



Safety and Efficacy of Insuget® (Human Insulin rDNA) in the Management of Patients with Type II Diabetes Mellitus: A Prospective Observational Study

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Abstract: This study aimed to assess the safety and efficacy profile of Insuget® (human insulin rDNA) in patients with T2DM. An open-label, prospective, observational, single-arm, multicenter, post-marketing surveillance study observed the safety and efficacy of Insuget® in patients with T2DM. Data on glycemic control, blood pressure, adverse events, and other relevant parameters were collected following patients for six months after initiating Insuget®. The 337 patients participated in the study, with 63.5% being males. The mean age was 53.27 ± 11.10 years. Treatment with Insuget® significantly reduced mean HbA1c and fasting blood sugar levels ($p < 0.01$) with a significant improvement in systolic and diastolic blood pressure. However, the mean weight significantly increased ($p < 0.01$). The frequency of adverse events related to hypoglycemia and hypokalemia decreased over time, whereas injection site-related adverse events increased by the last follow-up visit. Comparison with other studies revealed that the findings are consistent with earlier research on recombinant insulin. This study emphasizes the potential advantages of Insuget® in managing T2DM, particularly in individuals who have uncontrolled diabetes despite previous medications. The observed improvements in glycemic control and blood pressure highlight the relevance of recombinant insulin in diabetes care regimens. The complete evaluation of numerous parameters, including glycemic control, blood pressure, and adverse events, provides full knowledge of the safety and efficacy of Insuget® and strengthens the study. Limitations include the small sample size and the relatively short follow-up time, which make it difficult to draw conclusive conclusions. Additional studies, including varied individuals and direct comparisons with alternative insulin formulations, should improve the knowledge of Insuget® comparative efficacy.

Keywords: human insulin rDNA, type II diabetes mellitus, HbA1c, hypoglycemia, hypokalemia.

因苏盖特® (人胰島素重組脫氧核糖核酸) 治療 II 型糖尿病患者的安全性和有效性：一項前瞻性觀察研究

摘要：本研究旨在評估因苏盖特® (人胰島素重組脫氧核糖核酸) 在 II 型糖尿病 患者中的安全性和有效性。一項開放標籤、前瞻性、觀察性、單臂、多中心、上市後監測研究觀察了因苏盖特®在 II 型糖尿病 患者中的安全性和有效性。在開始因苏盖特®後六個月內，收集患者的血糖控制、血壓、不良事件和其他相關參數的數據。337 名患者參與了這項研究，其中 63.5%是男性。平均年齡為 53.27 ± 11.10 歲。因苏盖特®治療顯著降低了平均糖化血红蛋白和空腹血糖水平($p < 0.01$)，同時顯著改善了收縮壓和舒張壓。然而，平均體重顯著增加 ($p < 0.01$)。與低血糖和低鉀血症相關的不良事件的頻率隨著時間的推移而減少，而與注射部位相關的不良事件在最後一次隨訪時有所增加。與其他研究的比較表明，該發現與重組胰島素的早期研究一致。這項研究強調了因苏盖特®在治療 II 型糖尿病方面的潛在優勢，特別是對於那些儘管以前接受過藥物治療但糖尿病仍未得到控制的個體。觀察到的血糖控制和血壓的改善凸顯了重組胰島素在糖尿病護理方案中的相關性。對血糖控制、血壓和不良事件等眾多參數的全面評估，提供了對因苏盖特® 安全性和有效性的全面了解，並加強了研究。局限性包括樣本量小和隨訪時間相對較短，這使得很難得出結論性結論。其他研究，包括不同的個體以及與替代胰島素製劑的直接比較，應該可以提高對因苏盖特®比較功效的了解。

关键词：人胰島素重組脫氧核糖核酸，II 型糖尿病，糖化血红蛋白，低血糖，低鉀血症。

1. Introduction

Diabetes mellitus is a complex metabolic disease characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both [1]. Chronic hyperglycemia in patients with diabetes is associated with acute and chronic complications that significantly affect the quality of life of affected individuals. Pakistan, with a population estimated at 231.4 million, currently has one of the highest diabetes rates in the world, reported at 30.8%, followed by French Polynesia and Kuwait in terms of diabetes prevalence [2, 3].

Achieving proper glycemic control has been shown to reduce the risk of chronic complications associated with diabetes, as demonstrated by studies such as the Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS) [4]. Insulin therapy plays a crucial role in the management of diabetes to achieve glycemic control, particularly as the disease progresses over time. The combination of insulin and oral antidiabetic agents has been widely used and proven effective in improving glycemic control [5, 6].

International organizations such as the International Diabetes Federation (IDF) and the American Diabetes

Association (ADA) recommend the use of insulin in combination with oral agents when normoglycemia is not achieved [7, 8]. However, in developing countries, including Pakistan, the use of insulin therapy remains relatively low, with the World Health Organization (WHO) estimating that only 3% of people with diabetes receive insulin treatment [9].

While recombinant human insulin has demonstrated safety and efficacy in healthy volunteers [9, 10], further research is required to validate its clinical outcomes in individuals with diabetes, especially in regions with limited data on insulin safety and efficacy. Continuous surveillance is essential for identifying any potential adverse effects associated with recombinant human insulin. Therefore, this study aimed to assess the safety and efficacy of Insuget® (Human Insulin rDNA) in patients diagnosed with type II diabetes mellitus.

This is the first thorough assessment of the safety and effectiveness of Insuget® (human insulin rDNA) in Pakistani patients with type II diabetes mellitus (T2DM). Previous research on the safety and efficacy of recombinant insulin in this group has been limited, and this study fills that information gap. The researchers were able to closely evaluate the effects of Insuget® on patients with T2DM over six months by

performing an open-label, prospective, observational, single-arm, multicenter, post-marketing surveillance study. According to the findings, therapy with Insuget® resulted in considerable improvements in glycemic control and blood pressure.

2. Methods

2.1. Study Design

This study employed an open-label, prospective, observational, single-arm, multicenter, post-marketing surveillance design. The study duration was twelve months, with each participant enrolled for six months, from the start of therapy until the final assessment.

2.2. Ethics Approval and Registration

The study protocol was approved by the AEIRC Ethics Committee (Ref No. ERC/S20/P-005), and the study was registered on clinicaltrials.gov (NCT05161741) before participant enrollment.

2.3. Sampling Method and Sample Size Calculation

A non-probability consecutive sampling method was used to screen eligible patients for the study. Based on previous literature reporting a hypoglycemia rate of 41% in patients treated with regular human insulin, an estimated 10% increase in hypoglycemia incidence was considered for the current study. With a 95% confidence level, 5% margin of error, and 80% power of the study, the calculated sample size was determined to be $n = 191$.

2.4. Participant Selection

Male and female participants aged 18 years and above, diagnosed with type II diabetes mellitus (T2DM), with an HbA1c value of 7.0% or above, and exhibiting uncontrolled diabetes despite lifestyle modifications and oral or insulin therapy, were enrolled in seven tertiary care facilities. Specific exclusion criteria were applied to ensure the study's focus on patients with T2DM and minimize confounding factors. Patients with type I diabetes mellitus, severe hypoglycemia, hypersensitivity, coronary syndrome, renal or hepatic dysfunctions, psychiatric disorders, or any significant history of allergic drug reactions were excluded, and pregnant or lactating patients because of potential differences in metabolic needs during this period.

2.5. Intervention and Follow-up

After obtaining informed consent and conducting baseline assessments, the participants were advised to initiate Insuget® (Human Insulin rDNA) therapy. The investigator recommended the appropriate dose of Insuget® 70/30 and/or Insuget® N and/or Insuget® R based on standard clinical practices and individual patient requirements. Concomitant treatment for hypertension, dyslipidemia, and other associated

diseases was continued at the physician's discretion.

The choice of Insuget® was motivated by its novelty in the Pakistani environment, as prior research on the safety and effectiveness of recombinant insulin in patients with T2DM in Pakistan was limited. Furthermore, considering the expanding usage of Insuget® in clinical practice, the researchers were motivated by the need to assess the advantages and dangers of the drug in real-world settings. The 6-month research period may not represent the long-term benefits and safety profile of Insuget®. Long-term research is critical for evaluating the long-term benefits and possible side effects of insulin therapy. Furthermore, the study did not investigate possible differences in Insuget® response among patient subgroups according to age, gender, or comorbidities. Different populations may react differently to the insulin formulation, which should be considered when applying the findings to specific patient groups.

2.6. Data Collection and Assessments

Demographic information was collected during the baseline screening. Follow-up assessments were conducted at specific time points, including the first follow-up (4 to 6 weeks after therapy initiation), the second follow-up (3 months after therapy initiation), and the third follow-up (6 months after therapy initiation). Efficacy parameters, such as weight, blood pressure, HbA1c levels, and fasting blood sugar levels (FBS) were sequentially assessed during each follow-up visit. In addition, self-monitored blood glucose readings and adverse events related to hypoglycemia, hypokalemia, injection sites, and occurrences of serious adverse events leading to hospitalization were evaluated and recorded in patient diaries reviewed at each follow-up visit.

2.7. Statistical Analysis

To investigate the data and gain useful insights, statistical analyses used SPSS version 22.0. For continuous variables such as age, height, weight, BMI, blood pressure, diabetes duration, HbA1c, and FBS, descriptive statistics such as mean and standard deviation were determined. To provide a full overview of the study population, categorical data such as gender, smoking status, education level, comorbidities, and adverse events were provided as frequencies and percentages. A paired-sample t-test evaluated changes in variables, including HbA1c, FBS, weight, and blood pressure, from baseline to the 6-month follow-up. Additionally, an independent sample t-test compared the differences between patients who were already on insulin and those who were insulin-naïve. A p-value of 0.05 was considered statistically significant.

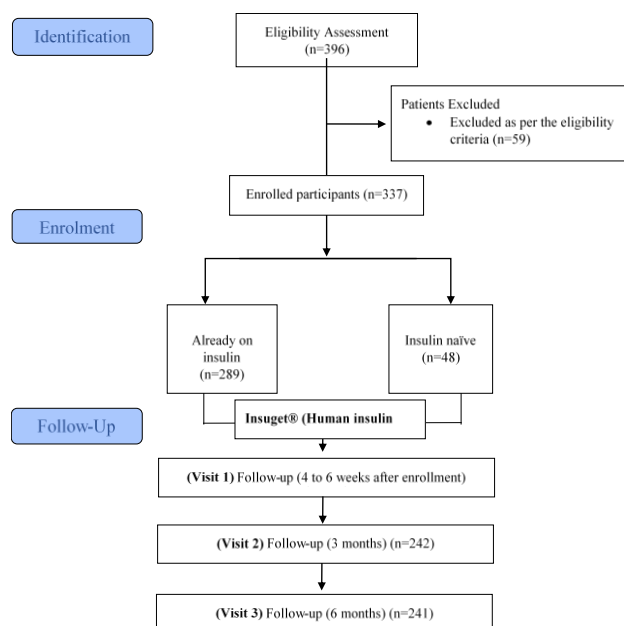


Fig. 1 CONSORT diagram of study flow

3. Results

3.1. Baseline Characteristics

Among the 337 enrolled patients, 63.5% were males and 17.5% were smokers. The most common concomitant disease was dyslipidemia (21.1%), followed by ischemic heart disease (9.8%). The mean duration of diabetes was 9.13 ± 5.59 years (Table 1).

Table 1 Baseline characteristics of the study participants (n = 337)

Variables		Mean $\pm$ SD
Age (years)		53.27 $\pm$ 11.10
Weight (kg)		76.30 $\pm$ 14.89
Height (inches)		65.07 $\pm$ 4.21
BMI (kg/m ²)		27.90 $\pm$ 5.10
The duration of diabetes (years)		9.13 $\pm$ 5.59
		n (%)
Gender	Female	123 (36.5)
	Male	214 (63.5)
Education level	Graduate or above	21 (6.2)
	Secondary or below	156 (46.3)
	Uneducated / No formal education	160 (47.5)
Concomitant diseases	Hypertension	195 (57.9)
	Dyslipidaemia	71 (21.1)
	Ischemic heart disease	33 (9.8)
	Chronic kidney disease	7 (2.1)
	Others	15 (4.5)

3.2. Efficacy Parameters

Table 2 demonstrates a substantial decrease in mean HbA1c and fasting blood sugar (FBS) levels after a 6-month treatment with Insuget® among patients who were already on insulin therapy and those who were insulin-naïve ($p < 0.01$). The reduction in HbA1c and FBS levels was greater in insulin-naïve patients; however, the difference was not statistically significant. The mean systolic and diastolic blood pressure also significantly improved (Table 2). However, there was a significant increase in the mean weight after treatment ($p < 0.01$).

Table 2 Comparison of efficacy parameters before and after treatment

Variables	Before treatment Mean $\pm$ SD	After treatment Mean $\pm$ SD	Mean difference	p-value
HbA1c (%)	9.81 $\pm$ 1.647	7.85 $\pm$ 1.34	1.95 $\pm$ 1.57	0.000*
Fasting blood sugar (mg/dl)	203.22 $\pm$ 60.82	125.53 $\pm$ 31.47	77.69 $\pm$ 60.83	0.000*
Systolic blood pressure (mm Hg)	137.58 $\pm$ 17.46	129.77 $\pm$ 9.88	7.80 $\pm$ 15.77	0.000*
Diastolic blood pressure (mm Hg)	85.99 $\pm$ 9.69	83.47 $\pm$ 7.09	2.51 $\pm$ 9.38	0.000*

* $p < 0.05$ is considered significant.

3.3. Adverse Events

The frequency of adverse events related to hypoglycemia and hypokalemia gradually decreased by the third follow-up visit (after 6 months) compared with the baseline measurement. However, the

frequency of injection site-related adverse events increased at the third follow-up visit compared with the first. The reported adverse events were generally mild (Table 3).

Table 3 Frequency of adverse events (safety parameters) before and after treatment

Variables	Follow-up visit 1 N (%)	Follow-up visit 2 N (%)	Follow-up visit 3 N (%)
Hypoglycemia related adverse event	63 (18.7)	44 (13.1)	47 (13.9)
Headache	37 (11.0)	25 (7.4)	35 (10.4)
Feeling of hunger	31 (9.2)	18 (5.3)	23 (6.8)
Drowsiness	17 (5.0)	22 (6.5)	26 (7.7)
Blurred vision	29 (8.6)	19 (5.6)	22 (6.5)
Sweating	17 (5.0)	9 (2.7)	8 (2.4)
Nausea	7 (2.1)	6 (1.8)	6 (1.8)
Confusion	16 (4.7)	13 (3.9)	13 (3.9)
Dizziness	21 (6.2)	11 (3.3)	17 (5.0)
Tachycardia	25 (7.4)	15 (4.5)	15 (4.5)
Tremor	13 (3.9)	6 (1.8)	8 (2.4)
Hypokalaemia related adverse event	55 (16.3)	38 (11.3)	45 (13.4)
Muscle Cramps	50 (14.8)	34 (10.1)	45 (13.4)

Continuation of Table 3

Weakness	39 (11.6)	22 (6.5)	25 (7.4)
Irregular heartbeat	5 (1.5)	6 (1.8)	6 (1.8)
Injection site-related adverse event	25 (7.4)	26 (7.7)	33 (9.8)
Pain	11 (3.3)	12 (3.6)	15 (4.5)
Redness	11 (3.3)	12 (3.6)	16 (4.7)
Irritation	17 (5.0)	19 (5.6)	21 (6.2)
Lipodystrophy	-	7 (2.1)	6 (1.8)

Follow-up visit 1 was after 4 to 6 weeks of initiation of therapy; follow-up visit 2 was after 3 months of initiation of therapy; follow-up visit 3 was after 6 months of initiation of therapy.

4. Discussion

The increasing burden of type II diabetes mellitus (T2DM) in developing countries, such as Pakistan, highlights the importance of accessible and affordable insulin options. Recombinant human insulin formulations have emerged as a cost-effective alternative that offers similar therapeutic effects at a lower cost. This improved accessibility reduces the need for medication rationing and enables individuals to receive adequate treatment despite limited healthcare resources. Existing literature supports the effectiveness of recombinant human insulin in individuals with T2DM who do not achieve glycemic control through diet and exercise alone, as well as in those with an inadequate response to oral agent regimens [11]. Intensive insulin therapy reduces the likelihood of diabetes complications. However, patient concerns regarding the fear of injections, hypoglycemia, or weight gain often lead to delays in initiating insulin therapy, thereby increasing the risk of complications for diabetic patients [12].

Treatment with human insulin rDNA in patients with T2DM offers several potential benefits, with improved glycemic control being the primary advantage. Our study observed significant improvements in glycemic control during the follow-up visits ($p < 0.01$). Specifically, 27.4% of patients achieved an HbA1c level below 7%, and 49.4% demonstrated fasting blood sugar (FBS) levels between 110 and 120 mg/dL at the final follow-up visit. These findings align with previous studies investigating recombinant human insulin formulations, which also reported substantial improvements in HbA1c and fasting blood glucose (FBG) levels [13,14]. Consistent with improved glycemic control, we observed a significant decrease in systolic and diastolic blood pressure after treatment. In poorly controlled Type II diabetes patients, initiating insulin therapy may temporarily raise blood pressure. However, over time, blood pressure tends to decrease. After four months of insulin treatment, blood pressure values continue to decline, sometimes reaching levels lower than before therapy, indicating the beneficial impact of insulin on blood pressure control in type II diabetes [15].

Aside from the benefits, it is critical to consider the

risk of weight gain linked to treatment with human insulin rDNA, as also found in our study. Individual factors impacting weight gain with insulin therapy may vary and include insulin dosage, food preferences, physical activity levels, and other related features [16, 17]. Hypoglycemia, a common adverse effect of insulin therapy, may lead to weight gain by boosting food consumption. Edgerton et al. compared weight gain with inhaled human insulin and subcutaneous insulin and found weight gain in both groups but significantly less in the inhaled insulin group. This shows that inhaled insulin may affect energy balance and hypoglycemic snacking [18]. Moreover, studies have demonstrated that long-acting insulin analogs such as glargine, detemir, and deluded are associated with a lower incidence of nocturnal hypoglycemia compared with intermediate-acting human insulin (Neutral protamine Hagedorn-NPH), as reported in [19] and [20]. A systematic review of 70 studies compared the advantages and disadvantages of insulin analogs, specifically insulin degludec, detemir, and glargine, in patients with diabetes. The review indicated that deluded was associated with a lower incidence of hypoglycemia than glargine. Additionally, individuals taking detemir experienced less weight gain compared with those receiving degludec or glargine [21]. Notably, in adults with type II diabetes, insulin detemir showed a slight advantage over glargine in terms of weight gain, as proposed in [21].

Safety data from our study revealed mild adverse events in patients treated with Insuget® (human insulin rDNA), with no serious adverse events reported. The frequency of hypoglycemia and hypokalemia-related adverse events decreased by the third follow-up visit. In contrast, injection site-related adverse events increased during follow-up visits. These findings are supported by existing literature, which indicates that patients treated with recombinant human insulin commonly experience at least one episode of symptomatic hypoglycemia, with a few cases being moderate or severe [13]. A critical systematic review [21] concluded that detemir had a higher likelihood of causing adverse events leading to treatment discontinuation than glargine. In addition, mild or moderate hypersensitivity events were found to be more frequent in patients receiving recombinant human insulin than in those receiving semisynthetic human insulin [13]. Some evidence shows that rapid-acting insulin agents may have lower antigenicity than long-acting agents. The authors of [22] discovered that the persistent cutaneous insulin allergy is associated with

the aggregation of high-molecular-weight insulin molecules. Consequently, rapid-acting insulin analogs that rapidly dissociate into monomers may have a reduced likelihood of inducing allergies [23]. This theory is supported by several case reports in which successful management of insulin allergy was achieved by transitioning to rapid-acting agents such as insulin lispro, insulin aspart, or insulin glulisine [24-26]. Conversely, the authors of [27] proposed that the long-acting insulin analog glargine might have lower antigenicity than other analogs because its slow dissolution could mimic a desensitization process. In addition, the continuous subcutaneous insulin infusion has been linked to decreased allergenicity, potentially due to the smaller amounts of insulin delivered [28]. These injection site-related AEs frequently occur because of the poor injection technique. The literature contains evidence that injection-site reactions can be significantly reduced through educational training on regular site rotation and improved injection techniques [29].

Our study demonstrates that recombinant insulin therapy has a significant positive impact on glycemic control and various patient-related factors, including blood pressure and symptoms related to hypoglycemia and hypokalemia. Therefore, this therapy contributes to an overall improvement in patient care. These conclusions align with previous studies, highlighting the crucial role of recombinant human insulin therapy, accompanied by effective education and counseling, in treating diabetes. Therefore, ongoing patient education and support programs on disease management and the proper use of human insulin are essential. Expanding the availability of human insulin in LMIC nations can support programs that promote early initiation of insulin therapy, enhance glycemic control in local populations, and ultimately delay or prevent the long-term consequences of diabetes [30].

Various limitations exist to the current study that must be addressed when interpreting the findings. The study sample size was modest, which may restrict the data's generalizability to a larger population. More studies and continued monitoring are needed to assess the long-term safety and efficacy of human insulin rDNA, particularly in diverse people and real-world situations. Efforts should also be made to enhance patient education and support programs focusing on illness management and the proper use of human insulin. We can make substantial progress in treating diabetes and enhancing the quality of life for patients with this chronic condition if we address the difficulties and ensure widespread access to effective insulin therapy.

5. Conclusion

This study confirms the safety and efficacy of Insuget® (human insulin rDNA) in patients with T2DM, consistent with previously published studies on

recombinant insulin. It has been demonstrated that human insulin rDNA was effective in maintaining glycemic control and exhibited a good safety profile with minimal adverse events reported.

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Informed Consent Statement

Informed consent was obtained from all individual participants involved in the study.

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