

## INSULIN-INDUCED WEIGHT GAIN AS A POTENTIAL RISK FACTOR FOR CARDIOVASCULAR DISEASE: A NARRATIVE REVIEW.

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Page | 1 **ABSTRACT.**

Diabetes mellitus, a chronic metabolic disorder characterized by high blood glucose levels, is a significant global health concern. Insulin therapy, essential for managing diabetes, is often linked with weight gain. This weight gain, while beneficial in some patients, poses risks for overweight or obese individuals, particularly in terms of cardiovascular disease (CVD), the leading cause of mortality in this population. This review aims to combine current research on the relationship between insulin-induced weight gain and cardiovascular disease risk, exploring mechanisms, clinical implications, and management strategies. The several pathways of insulin-induced weight gain are covered in the review, including impacts on anabolism, increased adiposity, and fluid retention. It explores the pathophysiological mechanisms that relate weight gain to cardiovascular disease (CVD), including endothelial dysfunction and oxidative stress, and looks at how weight gain impacts cardiovascular risk factors like hypertension, dyslipidemia, and inflammation. In addition, the review assesses data from clinical trials and epidemiological studies, contrasting various insulin dosage schedules and their relationships to CVD outcomes. Lastly, it discusses how to control weight gain while on insulin therapy, with a focus on dietary changes, exercise, medication modifications, and patient education. The review highlights the need for further research to clarify the causal relationships and to develop more effective strategies for managing weight gain in insulin-treated patients. It suggests exploring personalized medicine approaches and newer pharmacological agents to optimize diabetes care while minimizing cardiovascular risks. This review underscores the importance of incorporating weight management into the clinical management of diabetes. It advocates for a holistic approach that includes regular monitoring, patient education, and tailored treatment plans to mitigate cardiovascular risks associated with insulin-induced weight gain.

**Keywords:** *Insulin Therapy, Weight Gain, Cardiovascular Disease, Diabetes Management*

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### INTRODUCTION.

The chronic metabolic disease known as diabetes mellitus, which is characterized by high blood glucose levels, is a major threat to world health. Approximately 537 million persons had diabetes as of 2021; by 2030, that figure is expected to increase to 643 million [1]. Insulin therapy is still the mainstay for the treatment of diabetes, especially advanced type 2 and type 1 diabetes. Even though insulin successfully lowers blood glucose levels, using it is frequently linked to weight gain.

Gaining weight while on insulin therapy might be advantageous for underweight or recently diagnosed patients, but it can also be harmful for overweight or obese people, increasing their risk of cardiovascular disease (CVD). Up to 52% of diabetic patient deaths are attributed to cardiovascular disease, making it the primary cause of death in this population [2]. This concerning figure emphasizes how crucial it is to comprehend how insulin-induced weight gain and CVD risk interact.

There is a complicated and nuanced link between weight growth, insulin therapy, and CVD. In addition to being essential for the proper metabolism of glucose, insulin possesses anabolic properties that can increase body fat

and cause fluid retention, which can result in weight gain. Consequently, endothelial function, dyslipidemia, and hypertension—all cardiovascular risk factors—may be negatively impacted by this weight gain [3].

It is critical to investigate how weight growth affects cardiovascular health given the ubiquity of insulin therapy in the management of diabetes and the risk of weight gain that goes along with it. To provide insights into the processes, clinical implications, and management options of insulin-induced weight gain as a possible risk factor for cardiovascular disease, this review attempts to summarize the most recent studies in this area. By doing this, it aims to offer a thorough understanding that helps direct medical professionals in maximizing diabetes treatment while lowering cardiovascular risks.

### METHODOLOGY.

Electronic databases such as PubMed, MEDLINE, EMBASE, and the Cochrane Library were searched to conduct the review. Only research published in English between January 2000 and December 2023 was included in the search. The search parameters included the following: "insulin therapy," "weight gain,"

"cardiovascular disease," "type 1 diabetes," "type 2 diabetes," "insulin-induced obesity," "hypertension," "dyslipidemia," "endothelial dysfunction," as well as "oxidative stress."

Studies that explicitly addressed the connection between insulin therapy and weight increase and the ensuing effects on cardiovascular health were included in the selection process. There were randomized controlled trials (RCTs) and observational studies included. The selection of studies was based on three criteria: methodological excellence, novelty of contributions, and relevance to the topic. Studies written in languages other than English, research involving animals, and studies that did not specifically address the relationship between insulin-induced weight gain and cardiovascular risk were all excluded.

## DISCUSSION.

### Mechanism of Insulin-Induced Weight Gain.

Weight gain is a common side effect of insulin therapy, which is a crucial part of managing diabetes. This side effect can have a major influence on the health of the patient. Numerous factors, including increased adiposity, fluid retention, and the anabolic actions of insulin, are involved in this weight gain.

Insulin-induced weight gain is primarily caused by increased adiposity. One important anabolic hormone that helps with glucose uptake into adipose tissue and encourages fat storage is insulin. When there is an excessive calorie intake, especially from a diet heavy in fats and carbohydrates, this process is most noticeable. Moreover, insulin's capacity to impede lipolysis adds to the overall increase in fat accumulation [3].

Fluid retention is another aspect that contributes. Insulin treatment may cause salt retention and increase sodium reabsorption through the kidneys, which can result in fluid retention and weight gain. Higher insulin dosages are frequently needed in people with insulin resistance, where this effect is more pronounced [5].

Significant influence is also played by insulin's anabolic properties. An overall anabolic state is achieved through insulin's promotion of protein synthesis and inhibition of protein breakdown. For underweight or recently diagnosed patients, this may be helpful, but for overweight or obese patients, it may worsen weight gain.

### Factors Influencing Weight Gain in Insulin-Treated Patients.

Patients on insulin therapy experience varying degrees of weight gain, which is impacted by multiple factors. One important consideration is the type of insulin used; patients on insulin analogues, such as insulin detemir, may gain less weight than those on NPH insulin or insulin glargine [6]. Another important factor is dosage; in

general, higher insulin dosages are linked to greater weight gain, especially in people with insulin resistance. Diet and exercise levels are two lifestyle factors that have a major impact on weight gain in people receiving insulin. Sedentary behavior and a high-calorie diet, especially one high in fats and carbohydrates, might aggravate insulin-induced weight gain. Individual variability also affects how individuals respond to insulin therapy in terms of weight gain. This includes genetic characteristics, age, and baseline body weight. Regardless of the type or dose of insulin, some people may be more likely than others to gain weight [7].

### Impact of Weight Gain on Cardiovascular Health.

Weight gain has a major negative influence on cardiovascular health, especially when it is linked to insulin therapy for the management of diabetes. It is generally known that weight gain and cardiovascular risk factors such as inflammation, dyslipidemia, and hypertension are related. Managing the general health of diabetic patients requires an understanding of these relationships.

One typical side effect of weight increase is hypertension. Visceral fat in particular is metabolically active and secretes several chemicals that might raise blood pressure. Angiotensinogen is one such material that functions in the renin-angiotensin system, a vital blood pressure regulator. Research has demonstrated a strong correlation between elevated levels of obesity and hypertension, as has been widely reported.

Dyslipidemia and weight gain are tightly related in terms of lipid metabolism. Triglycerides usually rise and high-density lipoprotein (HDL) cholesterol usually falls as a result of it. Moreover, a known risk factor for CVD, the quality of low-density lipoprotein (LDL) particles may decline, becoming denser and smaller. One of the main contributing factors to the onset of CVD is the change in lipid profile brought on by weight increase.

Another noteworthy consequence of weight increase is the initiation of persistent low-grade inflammation. The growth of adipose tissue causes adipocytes and macrophages that have invaded the tissue to produce more pro-inflammatory cytokines, such as interleukins and tumor necrosis factor-alpha (TNF- $\alpha$ ). The pathophysiology of atherosclerosis is largely dependent on endothelial dysfunction and systemic inflammation, both of which are exacerbated by this persistent inflammatory state [8].

One important pathophysiological process that connects weight increase to CVD is endothelial dysfunction. Increased body weight is linked to compromised endothelial function, especially when it manifests as visceral adiposity. A lower bioavailability of nitric oxide (NO), a crucial chemical for vascular health, is the hallmark of this dysfunction. Atherosclerosis is frequently preceded by endothelial dysfunction, which is a sign of an increase in cardiovascular events [9].

Moreover, oxidative stress, which is a major factor in endothelium damage, is made worse by weight gain. Reactive oxygen species (ROS) produced by the extra adipose tissue cause oxidative damage and inflammation. Weight gain is further associated with an increased risk of cardiovascular events due to this oxidative stress, which plays a major role in the onset and progression of CVD.

### **Evidence Linking Insulin-Induced Weight Gain to Cardiovascular Disease.**

Vast study has been done on the relationship between insulin-induced weight gain and CVD; several epidemiological studies and clinical trials have provided insight into this intricate interaction. Comprehending this correlation is imperative, given its noteworthy consequences for the handling of diabetes and the avoidance of cardiovascular issues.

Weight gain and elevated cardiovascular risk have been repeatedly linked to insulin therapy in epidemiological research. In contrast to those who maintained or decreased weight, those with type 2 diabetes who gained weight while on insulin therapy had a higher risk of CVD events, according to a study conducted by the American Heart Association (AHA) [10]. Clinical trials have also shown data in favor of this connection. In comparison to traditional treatment, the UK Prospective Diabetes Study (UKPDS) found that individuals with type 2 diabetes who had intensive glucose control with insulin or sulfonylureas experienced weight gain and an increased risk of heart attacks [11].

The effects of various insulin regimens on weight gain and CVD consequences differ. Research like the Treat-to-Target Trial [12] has demonstrated that long-acting insulin analogues, like insulin detemir and insulin glargine, have been linked to reduced weight gain more than NPH insulin. Additionally, however, the data is inconclusive, a meta-analysis revealed that insulin analogues may be linked to a somewhat decreased risk of cardiovascular events when compared to human insulin [14].

Genetic predispositions and patient variables also have an impact on the association between insulin-induced weight gain and CVD. The risk can be modulated by variables like age, sex, baseline body weight, and the existence of other comorbidities like dyslipidemia or hypertension. There is also an element of genetic predisposition, as specific genotypes might affect how people react to insulin therapy in terms of obesity and CVD risk.

### **Managing Weight Gain in Insulin Therapy.**

An essential component of diabetes care is controlling weight gain in individuals receiving insulin therapy while preserving ideal glycemic control. To mitigate obesity without compromising blood sugar management, effective techniques combine dietary modifications, physical exercise, medication adjustments, and patient education.

Making dietary changes is essential for controlling weight gain brought on by insulin therapy. It is advised to eat a balanced diet high in fiber-containing foods such as whole grains, fruits, and vegetables and low in calories and saturated fats. Controlling portion sizes is also essential because it lowers caloric intake overall. Low-glycemic diets have been linked to better glycemic control and may help with weight management, according to studies [14]. Additionally, individuals receiving insulin therapy may benefit especially from meal planning techniques and carbohydrate monitoring.

Maintaining a regular exercise schedule is also essential for controlling weight gain. Exercise increases insulin sensitivity, which can assist in lowering insulin dosages and lessen the negative effects of being overweight. It's usually advised to combine resistance and cardio training. The American Diabetes Association recommends two to three sessions of resistance training per week in addition to at least 150 minutes of moderate-intensity aerobic activity per week [15].

Changing prescription schedules can also be quite helpful in controlling weight. Using insulin analogues, which are linked to less weight gain than regular human insulin, is one method. Additionally, there has been promise in weight loss when insulin and GLP-1 receptor agonists are combined. When combined with insulin, GLP-1 receptor agonists like liraglutide can improve glycemic control and have a weight-reducing impact [16].

It is essential to inform patients about the significance of lifestyle changes in controlling their diabetes and related weight gain. Patients can take an active part in managing their diabetes by using behavioral therapies, such as goal-setting, problem-solving techniques, and self-monitoring of blood glucose and food consumption. Patients may find that support groups and counseling help them stick to their drug schedules and lifestyle modifications.

The narrative review highlights the importance of monitoring and managing weight gain in individuals undergoing insulin therapy for diabetes. It emphasizes the need for personalized approaches to balance glycemic control with weight management strategies, involving multidisciplinary teams for optimal patient outcomes. The review underscores the significance of healthcare policies promoting holistic care for diabetic patients and identifies areas for future research, including mechanistic pathways, comparative effectiveness of insulin regimens, and novel therapeutic approaches. Overall, it aims to improve diabetes care and minimize cardiovascular risks through comprehensive understanding and intervention.

### **CONCLUSION.**

This analysis concludes by highlighting the intricate and noteworthy correlation between insulin-induced weight gain and the risk of CVD in individuals with diabetes. Insulin therapy is essential for controlling diabetes, but it requires careful balancing to prevent the weight gain that comes with it. Weight increase can aggravate CVD risk factors such as inflammation, dyslipidemia, and

hypertension. The data from several research emphasizes the necessity of individualized treatment plans that include physical exercise, dietary changes, and maybe the combination of insulin with additional medications such as GLP-1 receptor agonists to maximize weight management and glycemic control. To address this dual problem in diabetes management, this study urges healthcare providers to be more proactive and cognizant of the risks associated with cardiovascular complications. The ultimate goal is to enhance patient outcomes overall.

### RECOMMENDATIONS.

The review emphasizes the intricate relationship between insulin therapy, weight gain, and cardiovascular disease (CVD) risk in diabetes management. To mitigate cardiovascular risks, tailored treatment plans should prioritize lifestyle modifications, including dietary changes and regular exercise, alongside a careful selection of insulin formulations with lower weight gain potential, such as insulin analogues. Combination therapies involving insulin and adjunct medications like GLP-1 receptor agonists may offer synergistic benefits. Patient education and engagement are crucial for empowering individuals to actively participate in their treatment plans. Further research is needed to explore innovative therapeutic approaches and personalized medicine strategies to optimize patient outcomes.

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### LIST OF ABBREVIATIONS.

DTC:	Differentiated Thyroid Cancer
T2DM:	Type 2 Diabetes Mellitus
CVD:	Cardiovascular Disease
BMI:	Body Mass Index
SPSS:	Statistical Package for the Social Sciences
mCi:	millicurie
ATA:	American Thyroid Association
ETA:	European Thyroid Association
RCTs:	Randomized Controlled Trials
HDL:	High-Density Lipoprotein
LDL:	Low-Density Lipoprotein
NO:	Nitric Oxide
ROS:	Reactive Oxygen Species
AHA:	American Heart Association
UKPDS:	UK Prospective Diabetes Study
GLP-1:	Glucagon-Like Peptide 1

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### CONFLICT OF INTEREST.

The authors have no competing interests to declare.

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