during fasting. The hormone can regulate blood glucose by suppressing insulin release from beta cells. Ghrelin has been found to increase glucagon secretion. Ghrelin secretion has also been shown to be inhibited by glucagon level (Sakata. *et al.*, 2019).

4- Pancreatic Polypeptide (PP) Cells

Pancreatic Polypeptide cells make up about 1-2% of the islet population. Secretion of pancreatic polypeptide is regulated by vagal and enteric nervous input. It is not responsive to glucose. Pancreatic polypeptide has been shown to be an inhibitor of glucagon during low glucose (Breton *et al.*, 2015).

5- Delta cell

Pancreatic δ–cells secrete the hormone somatostatin (SST). δ–cells are also present in the hypothalamus, central nervous system (CNS), peripheral neurons and the gastrointestinal tract Somatostatin, also known as growth hormone inhibiting hormone (GHIH) or somatotropin release-inhibiting hormone (SRIF), inhibits most cellular secretions and was discovered in ovine hypothalamus.(Brereton, *et al*., 2015).

Somatostatin secreting cells, or δ-cells, is present in the pancreatic islets, the hypothalamus, the central nervous system, peripheral neurons and the gastrointestinal tract. Δ-cells make up about 10% of the islet cell population. Somatostatin is a negative regulator of insulin, glucagon and pancreatic polypeptide secretion under conditions of nutrient stimulus (Xavier, 2018).

2.2. Insulin

Insulin is a peptide hormone secreted in the body by beta cells of islets of Langerhans of the pancreas and regulates blood glucose levels (Thota and Akbar, 2021). The insulin molecule consists of 51 amino acids arranged in two chains, an A chain (21 amino acids) and B chain (30 amino acids) that are linked by two disulfide bonds (Donner and Sarkar, 2015). It regulates carbohydrate, fat, and protein metabolism by providing glucose in the blood to pass to fat, liver and skeletal muscle cells (AL.et *al*, 2017).

2-3. Insulin resistance

Insulin resistance is a complex condition in which the body does not respond adequately to insulin, a hormone secreted by the pancreas with an essential role in the regulation of blood sugar levels. This condition is one of the major factors in the pathology of cardio metabolic diseases, which are commonly associated with peripheral IR consists of an impaired biologic response to insulin stimulation of peripheral target

tissues, namely the liver, muscle and fat tissue. More recently, central insulin resistance has been highlighted as fundamental also in cardio metabolic diseases since insulin plays an important role at brain circuitries that control food behavior and autonomic activity Moreover, brain IR is associated with Alzheimer's Disease and Parkinson Disease (Martins and Conde ., 2022).

As well as, IR impedes glucose removal, giving rise to hyperinsulinemia, and it is a widespread condition affecting numerous organs and insulin-regulated pathways. patients with mild to moderate chronic kidney diseases (CKD) frequently have IR, individually identified as a nontraditional health concern and an important determinant of cardiac events in ESRD (Sinha and Haque., 2022).

Generalized IR occurs primarily as a result of obesity, a consequence of caloric excess, physical inactivity, genetics, and age. It is associated with many serious medical conditions, such as type 2 diabetes mellitus, hyper-tension, atherosclerosis, and metabolic syndrome (Abel and Ramasamy ., 2012).

Four types of insulin resistance have been described: type A, B, C, and secondary causes. Type A is associated with dysfunction or decreased number of insulin receptors; type B refers to antibodies against insulin receptors (e.g., leprechaunism with insulin-receptor mutations), and type C is characterized by post-receptor defects (lipodystrophies). The vast majority of patients, however, have secondary insulin resistance (e.g., impaired glucose tolerance, diabetes, obesity, stress, infection, uremia, acromegaly, glucocorticoid excess, and pregnancy) (Hermann's *et al.*, 2004).

Interestingly, around 50% of the patients with IR, despite compensatory hyperinsulinemia, present with some degree of hyperglycemia (100 mg/dl). Yet, not all patients with hyperinsulinemia and IR will develop glucose intolerance or diabetes. It is important to acknowledge that virtually every patient with T2D will have IR years or at least months before the diagnosis of diabetes (González *et al.*, 2017).

2.4 Insulin resistance in various organ and tissues

2.4.1 Insulin resistance in liver

Mice that lack insulin receptors specifically in the liver exhibit IR, glucose intolerance, and a failure of insulin to suppress hepatic glucose production and to regulate hepatic gene expression (Michael *et al.*, 2000). A similar phenotype was demonstrated for mice in which PI3K activity was inhibited specifically in the liver as a result of the expression of a dominant negative mutant of this enzyme. These observations suggest that insulin resistance in the liver contributes to the pathogenesis of type 2 D, consistent with results obtained with cultured cells (Miyake *et al.*, 2002).

2.4.2 Insulin resistance in muscles

Transgenic mice that express a dominant negative mutant of the IGF-1 receptor specifically in muscle develop IR and early-onset diabetes (Fernández *et al.*, 2001), loss of insulin signaling via insulin receptors in muscle may be compensated for by IGF-1 receptor signaling. Mice that lack insulin receptors in adipocytes are lean and are protected against obesity-related glucose intolerance. Suggesting that insulin signaling in adipocytes per se may not contribute to the systemic IR associated with obesity (Blüher, *et al.*, 2002).

2.4.3- Insulin resistance in brain

Surprisingly, studies of mouse models with targeted mutations in genes that encode mediators of insulin signaling have suggested that such signaling in neoclassical insulin target tissues, such as the brain and pancreatic b cells, plays an important role in the regulation of energy metabolism. The importance of insulin signaling in the central nervous system for the regulation of energy metabolism as well as for reproduction was directly demonstrated by the generation of mice that lack insulin receptors in the brain (Bruning *et al.*, 2000).

Transgenic rescue of insulin receptor–deficient mice also suggested that insulin action in the brain plays a dominant role in maintenance of energy homeostasis (Okamoto *et al*., 2004).

2.4.4- Insulin resistance in pancreas

In some people, the immune system attacks the islets, and they cease to produce insulin or do not produce enough. When this occurs, blood glucose stays in the blood and cells cannot absorb them to convert the sugars into energy. This is the onset of type 1 diabetes, and a person with this version of diabetes will need regular shots of insulin to survive (Sarode., *et al*., 2020).

2.4.5- Insulin resistance in adipose tissue

Adipocytes and adipose tissue are central players in the pathogenesis of IR associated with obesity. Adipocytes are not merely a site for storage of energy in the form of triglycerides but also a source of many adipokines, some of which including leptin, TNF-a, resistin, adiponectin, retinol-binding protein 4 (RBP4), and monocyte chemo attractant protein–1 (MCP-1) — are implicated in the pathogenesis of insulin resistance associated with obesity in rodents (Kadowaki *et al*., 2006).

In addition, Herman and Kahn describe the role of RBP4 in IR associated with obesity (Herman, 2006). Chronic inflammation of white adipose tissue characterized by macrophage infiltration (Furukawa *et al.*, 2017) is thought to contribute to insulin resistance associated with obesity. Adipocyte MCP-1 and its receptor CCR2 may play a role in the recruitment of macrophages to white adipose tissue and in the initiation of an inflammatory response in mice (Kanda *et al*., 2006).

Furthermore, increased secretion of MCP-1 from adipocytes of obese mice may thus trigger such macrophage recruitment, and the infiltrated cells may in turn secrete a variety of chemokine’s and other cytokines that further promote a local inflammatory

response and affect gene expression in adipocytes, resulting in systemic insulin resistance.(Kasuga,. 2006).

2.4.6- Insulin resistance in heart

Recent studies have implicated novel mechanisms that may directly contribute to the pathophysiology of insulin resistance and its cardiovascular complications (Samuel and Shulman, 2012) such as changes in AMPK signaling **(**Saha *et al*.,2011), oxidative stress **(**Folli *et al*., 2011), inflammation(Hardy *et al.*, 2012), advanced gyration end products (AGEs) **(**Puddu and Viviani, 2011), endoplasmic reticulum (ER) stress)(Cnop *et al.*,2012), autophagy(He *et al.*, 2012), and changes in adipokines (Ouchi *et al.*, 2011).

2.4.7- Insulin resistance in skin

It is important to acknowledge that obesity and T2D are associated with a considerable number of dermatomes, including acanthosis nigricans, acrochordons, hirsutism, and keratosis pilaris, among others (Yosipovitch *et al.*, 2007). Specifically in patients with diabetes, at least one-third will present some type of skin manifestation during the course of their disease. A recent study reported that 91% of patients with diabetes have at least one dermatologic manifestation (Murphy *et al.*, 2013).

2.5- Clinical correlations:

2.5.1- Insulin resistance and obesity

Obesity is the leading cause of IR, and obese individuals tend to have higher plasma FFAs as a result of decreased suppression of lipolysis by insulin resistance. It is also believed that an impaired ability of adipocytes to store excess calories as triglycerides also contributes to increased accumulation of lipids and their metabolites in other tissues that are not necessarily adapted to lipid storage such as muscle and liver. As a consequence, the accumulation of lipid metabolic intermediates incites a variety of

cellular abnormalities such as apoptosis, oxidative stress, and ER stress, which impairs cellular function (O'Shea *et al*., 2012).

2.5.2- Insulin Resistance and Type 2 diabetes mellitus

Fasting plasma C6H12O6 echelons of over 126 mg/dL, oral glucose tolerance test (OGTT) values of over 200 mg/dL after two hours, HbA1C values of over 6.5%, or the usage of antidiabetic drugs are all indicators of diabetes mellitus (Ghazanfari *et al.*, 2010). Chronic hyperglycemia gradually leads to IR and is thereby associated with the pathogenicity of T2DM (Sinha and Haque, 2022).

Rats fed a high-fat diet (HFD) along with the injection of low doses of streptozotocin (STZ) develop T2DM, which is an insulin-resistant condition (Guo *et al.*, 2018). Another study found that prostaglandin E1 (PGE1), one of the hormones most tissues produce to control blood flow, hindered IR and alleviated renal dysfunction in T2DM rats' kidneys. Furthermore, they showed that PGE1-persuaded IR was restored as a consequence of the decrease in autophagy and subsequent overexpression of the resultant molecule fibroblast growth factor-21 (FGF-21) (Li *et al*., 2018).

Numerous degenerative events in DN possibly are the major impairments in the stimulation by insulin and their transformation path in glomerular epithelial cells. Past research found a strong relationship between DN and glomerular podocyte structural damage and malfunction. In diabetic and nondiabetic glomerular pathologies, a decline in the proportion of podocytes results in proteinuria and glomerulosclerosis (Lewko and Stepinski, 2009).

Exposition to elevated glucose concentration causes many cellular abnormalities in insulins' usual target cells, such as muscles, adipocytes, and hepatocytes. Apart from the representative insulin target tissues, insulin affects the majority of human organs and cells, for instance, the kidneys and arteries, by modifying the hemodynamics, podocyte, and tubular function (Samir and Debleena 2007).

2.5.3- Acanthosis Nigricans

Acanthosis nigricans (AN) is a common cutaneous finding characterized by velvety, hyperpigmented plaques and is usually related to conditions associated with in IR (e.g., T2D and obesity). However, in rare cases it may develop as a sign of internal malignancy (e.g., aggressive adenocarcinomas of the gastrointestinal tract) (Sinha and Schwartz, 2007).

The pathogenesis is similar to that of acrochordons and results from growth factor stimulation of keratinocytes and fibroblasts in the dermis. The tyrosine kinase receptor family includes insulin, IGF, epidermal growth factor, and fibroblast growth factor receptors, among others. An increase in the insulin concentration translates into keratinocyte and fibroblast proliferation due to stimulation of IGF-1 receptors (Barbato *et al.*, 2012). Clinically AN is characterized by symmetrical, velvety, light brown to black thickened plaques with accentuation of skin marks, typically located in intertriginous areas **(**Kluczynik *et al*., 2012).

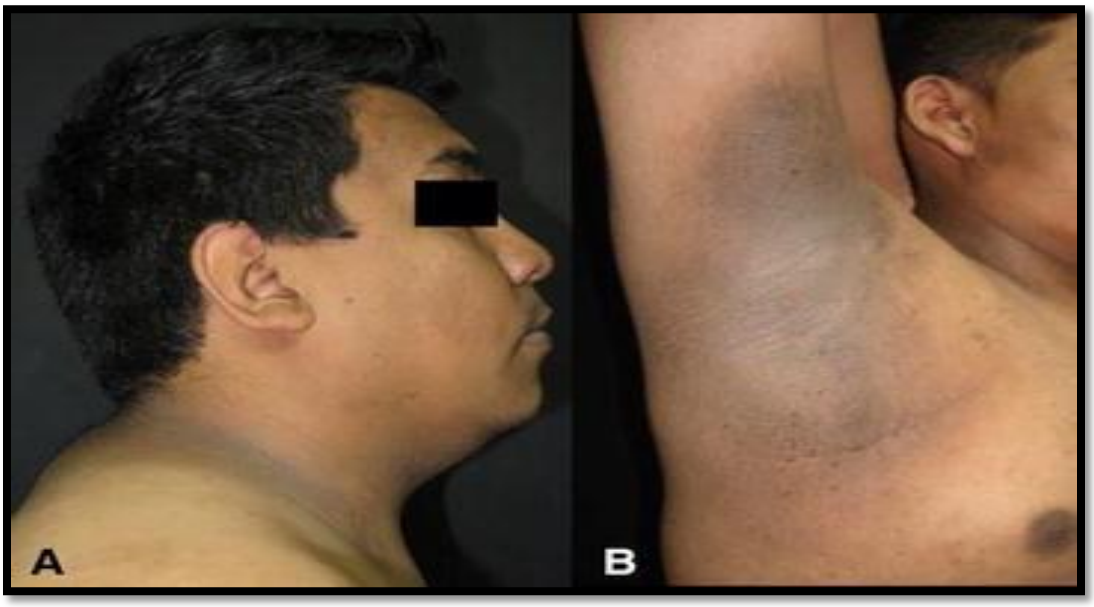

Figure 2.2- Acanthosis nigricans in the neck (a) and axillae (b). Characteristic hyperpigmented, thickened, brown plaques with a velvety and smooth appearance in a male patient (González *etal*., 2017).

Histopathology changes are subtle and consist of hyperkeratosis, acanthuses, and mild papillomatosis (Fig. 2.3). The dermis is usually normal, but can present with elongated dermal projections. One study demonstrated that the most frequent finding was hyperkeratosis in 100%, followed by papillomatosis in 90% of biopsies; a less frequent finding was irregular acanthosis in 26.6% of biopsies. The brownish color of this dermatosis is due to the thickening of the stratum corneum; however, a silver nitrate stain can sometimes show melanin. (Puri, 2011).

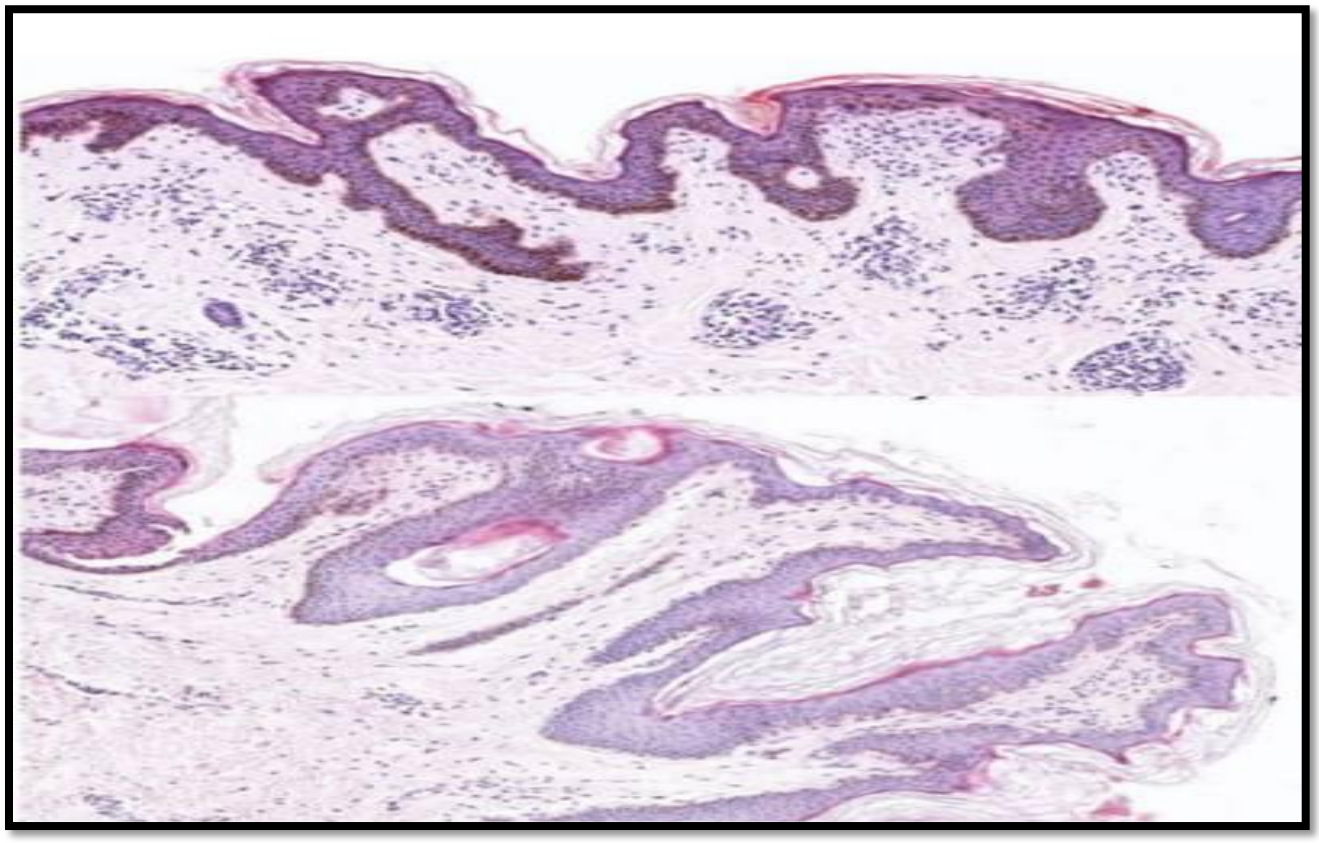

Figure 2.3- Biopsy from the neck of a patient with acanthosis nigricans, showin histological features of orthokeratotic hyperkeratosis, mild acanthosis, and papillomatosis (hematoxylin and eosin, original magnification 40x.

It is recommended that all overweight or obese patients are screened for abnormal fasting glucose and/or liver function tests. For most cases (obesity-induced AN), weight loss and exercise should be recommended as the first-line therapy (i.e., by

increasing insulin sensitivity and reducing insulin resistance) (Phiske, 2014) Some authors, however, have reported the use of oral or topical retinoids (probably regulating the proliferation and differentiation of keratinocytes) as effective treatments (Higgins *et al.*, 2008).

2.6. Treatment of Insulin Resistance

Given that IR can be treated as a symptom or consequence of obesity, the main causal treatment seems to be anti-obesity management, which consists of three main steps: lifestyle changes (nutritional treatment, exercise), pharmacotherapy and metabolic (bariatric) surgery (Gołacki *et al*., 2022).

2.6.1 Lifestyle Changes:

According to Kanaley *et al*., (2022) the mainstay of treatment for overweight and obesity is to achieve a negative energy balance by changing eating habits and increasing physical activity. In nutritional treatment, it is recommended that:

- The diet should be low energy (low carbohydrate, low glycemic index, low fat).
- It should be dependent on the patient's body weight and physical activity.
- The meals should be regular and frequent (4–5 times a day).
- Regular physical activity with weight loss can reduce the impact of manycardiometabolic risk factors, such as hyperglycemia and IR.
- Aerobic exercise (30–60 min of moderate to high intensity most days of the week) to achieve weight and adipose tissue loss, including a reduction in visceral abdominal and ectopic fat around the heart and in the liver. Brisk walking, Nordic walking, swimming and cycling are recommended (Paquin *et al.*, 2021).

2.6.2. Insulin resistance pharmacotherapy

The literatures recommend no pharmacological treatment for IR alone without obesity or other concomitant diseases. There are no recommendations for the use of thiazolidinediones—drugs that improve insulin sensitivity—in female patients without type 2 diabetes. The results of studies on specific combinations of bacteria in probiotic preparations have shown they can reduce IR (Szulińska *et al*., 2018).

3. Conclusion

We concluded from this review study the following;

1. Insulin resistance is a complex condition in which the body does not respond adequately to insulin, a hormone secreted by the pancreas with an essential role in the regulation of blood sugar levels.
2. IR occurs primarily as a result of obesity, a consequence of caloric excess, physical inactivity, genetics, and age. It is associated with many serious medical conditions, such as type 2 diabetes mellitus hyper-tension, atherosclerosis, and metabolic syndrome
3. Pharmacological treatment for IR alone without obesity or other concomitant disease

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