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Treatment of Type 2 Diabetes with Insulin: Life-saving or Life-threatening

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Diabetes, a condition with historical roots as early as 1500 B.C.E. with descriptions by the ancient Egyptians, derives its name from Greek and Latin roots signifying excess sugar in the urine. By the 5th century CE, physicians in India and China were able to differentiate between type 1 and type 2 diabetes (based on signs and symptoms), with the latter being associated with lifestyle factors such as diet and physical activity. A pivotal moment in understanding the disease occurred in 1776 when Matthew Dobson quantified glucose in urine, recognizing its potential severity and confirming the existence of two distinct forms of diabetes.[1] Further insight into the disease's mechanism came in 1889 when Joseph von Mering and Oskar Minkowski demonstrated that removing the pancreas in dogs induced diabetes and subsequent death, establishing the organ's critical role in blood glucose regulation.[2,3] By the early 19th century, effective treatments were nonexistent, and the prognosis for patients was often dire, with many succumbing to the disease within weeks or months of symptom onset. By 1920, scientists had identified the islets of Langerhans within the pancreas as the clusters of cells responsible for insulin production and had confirmed their destruction in type 1 diabetes, setting the stage for therapeutic breakthroughs.

In 1921, at the University of Toronto, Frederick Banting, with the assistance of Charles H. Best and under the supervision of J J R Macleod, successfully extracted insulin from a dog's pancreas. They demonstrated its blood-sugar-lowering effect by injecting the extract into dogs whose pancreases had been removed. By November, they had sustained a diabetic dog for 70 days using their extract. Biochemist James Collip subsequently joined the team, refining the extract using cattle pancreases to develop a purer form. This purified insulin was first tested on Leonard Thompson, a 14-year-old boy near death from type 1 diabetes. Although his blood sugar dropped dramatically within 24 hours, the initial injection caused an abscess, and ketone levels remained high. Collip further purified the extract, and a second injection was administered on January 23, 1922. This time, Thompson's blood glucose levels successfully dropped close to normal with no discernible side effects. For the first time in history, type 1 diabetes was no longer an immediate death sentence; Thompson lived another 13 years with the condition before ultimately dying of pneumonia.

In May 1922, Macleod formally presented the discovery of insulin to the international medical community at a meeting of the Association of American Physicians in Washington, D.C., in a paper titled "The Effects Produced on Diabetes by Extracts of Pancreas." This marked the first public use of the term "insulin," and the team received a standing ovation. As news of insulin's success spread, demand surged, prompting the team to refine production techniques for large-scale manufacturing. In recognition of this monumental, life-saving discovery, Banting and Macleod were jointly awarded the Nobel Prize in Physiology or Medicine in 1923. For decades following its discovery, exogenous insulin remained the mainstay of treatment for type 1 diabetes mellitus (DM). This successful experience in managing severe, often life-threatening hyperglycemia in type 1 DM led to the expansion of its use to patients with advanced type 2 DM (T2DM).

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Since then, many antidiabetic medications have also been developed to manage high blood sugar and its associated complications. The study of diabetes and glucose metabolism has been such a fertile ground of scientific investigation that, since 1923, ten scientists have earned the Nobel Prize for diabetes-related work. Despite these scientific efforts over the past two centuries, the ultimate goal of conquering the disease remains unmet. In fact, if we look at diabetes from a public health perspective, there's been minimal overall progress in curbing the disease and we are, arguably, worse off now than we were in 200 years back.[4]

When insulin was discovered in 1922, no other oral or injectable medications for diabetes existed. Furthermore, diabetes was rarely differentiated into type 1 and type 2 because the vast majority of clinically apparent cases were type 1 with severe insulin deficiency. Milder cases of T2DM may have existed but were largely undetected due to a lack of discernible signs or symptoms. Consequently, diabetes, regardless of type, was treated exclusively with insulin until the introduction of oral antidiabetic medications in 1956.[5] However, insulin continued to be viewed as a powerful tool for blood glucose control, particularly when other treatments failed. While long-term, stringent glycemic control in T2DM is known to result in a marked reduction in microvascular complications such as retinopathy, nephropathy, and neuropathy,[6] several observational studies have suggested that intensive insulin therapy may be associated with increased adverse cardiovascular (CV) events and mortality.[7,8]

To address this controversy, Stoekenbroek and colleagues[9] conducted a matched-control study comparing T2DM patients who began insulin after oral therapy to similar controls. Their findings indicated that higher average insulin doses were linked to an increased likelihood of CV events, an association that largely persisted even after adjusting for metabolic factors like HbA1c. The authors concluded that, among people with comparable diabetes control, those receiving larger insulin doses face a higher risk of CV events during follow-up. A related observational study by Holden and colleagues[10] also found a significant and proportional increase in mortality, major adverse cardiovascular events (MACEs), and cancer rates with increasing use of exogenous insulin. A case-control study further observed a closely proportional increase in heart disease-related mortality corresponding to the dose of insulin used.[11]

These observations are reinforced by a cohort study where Gamble and peers.10 followed 12,272 new users of oral antidiabetic therapy (1991–1996). Examining whether levels of insulin exposure, defined by annual total insulin dispensations [no exposure, low exposure (0-<3 μU/mL), moderate exposure (3-<12 μU/mL), high exposure (≥12 μU/mL)], were associated with all-cause and cardiovascular mortality, they used time-varying multivariable Cox models. Over a mean follow-up of 5.1 years, mortality rates rose with increasing insulin exposure: low (aHR 1.75), moderate (aHR 2.18), and high (aHR 2.79), with a significant trend ($p = 0.005$). Similar graded patterns were observed for cardiovascular and non-vascular deaths concluding that a significant, dose-response association exists between insulin exposure and mortality risk in this T2DM cohort, which remained even after adjustment for confounding variables.

Considering the potential complications of T2DM, some investigators advocate for the early initiation of insulin therapy in the long-term management of the disease, citing distinct advantages. However, as noted,[12] there is little evidence to support this idea. Insulin therapy does not reliably sustain glycemic control over time, nor is it unique in preserving β-cell function. Moreover, it has not been shown to yield better clinical outcomes compared to other antihyperglycemic medications. Insulin therapy also promotes dose escalation and more complex regimens, carries a higher risk of severe hypoglycemia, and raises potential concerns about increased mortality and possible associations with certain cancers.[12] Hanefeld's review[13] arguing for immediate insulin use upon diagnosis focuses primarily on glycemic control, potentially overlooking the long-term macrovascular complications linked to early insulin initiation.

An animal model study by Cao and associates[14] demonstrated that prolonged long-term use of the

long-acting insulin 'Detemir' worsened insulin resistance in mice. The findings suggest that heightened basal insulin signaling drives insulin resistance and elevated insulin levels by promoting ectopic fat buildup and oxidative stress keep blood glucose within normal ranges. This mechanism explains why many individuals with insulin resistance and hyperinsulinemia can maintain near-normal blood glucose levels and often do not progress to overt diabetes. Citing multiple studies,[15-18] they also claimed that lowering insulin levels reduces fat deposition in blood vessels and may even clear blockages through fat degradation.

A meta-analysis[19] of 20 unbiased controlled studies (1950–2013) on insulin use for T2DM concluded that long-term insulin treatment is not effective. Due to the risks of weight gain and hypoglycemia, the investigators discouraged insulin use compared to other treatments, concluding that there is no significant evidence of long-term efficacy on any clinical outcome in T2DM. Instead, they observed a trend toward clinically harmful adverse effects. In a separate review, Herman and colleagues[20] highlighted multiple complications caused by insulin use, discouraging its application in T2DM patients who already have hyperinsulinemia. They argued that this "over-insulinization" via injected insulin accelerates the processes of inflammation, atherosclerosis, hypertension, dyslipidemia, heart failure (HF), and arrhythmias. These findings are supported by Mendez and coworkers,[21] who showed that in patients with known insulin resistance, additional exogenous insulin, even when used for glycemic control, may further aggravate the underlying dysregulated metabolic process, resulting in increased complications. They argued that insulin-based therapy may be doing more harm than good for T2DM patients with insulin resistance. Mendez[22] subsequently claimed that insulin therapy in T2DM may be less beneficial and potentially harmful for patients with high insulin resistance. Given that recent studies suggest almost all T2DM patients exhibit some degree of insulin resistance, the broad benefit of insulin therapy is questioned. A recent study by Schwartz et al.[23] demonstrated that insulin-treated T2DM patients with low HDL cholesterol and acute coronary syndrome (ACS) are at high risk for recurrent MACE, an independent predictor even after adjustment for other characteristics associated with MACE. These associations support the findings of large-scale evaluations that strongly suggest insulin therapy has a poorer short-term and long-term safety profile compared to many other anti-T2DM therapies.[11]

Boels et al.[24] compared health and psychosocial functioning among people with T2DM based on treatment type. Insulin users had a longer duration of T2DM and more complications than those on oral antihyperglycemic agents (OHA) only or on insulin with/without OHA. After adjusting for confounding factors, insulin users showed significantly worse scores in vitality, general health, barriers to activity, and psychological distress.

DeFronzo, a central figure in developing the concept of insulin resistance, described it as a core factor in T2DM and related metabolic conditions like obesity and hypertension. His work established that insulin resistance is a state where the body's cells respond less effectively to insulin, forcing the pancreas to produce more to maintain normal blood glucose levels. This state can lead to a cluster of cardiometabolic abnormalities (obesity, hypertension, dyslipidemia, and atherosclerosis) known as the "insulin resistance syndrome (Fig. 1)," which is considered the earliest detectable abnormality, often far ahead of the development of overt T2DM.[25]

Based on the evidence from these studies, a clinician might reasonably consider using insulin only for short-term emergency situations, such as managing high blood glucose during surgery or infection or to prevent infection in T2DM patients, or in women with gestational diabetes mellitus. However, claiming insulin to be the "best" long-term treatment for T2DM patients is not scientifically supported and appears to be an expression of questionable over-enthusiasm.

Despite the mounting evidence, insulin is being rampantly used in the treatment of T2DM. According to the 'Hippocratic Oath', every physician should prioritize the potential for patient harm the most. Although, the Hippocratic Oath is an ancient ethical code for physicians, and it is no longer a requirement

in most medical schools, it lays the foundation for modern medical ethics, emphasizing principles like the patient's welfare and a commitment to the profession. Modern versions, such as the Declaration of Geneva, still reflect its core values of doing no harm and acting with integrity.

The global prevalence of T2DM and its micro- and macro-vascular complications has surged dramatically in recent decades. This is primarily because T2DM treatment often focuses on controlling glycemic status while neglecting its root cause: insulin resistance. While boosting the level of endogenous insulin with exogenous insulin undoubtedly helps overcoming insulin resistance temporarily and normalizes blood glucose level, only a fraction of the excess glucose is utilized for energy. Most is converted into fat and deposited in various ectopic locations, particularly the blood vessels, leading to the development of macrovascular complications. Thus, while microvascular complications (retinopathy, nephropathy, neuropathy, etc.) may be reduced to some extent, macrovascular complications (diffuse atherosclerosis leading to hypertension, ischemic heart diseases,

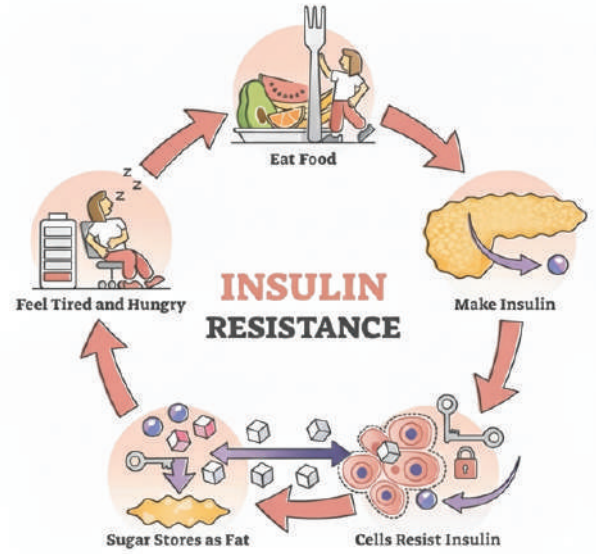

Fig. 1. Image of Insulin Resistance Syndrome where insulin (purple, round-shaped moleculesis trying to deliver glucose (represented by sugar cubes) into a cells

peripheral vascular diseases, stroke, etc.) are expedited, as is evidenced from the discussion hitherto. Macrovascular complications are only weakly associated with glycemic status and are the leading cause of mortality, accounting for about 75% of deaths from cardiac causes and stroke.[25] Then what could be done? The only sustainable solution is to address insulin resistance. However, no current antidiabetic medication successfully addresses insulin resistance because none accelerate the metabolic activities of muscle cells, where 80% of ingested glucose is utilized.[26] These cells are essentially rejecting the action of insulin (Fig 1). Lifestyle modification, particularly regular exercise, is the only cost-effective strategy capable of significantly improving the condition.

Given the surge in diabetes prevalence, timely prevention at the population level is essential. Accumulated evidence consistently and conclusively suggest that lifestyle modification will play a key role in the ultimate solution. However, a significant gap exists between these research findings and prevailing clinical practice, as clinicians appear reluctant to fully adopt this solution.

Currently an estimated 150–200 million people globally with T2DM are dependent on insulin therapy, a number that is likely an underestimate. A substantial proportion of these patients will potentially develop macrovascular complications due to insulin therapy, as suggested by the research data, leading to early death and disability. Therefore, treatment of T2DM patients with insulin in no way be considered as life-saving; rather, the evidence suggests it may be life-threatening.

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