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REVIEW ARTICLE

The complications of long time treatment of insulin therapy in type-2 diabetes patients: A Review

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ABSTRACT

Diabetes is a chronic metabolic disease characterized by elevated blood sugar levels. It can also mean long-term problems with the metabolism of carbohydrates caused by insulin deficiency, which leads to hyperglycemia and glycosuria. Weight gain is a common side effect of insulin therapy and other oral antidiabetic medications for diabetic patients, which can hinder their ability to meet strict glycemic targets and potentially reduce treatment success. Insulin-related weight gain is attributed to anabolic effects, appetite increases, and reduced glycosuria. Insulin therapy has been linked to increased cardiovascular risk and mortality in type 2 diabetes patients, as well as inflammation, atherosclerosis, hypertension, dyslipidemia, heart failure, and arrhythmias. Large-scale evaluations suggest that insulin therapy has a poorer short- and long-term safety profile than other anti-T2D therapies. To treat diabetes, a variety of insulin formulations are available, each acting at a distinct pace. Whether they are long-acting, intermediate-acting, or rapid-acting, there are similar adverse effects to be mindful of. Weight gain, injection site responses, and hypoglycemia (low blood glucose) are common side effects of insulin. Lipodystrophy, or improper fat distribution, and limb edema are uncommon adverse effects of insulin. When it comes to insulin introduction, titration, and follow-up treatment, doctors can manage patients with type 2 diabetes mellitus more effectively by employing simple algorithms. Primary care doctors and other medical professionals can manage patients with type 2 diabetes mellitus more easily by using streamlined insulin introduction and titration protocols.

Keywords: insulin therapy; diabetes mellitus; chd, cvd; wight gain

1. Introduction

Hyperglycemia, or elevated blood sugar, is a complication of diabetes mellitus (DM), a chronic illness that is complicated and results from insufficiencies in insulin secretion, action, or both. The persistent metabolic imbalance associated with this condition puts patients at considerable risk for long-term macro- and microvascular issues. They run a higher risk of recurring hospital stays and other problems, like a higher chance of cardiovascular diseases, if they do not receive high-quality care (CVDs)[1]. In other words, it is a complex metabolic disorder characterized by ongoing hyperglycemia and abnormalities in the metabolism of proteins,

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lipids, and carbohydrates brought on by insufficiencies in either insulin action or secretion, or both. Diabetes mellitus is considered one of the major threats to human health in the twenty-first century. The World Health Organization (WHO) estimates that 70 million people in developing countries suffer from diabetes mellitus. In these nations, diabetes is becoming more common. Type 2 diabetes (T2D) affects more than 200 million people worldwide, and by 2030, 438 million people are predicted to have the disease. Over the past century, changes in human behavior and lifestyle have led to a sharp rise in the incidence of diabetes globally[2].

Diabetes mellitus, either type 1 (T1DM) or type 2 (T2DM), is a complex autoimmune illness whose vulnerability is influenced by a mix of environmental and hereditary variables[3]. Diabetes is mostly caused by insulin resistance or a shortage of insulin. The most important energy source for all metabolic functions is glucose. The insulin hormone, which is secreted by the pancreas, is vital for regulating blood sugar levels and glucose transport. Usually, it is diabetes that is not insulin-dependent. Genetic susceptibility[3], environment, behavior (calorie intake and physical exercise), and as-yet-unexplained risk factors all contribute to type 2 diabetes. Adults and those who are overweight are usually affected. The symptoms of type 2 diabetes develop gradually. Furthermore, symptoms do not appear as quickly as they do in type 1 diabetes. Possible symptoms include fatigue, increased thirst and appetite, weight loss, blurred vision, and slow wound or sore healing. Some folks may not have any symptoms at all. Type 2 diabetes is primarily caused by three pathophysiological defects: increased β-cell apoptosis/insufficient insulin secretion, reduced peripheral glucose uptake by insulin-sensitive tissues, and excessive hepatic glucose synthesis[4]. When Type 2 Diabetes is clinically diagnosed, fasting glucose tolerance, fasting plasma glucose (FPG), and HbA1c can all be used to estimate the risk of mortality[5]. The main causes of the rising incidence of Type 2 diabetes in genetically predisposed persons are decreased physical activity, increased portion sizes from unhealthy foods, and poor dietary intake[6]. It is important to remember that because type 2 diabetes is progressive, achieving appropriate glycemic control necessitates a combination of antihyperglycemic medications and lifestyle adjustment, including diet and exercise[7]. Insulin is the most potent anabolic hormone that can lower blood sugar levels. It is advised for use as the only treatment for T1DM and in T2DM patients whose blood sugar levels cannot be controlled with oral hypoglycemic medications[2]. Insulin release from beta cells happens throughout the day in a dose-dependent way. Insulin is secreted in response to an oral carbohydrate diet in a dose-dependent way. This involves a significant release of insulin in the first phase, which suppresses the creation of glucose in the liver, and a slower release of insulin in the second phase, which covers the carbs that are consumed[3]. Diabetes mellitus is a chronic condition that affects a vast number of people worldwide. It is typified by a failure to maintain glycemic control and increasing beta cell failure[5]. Diabetes also puts a strain on health care systems, increasing both direct and indirect expenditures, and is a major cause of morbidity and mortality. Insulin doses are needed for treatment when multi-drug therapies and lifestyle changes are ineffective in lowering blood sugar levels[6]. Effective control of prandial and post-prandial sugar levels is crucial to prevent side effects and life-threatening complications of diabetes[8].

2. Discussion

2.1. Hypoglycemia and increased mortality

Insulin therapy has been linked to an increased risk of severe hypoglycemia in patients with type 2 diabetes. This is due to the drop in HbA1c to less than 7.0% in patients treated with rigorous insulin therapy and oral antihyperglycemic medications. Severe or continuous insulin therapy can increase the risk of experiencing hypoglycemia, which affects 10% of people with type 2 diabetes. Bilateral presbyopia, an uncommon ocular problem, is often associated with severe hypoglycemia when starting therapy[9].

Anecdotal reports reveal that severe hypoglycemia is more common in patients treated with insulin or insulin secretagogues, and that hypoglycemia and reduced glycated hemoglobin levels are associated with an increased risk of death in patients with diabetes or hyperglycemia hospitalized for myocardial infarction[10].

Recent studies on the impact of intensive glucose control on macrovascular outcomes in type 2 diabetes patients have not shown significant reductions in cardiovascular events or mortality, despite a 15% reduction in myocardial infarction risk[11].

2.2. Cardiovascular diseases

CVD-related mortality is higher in prandial insulin-treated individuals, with a progressive increase in mortality as the treatment median HbA1c decreases. The pathological processes and risk factors associated with CVD begin as early as childhood, with obesity and abnormal lipid profiles strongly correlated with insulin resistance[11]. Insulin stimulates metabolic substrates in various tissues, including heart, skeletal muscle, liver, and adipose tissue. Insulin resistance leads to hyperinsulinemia, causing the pancreas to secrete more insulin, resulting in hyperinsulinemia. This review will focus on the interactions between insulin resistance and vascular disease, focusing on major changes in glucose and lipid metabolism induced by insulin and their impact on CVD development. Elevated levels of LDL, smoking, elevated blood pressure, type 1 and type 2 diabetes, and inflammation can also lead to and predict adverse cardiovascular events. Insulin resistance is related to disorders such as hypertriglyceridemia and low HDL levels[6,8].

Long-chain fatty acid oxidation produces 50-70% of required ATP for the myocardium, while glycolysis contributes less than 10%. A balance between lipid degradation and glucose oxidation could decrease diabetic cardiomyopathy[9]. Dyslipidemia, induced by insulin resistance and type 2 diabetes, is characterized by high plasma triglycerides, low HDL levels, and small dense low-density lipoproteins. Hypertriglyceridemia increases the incidence of cardiovascular disease by 32% in men and 76% in women. Obesity is a global epidemic linked to type 2 diabetes and cardiovascular disease. Abnormal concentrations of lipids and apolipoproteins can cause changes in lipoprotein production, leading to increased basal lipolysis and proatherogenic phenotype[12].

2.3. Coronary heart disease

Type 2 diabetes (T2D) is a significant risk factor for cardiovascular disease, with hyperglycemia and

insulin resistance often linked to atherosclerosis. Insulin-containing regimens have been associated with a 2.5-fold increase in the risk of cardiovascular events, with no risk found for metformin use[13]. In the Saskatchewan Health registry, the relative risk for mortality increased from 1.75 to 2.79 as insulin exposure increased. Insulin induces vasorelaxation mediated by endothelium-derived nitric oxide (NO) in isolated rat skeletal muscle arterioles, and in healthy humans, it has a stimulating effect on NO-dependent basal blood flow and agonist-stimulated endothelium-dependent vasodilation[14]. However, these effects are blunted in patients with obesity-associated insulin resistance or type 2 diabetes. The U.K. Prospective Diabetes Study[15] (UKPDS) and the Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) trial have shown significant benefits in treating T2D, with the UKPDS showing a non-significant 16% reduction of the relative risk of myocardial infarction in patients managed with an intensive treatment policy of blood glucose control, and the DIGAMI trial showing a significant 28% reduction of the relative risk of 1-year total mortality in patients receiving an insulin-glucose infusion in the acute phase[16].

2.4. Weight gain

Insulin therapy often leads to weight gain, which can be influenced by factors such as the degree of glycemic control, treatment duration, the insulin regimen, and the combination of oral medications taken concurrently[17]. In Finland, a study involving patients with glucose intolerance found that adopting lifestyle modifications could maintain insulin secretion and raise insulin sensitivity, but only in those patients who could maintain weight loss[16]. The mean weight increase was 8.7 kg in a trial where intense multiple-dose insulin therapy was used for six months to normalize the HbA1c. Insulin patients may experience weight gain due to a mechanism involving a decrease in glycosuria. However, insulin's direct effects are evident, as other hyperglycemia treatments are either weight neutral or cause weight loss. Long-term educational interventions promoting lifestyle changes, including diet and exercise, are crucial for type 2 diabetes patients[18].

2.5. Risk of cancer

Insulin resistance is a significant risk factor for cancer in individuals with type 2 diabetes, with a higher incidence of pancreatic, hepatobiliary, colon, and breast cancer compared to control populations[19]. This association may be due to factors such as obesity, hyperglycemia, insulin resistance, and the type of anti-hyperglycemic therapy used. A retrospective analysis comparing patients with hepatocellular carcinoma and control subjects found an odds ratio (OR) for hepatocellular carcinoma in patients treated with sulfonylureas or insulin to be 2.99, compared to 0.33 for patients treated with metformin[20]. The prevalence of diabetes in patients with hepatocellular carcinoma was 31.2%, compared to 12.7% in control subjects[21].

The role of insulin as a risk factor for cancer remains unknown, with conflicting reports about the risk of cancer in insulin-treated patients. A systematic review and meta-analysis of case-control and cohort studies summarized the epidemiologic evidence on the risk of cancer associated with insulin-treated DM, aiming to evaluate whether the association varied by study design, type of DM, and site of cancer. Insulin use appeared to be a better predictor of cancer risk in North American populations than in European populations[22]. Several

mechanisms for the effect of insulin on cancer risk are proposed, including insulin resistance and consequence hyperinsulinemia, which are typical features in most patients with diabetes. To clarify the risk profile for individual forms of cancer in insulin-treated patients, a large database is needed[23].

2.6. Renal disease

Insulin therapy is a crucial component in managing diabetic patients with renal failure, a leading cause of end-stage renal disease (ESRD) in the United States[24]. Renal failure accounts for 10% of deaths in type 2 diabetes patients and 44% of ESRD incidence instances. Lipohypertrophy may arise from dermatological reactions to insulin, as the hormone is lipogenic and likely mediated by the immune system. Infections can complicate subcutaneous insulin injections if appropriate hygiene is not maintained[25]. Immunologic responses to insulin, particularly animal insulin formulations, include the formation of anti-insulin antibodies, which can prolong the insulin absorption half-life. Individuals may be especially sensitive to the metabolic adverse effects of insulin therapy when treating diabetic ketoacidosis (DKA)[26], which promotes phosphate's intracellular transport, often causing hypophosphatemia. Hematologic effects from insulin-induced hypoglycemia include an enhanced increase in the concentration of von Wile brand factor, which may predispose patients to reduced peripheral perfusion or embolic phenomenon. Cronic renal failure (CRF) is associated with diverse alterations in carbohydrate and insulin metabolism, and adequate glycaemic control has been associated with a reduction in the onset and progression of diabetic nephropathy, morbidity, and mortality in uraemic diabetic patients during dialysis[27].

Table 1. The list of side effect of long time treatment of Insulin therapy.

Authors Name	Year	Side Effect
Holman R; Farmer AJ et al	2009	Hypoglycemia and increased mortality
Steven E, Jeremy P, et al	2014	
Bonds DE; et al	2010	
Duckworth W , et al	2009	
Ryysy L, Vanamo R, et al	1999	Weight gain
Steven E, Jeremy P, et al	2014	
Heller S.	2004	
Skyler JS , et al	2009	
Vigneri P, Sciacca L, et al	2009	Risk of Cancer
SANNE G	2009	
Van S., Beulens, J. et al	2010	Renal Disease
SANNE G.	2009	
Holman RR , et al	2007	
Timar R, Pârv F, et al	2008	Coronary Heart Disease
Juutilainen A, et al	2005	
Roumie CL et al	2012	

Insulin is an effective therapy for type 2 diabetes because of its boundless ability to lower blood glucose. When metformin and one other glucose-lowering drug, when appropriate, have not been able to sufficiently control blood glucose, IDF suggests using it as an optional third line. A patient-centered strategy is advised by the ADA and EASD guidelines in order to achieve appropriate glucose management with the least amount of adverse effects. Insulin injection-related adverse effects include weight gain and hypoglycemia. Reduced weight gain is recommended for those with type 2 diabetes as it is linked to an increased risk of cardiovascular disease[25]. People who already have diabetes and cardiovascular disease are likely to be more susceptible to the vascular effects of both insulin and hypoglycemia[1,2]. In addition, as a growth factor, insulin may affect cancer progression[28]. In a complex area, high glucose levels are linked to increased cancer risk, and insulin use is associated with increased cardiovascular events, cancer, and all-cause mortality compared to other glucose-lowering therapies[29].

Insulin, a glucose-lowering medication for type 1 and type 2 diabetes, has raised concerns about its safety and cancer risk[30]. The long-acting insulin analogue, glargine, was initially suggested to increase cancer risk, but a prospective randomized clinical trial (RCT) found no evidence of increased cancer risk in patients receiving glargine over six years of follow-up. This finding lays the groundwork for further research on insulin functions and cancer risk, addressing concerns raised by pharmaco epidemiology and paving the way for further research on insulin functions and cancer risk[31].

3. Conculsion

Insulin therapy is crucial for managing type 2 diabetes mellitus, but the timing of insulin initiation remains a debate. Simplified insulin initiation and titration regimens can help healthcare professionals effectively treat patients with T2DM. By simplifying insulin therapy, physicians can better manage hyperglycemia and control diabetes mellitus. The dilemma regarding insulin initiation remains debatable, but simplified algorithms can help physicians effectively treat patients with T2DM.

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Conflicts of Interest

The author hereby declares that there are no conflicts of interest concerning this paper.

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