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Original article

INSULIN ALLERGY: A CASE STUDY.

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Abstract

Background:

Hypersensitivity to insulin is uncommon but difficult for diabetics. In light of the advancement of preparations containing human recombinant insulin, the incidence of insulin allergy has decreased. From erythema and edema at the site of the injection to anaphylaxis, hypersensitivity responses might occur. Many reactions are to recombinant insulin itself, even though others are to excipients (such as zinc, protamine, or meta cresol). We present a case of insulin-dependent type 2 diabetes mellitus (T2DM) in which a patient developed type 1 hypersensitivity to several insulin formulations.

Case Representation:

A 55-year-old woman was referred for assessment of insulin reactions after having insulin-dependent T2DM for 7 years and essential hypertension for 4 years. The patient arrived complaining of many abdominal ulcers at the locations of insulin injections on the belly and thigh. After receiving treatment from a local doctor using Insulin Glargine and OHA, she later developed abdominal ulcers. A village surgeon administered antibiotics.

Conclusion:

Our instance emphasizes the value of establishing a correct insulin sensitivity diagnosis through a thorough history and targeted testing. Avoidance, insulin substitutes, different insulin formulations, and desensitization are all examples of therapeutic approaches. Pancreatic transplantation or the drug omalizumab have both been effective in treating severe recurring hypersensitivity reactions.

Keywords: Diabetes Mellitus, Hypertension, Insulin Allergy, Submitted: 2023-06-23 Accepted: 2023-06-26

1. Introduction:

Insulin, a polypeptide hormone, is essential for controlling serum glucose levels. [Figure 1; 1]. In reaction to hyperglycemia, beta cells in the pancreatic islets make it. It is the cornerstone of care for those with severe T2DM and type 1 diabetes mellitus (T1DM) who have poor glycemic control despite taking the maximal recommended dose of oral hypoglycemic medicine [2]. Reactions caused by hypersensitivity to insulin are rare, despite the existence of Type I, Type III, and Type IV reactions. Typically, IgE-mediated reactions appear an hour after injection [3].

There are many different manifestations, ranging from localized erythema and edema at the location of the injection to severe generalized reactions like anaphylaxis [4]. In comparison to human insulin, preparations of pig and bovine insulin as well as other animal insulins significantly increased the risk of reactions associated with hypersensitivity. However, it is now estimated that less than 2.4% of people receiving insulin therapy experience insulin hypersensitivity reactions due to the development of human synthesized insulin

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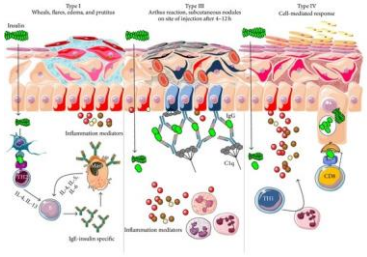

Figure 1: **Insulin Allergy**

and slight changes to the human insulin's amino acid sequence [5]. Patients may also develop an allergic reaction to inert excipients contained in insulin preparation, such as protamine, zinc, or meta cresol, however, some cases of insulin allergy are caused by recombinant human insulin [6]. People who have an allergy to insulin might therefore have difficulty finding suitable therapies.

The case of a woman with essential hypertension, T2DM, and more than 7 years of insulin administration is provided in the current article, along with a method for identifying patients who are experiencing insulin hypersensitivity reactions and a rundown of the treatment choices that are available. This study aimed to determine a precise diagnosis of insulin allergy.

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2. Case Representation:

This study was conducted in Dr. Prakash Diabetes Specialities Centre, Patna, Bihar, India. The patient's consent had been gathered before conducting the study. After suffering from essential hypertension for four years and insulin-dependent T2DM for seven years, a 55-year-old lady was recommended for a review of her insulin reactions. The woman complained of having numerous stomach ulcers where she had received insulin injections in her thigh and abdomen [Figures 2-4]. She eventually got stomach ulcers following treatment with Insulin Glargine and OHA from a nearby doctor. Antibiotics were administered by a community doctor.

These reactions took place in the absence of additives, like physical activity or any drugs consumed. The brand-new bottle of insulin she used was kept in her fridge. She had been taking the same drug for more than 6 years without experiencing any previous responses to it, and she had never missed a dose. Long-term type 2 diabetes (T2DM) with a hemoglobin A1c level of 8.1% gm was a part of her medical history and recently, an E. coli hospitalization, and the presence of pallor. There was no prior history of atopy, autoimmune illness, or drug or insect sting allergies in the patient.

Her most recent prescription, which included injection Apidra Cartridges, Tresiba Penfill-lapidra, tablet Trajenta 5 mg [linagliptin], Euclide XR 60, Ecospirn AV, and ointment Hydroheal AM to apply twice daily, are listed below in **Figure 3**. The medication was given for a month. She had previously taken Trejenta 5, Glizid 160, Cilacar 10, Arkamine 100, Ajadeo 5/25, and GLARGINE 24 UNITS.

Initial and interim clinical examinations, blood glucose readings, and vital sign evaluations were done throughout the SPT and intradermal assessments without modifying the clinical examination. The result of the Biochemistry examination done o the patient is listed in **Table 1.**

This table shows that the glycosylated hemoglobin, Mean blood sugar, fasting blood sugar, and Post Prandial blood sugar were all poorly controlled. At 2.82 kU/L, serum IgE insulin was increased. The levels of serum tryptase

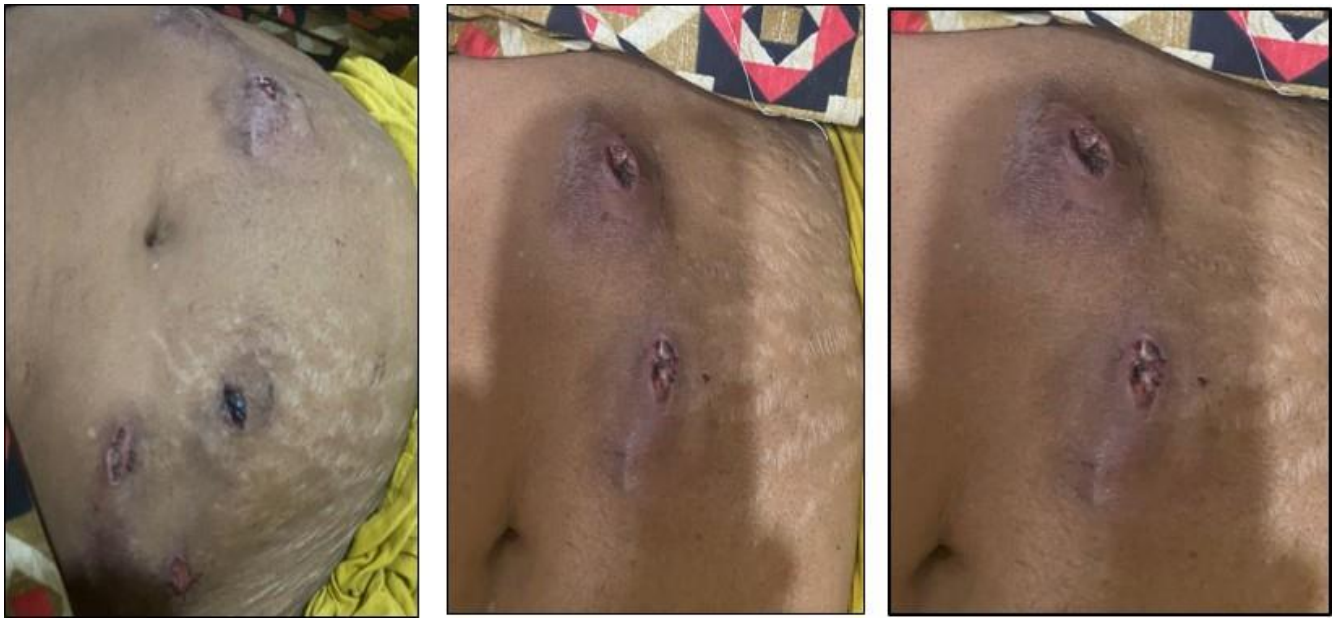

Figure 2: Site of Ulcer on Abdomen

Sl. No.	Drugname	Mor	Aft	Ngt	Comments	Duration
1)	INJ.APIDRA CARTRIDGES	16	10	0	16 before breakfast - 10 before lunch	(1 Month)
2)	INJ.TRESIBA PENFILL	0	0	24	24 bed time	(1 Month)
3)	TAB.TRAJENTA 5 MG linagliptin	0	0	1	1 tablet before dinner	(1 Month)
4)	TAB.EUCLIDE XR 60	1	0	0	1 tablet before breakfast	(1 Month)
5)	OINT.HYDROHEAL AM	Apply two times daily				
6)	TAB.ECOSPRIN AV 75/10	0	0	1	1 tablet after dinner	(1 Month)

Figure 3: **Recent Prescription of medication**

Table 1: **Blood Glucose Estimation**

CRITERIA	OBTAINED RESULT	NORMAL RANGE
GLYCOSYLATED HAEMOGLOBIN	8.1% Gm	4.3 to 6.1% Non Diabetic level < 6.0% Diabetic Good Control < 7 .0% Poor Control : > 8.0%
MEAN BLOOD SUGAR	185 mg/dL	Upto 140 mg/dL
FASTING BLOOD SUGAR	410 mg/dL	70 – 110
POST-PRANDIAL BLOOD SUGAR	379 mg/dL	70 -140

and C4 were both regular, at 3.8 ng/mL and 0.33 g/L, respectively. At <0.2 kU/L, the latex IgE level was also acceptable.

3. Discussion:

There have been numerous dose forms created since the release of Humulin, the first recombinant human insulin, ranging from short-acting to long-acting [7]. Bovine insulin is more likely to cause an allergic reaction than porcine insulin, and animal insulin compositions were highly immunogenic [1]. On the other hand, recombinant human insulin's immunogenicity has significantly decreased [5]. Despite this, reactions to various compounds in an insulin preparation, including the insulin ingredient, preservatives, and other additives including zinc, the hormone protamine, and meta cresol, have been documented, and can still cause hypersensitivity [8-10].

The most frequent allergic reaction to synthesised human insulin is a type I acute hypersensitivity reaction [5]. The reaction frequently happens an hour after the injection or seven days after starting insulin therapy. After the initial reaction, biphasic reactions have happened 4-6 hours later [5, 7]. Patients on insulin therapy who take extended absences from their medications have been known to have a Type I acute hypersensitivity reaction [7]. Reactions of types III [11] and IV have also been reported [5]. It's important to remember that IgG antibodies also affect insulin resistance. Type IV hypersensitivity reactions generally start 8 to 12 hours after the substance is administered, peak at 24, and last for 4 to 7 days [5]. Recombinant insulin caused a postponed response in a T1DM patient that eventually led to leukocytoclastic vasculitis [12]. Although they are theoretically possible, both regional and systematic reactions to allergens to endogenously produced insulin when combined with transgenic therapy with insulin are relatively rare [13].

There is little understanding of the pathophysiology of insulin-related hypersensitivity reactions. The hypothesis is that insulin subunits aggregate to form bigger molecules, which promotes the production of anti-insulin antibody in skin tissue [14–16]. Newer recombinant insulins are less likely to produce these aggregates because they are absorbed more quickly and have lower antigenicity, which lowers exposure to mast cells and increases the probability of anti-insulin antibody production [17]. Additionally, A suggestion has been made that the method of administration may be significant, with insulin injections given subcutaneously having a higher likelihood of causing hypersensitivity than those given intravenously [18]. Genetics appears to play a factor since the HLA gene DR4 has been linked to higher insulin antibody production [7].

A test is used to identify insulin allergy thorough medical a physical examination and history is necessary to rule out any other likely causes. Because latex is frequently discovered in insulin containers, it is crucial to keep in mind that pulling up insulin could result in latex contamination of the insulin needle [19]. As a result, it's crucial to exclude latex allergy or, if there's a good chance a person has it, use latex-free insulin containers. Skin prick testing (SPT) should be used to check for allergies to substances such as zinc, protamine, and meta cresol, used with various insulin formulations and found to be potential sources of systemic responses [9–12]. It has been recommended that to identify insulin allergy intradermal skin testing is more accurate than SPT. Due to the prevalence of false positive skin test results in 27% of diabetics with low specific IgE titers, the results of the skin test should be evaluated alongside with clinical manifestations [20]. Up to 40% of diabetics who are undiagnosed may have an elevated skin test response or particularly to IgE insulin, based on one idea [21].

The first course of treatment for insulin-induced anaphylaxis is the same as for other types of anaphylaxis: administer epinephrine right away. Second-generation antihistamines may be used to treat cutaneous complaints. Treatment with systemic steroids is an option, but it's important to watch for insulin resistance and hyperglycemia. This could result in more people being exposed to allergens as a result of their increased requirement for insulin. The administration of systemic steroids may result in unfavorable side effects as

well. The present evidence also does not sufficiently support the use of corticosteroids or antihistamines to stop a biphasic anaphylactic reaction [22]. A interdisciplinary group should be involved because managing insulin allergy over the long term can be challenging [23]. Avoiding insulin or moving to a different insulin formulation is the cornerstone of long-term insulin allergy treatment. If T2DM patients with confirmed insulin allergies are able to maintain adequate glycemic control, insulin should be replaced to oral hypoglycemic medications [23]. Fortunately, intradermal testing as well as SPT using different insulins worked well for our patient. Patients who have been medically determined to be hypersensitive to excipients such as protamine, zinc, or meta cresol that are present in commercial insulin preparations ought to switch to a different product [9].

Unfortunately, quitting insulin medication is not an option for people with insulin-dependent illnesses like T1DM or diabetes acquired after a full pancreatectomy. A different insulin formulation from the one that causes the insulin reaction of hypersensitivity must be sought after. On the other side, desensitization to insulin is a potential, particularly for people who have allergies to various forms of exogenous insulin. It is necessary to provide insulin analogs, which are frequently less immunogenic, continuously or repeatedly in steadily increasing dosages to induce tolerance [3, 9]. Desensitization with longer-acting insulin formulations, like glargine, has also been proven to be successful. This is due to the less immunogenic and potentially immunosuppressive amino acid makeup of glargine.

Additionally, like CSII displays an antigen, glargine after injection creates a precipitate that progressively dissolves [24]. For normal administration, injections may be given subcutaneously, intravenously, or intradermally [5, 9, 22]. It is thought that the process involves the generation of anti-insulin IgG-blocking antibodies as well as the gradual induction of T-regulatory cells at rising doses, which lowers the release of allergy cytokines from mast cells [6, 9]. It has been demonstrated that gradually increasing the dose lowers symptoms and IgE levels [9]. Blood sugar levels must be checked continuously during desensitisation, and any notable spikes in blood sugar should be handled using an insulin pump and insulin formulations that are distinct from those used for desensitisation.A glucose solution should be supplied to counteract the detrimental effects of utilizing high insulin levels [9]. Desensitization can have small, temporary consequences with a possibility of recurrence of symptoms, even though this is uncommon [22]. Insulin resistance may also occur as a result of IgG antibody production [23]. Numerous treatments have been created to aid in the way insulin works desensitization both in the hospital and outside the hospital [3, 24].

4. Conclusion:

This case illustrates the possible challenges in controlling insulin allergy, albeit rare. Making a precise diagnosis of insulin allergy requires a thorough medical history and a focused physical examination. Smaller gaps might cause concern, therefore it's critical to pay close attention to when symptoms develop after taking insulin. Research is a must to concentrate on excluding any additional potential explanations for the signs, which can include latex and excipient allergy in insulin formulations. In addition to determining IgE levels specific to insulin, SPT and intradermal testing for both short- as well as long-acting insulins should be carried out. The use of oral hypoglycemics, switching to a different insulin composition, forgoing the injection of insulin, and desensitization are a few treatment options. Omalizumab treatment and, depending on severity, pancreas or islet transplantation may be explored in situations of persistent insulin hypersensitivity reactions after earlier desensitization.

5. List of Abbreviation:

T2DM- Type 2 diabetes mellitus
OHA- Oral antihyperglycemic agents
SPT- Skin Prick Testing
T1DM- Type 1 diabetes mellitus

6. Acknowledgement:

We appreciate our patient allowing us to share her story and add it to the body of scientific literature.

7. Conflict of Interest:

The author states that they have no conflicts of interest.

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