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QUESTIONARY BASED AWARENESS FOR INSULIN PRODUCT BY COMMUNITY PHARMACIST IN AMRAVATI DISTRICT.

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1. Abstract:

Insulin is a hormone created by our pancreas that controls the amount of glucose in our bloodstream at any given moment. The hormone insulin is made in the beta cells, which are part of the Islets of Langerhans. These islets also have alpha cells, which make glucagon, as well as delta cells. With each meal, beta cells release insulin to help the body use or store the blood glucose (blood sugar) it gets from food. The study aimed to assess the perception of adverse drug reactions (ADRs) of insulin and investigate the effect of being a member of a patient organization for insulin on these factors.

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2. INTRODUCTION:

Insulin is a peptide hormone produced by beta cells of the pancreatic islets encoded in humans by the INS gene. Insulin, a hormone composed of 51 amino acids, plays important roles in glucose homeostasis, cell growth, and metabolism[1]. Insulin is a hormone created by our pancreas that controls the amount of glucose in our bloodstream at any given moment[2]. It also helps store glucose in your liver, fat, and muscles, it regulates your body's metabolism of carbohydrates, fats, and proteins. The pancreas is an organ behind the stomach that is the main source of insulin in the body. Clusters of cells in the pancreas called islets produce the hormone and determine the amount based on blood glucose levels in the body[3]. The higher the level of glucose, the more insulin goes into production to balance sugar levels in the blood. Insulin also assists in breaking down fats or proteins for energy[4]. A delicate balance of insulin regulates blood sugar and many processes in the body. If insulin levels are too low or high, excessively high or low blood sugar can start to cause symptoms. If a state of low or high blood sugar continues, serious health problems might start to develop[5].

In addition to its role in diabetes, the recent literature indicates that insulin acts on several key organs in the body, including the brain, heart, kidney, bone, skin, and hair follicles, to perform important physiological roles[6]. Insulin aids bone formation, attenuates osteoporosis-related inflammation, acts on the central nervous system, and performs pro- and anti-atherogenic functions in the vascular system. Recent advances in insulin research have led to insulin-signaling targeted therapies and insulin-signaling activators being used as protective measures against several diseases[7]. Clinical and laboratory studies have indicated that metformin, an insulin-receptor activator, has properties that protect the kidneys from injury. Similarly, sulfonylurea, through its activities on enhanced insulin secretion via its actions on pancreatic β cells, augmented insulin secretion. Currently, available forms of insulin include insulin mixtures, concentrated insulins, and insulins with alternate routes of administration, providing several options for people living with diabetes. Exogenous insulins are now available in the form of rapid-acting, short-acting, intermediate-acting, and long-acting[8].

Types of insulin

A person can take different types of insulin based on how long they need the effects of the supplementary hormone to last. People categorize these types based on several different factors[9]:

Three main groups of insulin are available.

1)Fast-acting insulin

The body quickly absorbs this type into the bloodstream from the subcutaneous tissue. People use fast-acting insulin to correct hyperglycemia, or high blood sugar, as well as control blood sugar spikes after eating. This type includes:

Rapid-acting insulin analogs: These take between 5 and 15 minutes to have an effect. However, the size of the dose impacts the duration of the effect. Assuming that rapid-acting insulin analogs last for 4 hours is a safe general rule. Examples: Aspart (Novolog), and Lispro (Humalog).

Regular human insulin: The onset of regular human insulin is between 30 minutes and an hour, and its effects on blood sugar last around 8 hours. A larger dose speeds up the onset but also delays regular human insulin's peak effect. Examples: Humulin R, Novolin R

2)Intermediate-acting insulin This type enters the bloodstream at a slower rate but has a longer-lasting effect. It is most effective at managing blood sugar overnight, as well as between meals.

Options for intermediate-acting insulin include:

NPH human insulin: This takes between 1 and 2 hours to onset, and reaches its peak within 4 to 6 hours. It can last over 12 hours in some cases. A very small dose will bring forward the peak effect, and a high dose will increase the time NPH takes to reach its peak and the overall duration of its effect. Examples: Humulin N, Novolin N.

Pre-mixed insulin: This is a mixture of NPH with fast-acting insulin, and its effects are a combination of intermediate- and rapid-acting insulins. The mixtures can be in various combinations from 50:50 to 75:25 or 70:30. An example includes Novolog 70/30.

3)Long-acting insulin

While long-acting insulin is slow to reach the bloodstream and has a relatively low peak, it stabilizes the "plateau" effect on blood sugar that can last most of the day. Glargine (Lantus) is an example. It is useful overnight, between meals, and during fasts.

Long-acting insulin analogs are the only available type, and these have an onset of between 1.5 and 2 hours. While different brands have different durations, they range between 12 and 24 hours in total.

4) Ultra-long-acting insulin

Reaching the bloodstream in about six hours, this type of insulin has the same level of effectiveness for several hours (it does not peak). It can last up to two days[10].

2.2 Regulation of Insulin Secretion

The human pancreas contains one to two million pancreatic islets housing different endocrine cells, primarily insulin-secreting β cells, glucagon-producing α cells, and somatostatin-secreting δ cells. Although islets compose only 1–2% of the human pancreas, they receive up to 10% of the total pancreatic blood supplies. Generally, insulin is released after ingesting glucose in a process named glucose-induced insulin stimulation. This process requires both the intracellular uptake and metabolic degradation of ingested glucose. In human β cells, glucose transporter 1 (GLUT1, encoded by SLC2A1) and GLUT3 (encoded by SLC2A3) are the prominent glucose transporters, whereas GLUT2 (encoded by SLC2A2) has been reported as a major glucose transporter in rodent. This difference could be attributed to the differences in Km values of different isoforms of glucose transporters.

The phosphorylation of glucose by the enzyme glucokinase (GCK) is the first step in glucose metabolism. Glucose phosphorylation by GCK is related to insulin secretion; therefore, GCK gene dysfunction or aberration leads to decreased glucose-mediated insulin release and glucose intolerance or diabetes. A major understanding of insulin secretion is derived from the research using rodent models, whereas few studies have been described in humans.Research has indicated that incretins are capable of binding to G-protein-coupled receptors on β cell membranes and increasing cellular 30,50 -cyclic adenosine monophosphate (cAMP) levels and glucose-stimulated insulin secretion (GSIS) in the presence of higher glucose levels. Indeed, the action of incretins is somewhat resistant to diazoxide; therefore, it is independent of KATP channel closure. As a consequence, cAMP induces an upsurge in the size/amount of readily releasable pools in a glucose concentration-dependent manner within insulin granule dynamics. It is worth noting that incretin peaks the activity of the β cells in the presence of active glucose concentrations in a Ca2+-independent manner, even in Ca2+-devoid conditions[11].

2.3 Insulin Signaling Pathways

This results in the phosphorylation of insulin receptor substrate (IRS) and the subsequent activation of two primary signaling pathways, viz. the phosphoinositide3-kinase (PI3K)/protein kinase B (Akt)pathway and the mitogen-activated protein kinase (MAPK) pathway[12].

2.4 The PI3K/Akt Signaling Pathway

The regulatory roles of insulin in cellular function and energy metabolism are largely mediated by the PI3K/Akt pathway. Once activated by IRS, PI3K phosphorylates phosphatidylinositol 4,5-bisphosphate to produce phosphatidylinositol 3,4,5-triphosphate, which phosphorylates and thus activates, 3-phosphoinositide-dependent protein kinase-1(PDK1). PDK1 then activates Akt, which mediates multiple cellular functions. Activated Akt phosphorylates glycogen synthase kinase to deactivate it and inhibits glycogen synthase and ATP-citrate lyase activity, thereby inhibiting glycogen and fatty acid synthesis, respectively. Akt also inactivates the mammalian target of rapamycin complex 1 to promote protein synthesis[13]. In addition, Akt mediates cell survival by inhibiting the proapoptotic pathway, and it activates sterol regulatory binding proteins (SREBPs), which translocate to the nucleus to transcribe genes associated with fatty acid and cholesterol synthesis. The PI3K/Akt signaling pathway also regulates the translocation of the insulin-sensitive glucose transporter GLUT4 to the membrane of muscle and fat cells for glucose uptake.GLUT4 translocation involves the IR-facilitated phosphorylation of Cbl-associated protein (CAP) and the production of the CAP:CBL: CRKII compex.

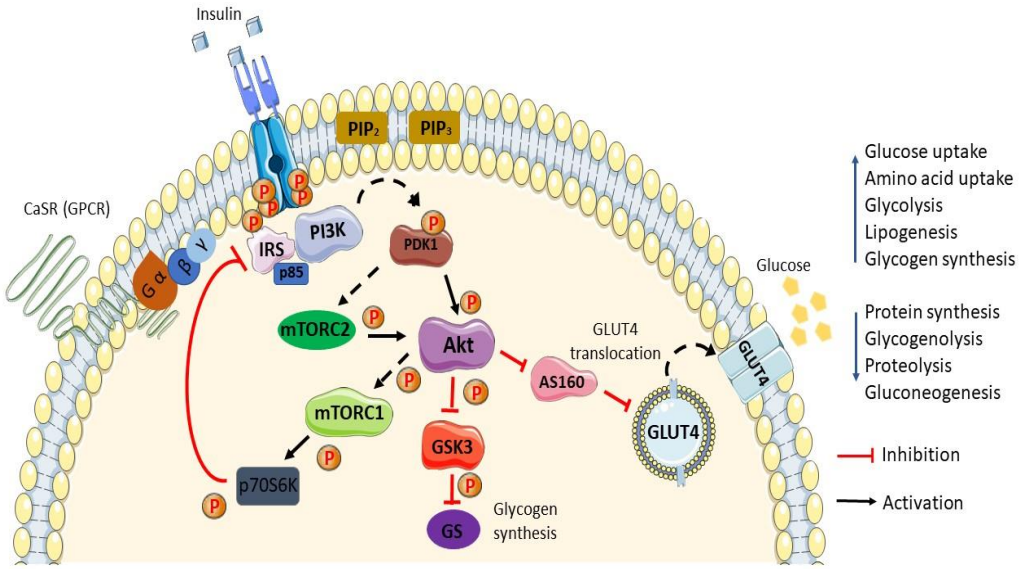

Fig 1:- The PI3K/Akt Signaling Pathway.[1]

2.5 The MAPK Signaling Pathway

The MAPK pathway is activated when IRS-1 binds to growth factor receptor-bound protein 2 (Grb2). SOS binds to Grb2 and then to Ras, causing GDP–GTP exchange and the activation of RAS

Activated Ras recruits c-Raf, which phosphorylates and activates MAPK/Erk kinase (MEK). MEK then phosphorylates extracellular signal-regulated kinase (Erk). Once activated, Erk is translocated to the nucleus, where it is subsequent phosphorylation and transcriptional activation by transcription factors, such as ELK1, ultimately promote cell division, protein synthesis, and cell growth[14].

2.6 Side Effects of Insulin:

The more common side effects that occur with insulin regular (human) include:

- Swelling of your arms and legs
- Weight gain
- Trouble concentrating or confusion
- Blurred vision
- Slurred speech
- Itching
- Shrinking or thickening skin at the injection sites
- If these effects are mild, they may go away within a few days or a couple of weeks. If they're more severe or don't go away, talk to your doctor or pharmacist[15].

2.7 Severe Side Effects:

- Blurred or impaired vision
- Weakness
- Muscle cramps
- Constipation
- Breathing problems (at a severe stage without medical attention)
- Heart rhythm problems (at a severe stage without medical attention)
- Serious allergic reaction. Symptoms include:
- Sudden weight gain[16].

Drug forms and strengths

Brand: Humulin R

- Form: injectable solution, 3 mL and 10 mL vials
- Strength: 100 units/mL
- Form: injectable solution, 20 mL vial
- Strength: 500 units/mL
- Form: injectable solution, 3 mL KwikPen
- Strength: 500 units/mL[17].

Dosage for type 1 diabetes

✓ Adult dosage (ages 18–64 years)

Insulin regular (human) is usually given three or more times per day before meals.

You should eat your meal within 30 minutes after giving an injection.

Average insulin requirements range between 0.5 and 1 unit/kg per day.

If you're just starting insulin therapy, your dosage may be lower, between 0.2 and 0.4 units/kg per day.You'll inject insulin regularly (human) under your skin in the fatty part of your abdomen, thigh, buttocks, or back of your arm.[18].

✓ Child dosage (ages 0–17 years)

The total daily insulin requirements for children are usually between 0.5 and 1 unit/kg per day.

Children who haven't gone through puberty yet may need more insulin. Dosages may be between 0.7 and 1 unit/kg per day.

✓ Senior dosage (ages 65 years and older)

Your body may process this drug more slowly. Your doctor may start you on a lower dosage so that too much of this drug doesn't build up in your body. Too much of the drug in your body can be dangerous[19].

Dosage for type 2 diabetes

✓ Adult dosage (ages 18–64 years)

Insulin regular (human) is usually given three or more times per day before meals.

You should eat your meal within 30 minutes after giving an injection.

Average insulin requirements range between 0.5 and 1 unit/kg per day.

If you're just starting insulin therapy, your dosage may be lower, between 0.2 and 0.4 units/kg per day.

You'll inject insulin regularly (human) under your skin in the fatty part of your abdomen, thigh, buttocks, or back of your arm. This is where insulin is absorbed fastest.

✓ Child dosage (ages 0–17 years)

The total daily insulin requirements for children are usually between 0.5 and 1 unit/kg pday. Children who haven't gone through puberty yet may need more insulin. Doses may be between 0.7 and 1 unit/kg per day.[20].

Special dosage considerations

For people with kidney disease: Insulin is generally removed from your body by your kidneys. If your kidneys aren't working as well, insulin may build up in your body and cause low blood sugar. Your doctor may start you at a lower dosage and slowly increase it if needed.

For people with liver disease: If you have liver disease, this drug may build up in your body. Your doctor may start you at a lower dosage and slowly increase it if needed. You and your doctor should monitor your blood sugar very closely[21].

2.9 Factors responsible for insulin ADR

Factor	Reason for ADR	Prevention/Treatment
Age	Age 45–64 years	withdrawing inappropriate medication
Medication history	Possibility Drug-Insulin interaction can cause ADR	Safe prescribing the drug is a key aspect
Exercise of injected area	Strenuous exercise of a limb within an hour of injection will speed insulin absorption. Clinically significant for regular insulin analogs.	Wait for at least 45 minutes after the injection to exercise a part of the body that is near the injection site.
Obesity	Obesity especially excess fat in your belly and around your organs (visceral fat), is a primary cause of ADR	Certain insulin preparations eg Determir and Degludec are commercialized and promoted with less risk of weight increase as one very important property and therefore suitable also for
Temperature	Heat can increase absorption rate, including the use of a sauna, shower, or hot bath soon after injection. Cold has the opposite effect.	you can always keep an ice pack with you when you're out. Keep the ice pack in the same bag as your diabetes kit containing your insulin.
Insulin dose	Larger doses delay insulin action and prolong duration.	Dose adjustment/take the prescribed dose within time.

Table no 1 Factors responsible for insulin ADR [22]**.**

2.10 Line of treatment/ Options for second-line insulin regimens:

When treatment, including lifestyle and oral hypoglycaemic drugs, has been optimized but glycaemic control is still unsatisfactory, the options for second-line insulin therapy are [23].

1. Substituting a twice-daily premixed insulin, increasing it to three times daily if required. When switching from a basal regimen to twice-daily injections of premixed insulins, the initial dose should be 80% of the final basal dose; this should then be titrated to target over 2 weeks [24].
2. Basal plus meal-time injections with a short-acting insulin analog, beginning with one additional injection per day (determined by the highest postprandial reading from blood glucose monitoring), and increasing injection frequency according to need (basal-plus); meal-time doses are adjusted according to blood glucose measurement. This regimen is not common clinical practice [25].
3. A full basal-bolus regimen (a basal dose plus injections of a short-acting insulin analog with every meal); meal-time doses are calculated according to blood glucose measurement [26].

The Expert Panel did not make recommendations for choosing specific insulins. Clinical experience shows that the preferences and capabilities of patients and the support available to them are the main determinants for choosing a second-line insulin regimen [27]. These options should be discussed with the patient, who should participate fully in the decision to agree on a regimen. GPs and practice nurses should consider requesting specialist help at any stage[28].

2.11 Insulin drug interaction

Insulin interacts with several medications. These include other diabetes medications, blood pressure medications, and atypical antipsychotics. Corticosteroids, certain antibiotics, and even alcohol can also pose issues. These interactions often cause low blood glucose. But some of them weaken the effects of insulin, which causes high blood glucose[29].

Proper diabetes management is key to a healthy life. If you're taking insulin, check with your pharmacist or healthcare provider about any possible interactions that need to be addressed. In most cases, these interactions can be managed by adjusting your insulin dose[30].

3. METHODOLOGY:

A validated self-administered questionnaire that was created with assistance from a professor from our college and several articles was given to 20 pharmacists in the Amravati/dharni region as part of a cross-sectional study. There were 20 questions in this cross-sectional questionnaire-based observational survey. Within the following 10 minutes, the respondents completed the questionnaires and returned them to us. Thus, data from completed questionnaires were analysed.

The study is set up as follows:

1. A questionnaire was created based on themes like pharmacovigilance, fundamental ADR knowledge, the process of reporting an ADR, and some of the pharmacists' own opinions on ADRs.
2. Completed and printed survey questionnaire forms.
3. We physically visited every medical retailer, and we filled up survey questionnaires with the pharmacists' opinions.
4. Responses of the YES, NO, or MAY BE kind were collected.
5. A review of the information gathered.

The following criteria were used to develop the questionnaire:

Whether the chemist is aware of the fundamentals of pharmacovigilance and about pharmacovigilance and its goals is the first pharmacovigilance perspective. Indian National Pharmacovigilance Program

1. Knowledge of adverse drug reactions (ADR) and its implications.
2.Helpline number to report ADR Reported; new technique to locate the ADR.
3. Knowledge of ADR reporting.
4. The chemist's competence in filing an ADR.
5. If and how to recognise an ADR.
6.Whether or not pharmacists should be required to report ADRs.
7.The most typical kind of ADR.
8. ADR reporting practises in the workplace
9. Pharmacists are among the most crucial health care providers for ADR reporting.
10. If any training is required before reporting an ADR.
11. Participation in treatment selection decisions.

Dr. Rajendra Gode Institute of Pharmacy, Amravati
ADR Survey Form
Questionary Based awareness for Insulin Product by Community pharmacist in Amravati District

Sr.No	Questions related to Insulin Product	% Response
1	Do you know about pharmacovigilance and its purpose?	89%
2	Do you know how to identify Adverse drug reaction?	90%
3	Do you know which new techniques are used in finding Adverse Drug Reaction?	25%
4	Do you know how and where to report an Adverse drug reaction to an authorized person or in ADR center?	75%
5	Do you know about help line number of ADR office or where it located	75%
6	Do you know the difference between Adverse drug reaction and Adverse Event?	35%
7	Is it safe to take insulin with a pen device?	95%
8	Is insulin the best treatment for type 2 diabetes?	45%
9	Is type 1 diabetes is rare in adults?	55%
10	Do you need a prescription to buy insulin?	90%
11	Is taking insulin daily harmful?	40%
12	Did you know the proper storage of Insulin?	60%
13	Does Insulin affect other medicine I take?	35%
14	Is it more effective if I take my insulin in the morning instead of the evening?	45%
15	Do you believe Insulin available in market are safe?	75%
16	Do you experienced adverse drug reaction during Insulin treatment?	35%
17	Can type 2 diabetes go without insulin?	40%
18	Is there any line of treatment to prevent ADR from insulin?	45%
19	Is there maximum percentage of people showing ADR caused by insulin?	20%
20	Does previous treatment of patient can cause ADR related to insulin?	30%

Table no 2 ADR Survey Form

4.RESULTS AND DISCUSSION:

This is the first study we have performed to analyse and compare Information and Vision regarding pharmacovigilance and ADR reporting among community Pharmacists in the Amravati/Dharni District. The current study had a 100% response rate, and the results showed that knowledge and opinion were better among the young chemists than the elderly ones, which is not surprising given that pharmacy students are exposed to all the basic features of pharmacovigilance in their syllabus during the academic years. It was also visible in the knowledge-based study question to the community chemist, who were found to be better knowledgeable about pharmacovigilance and fundamental common ADRs reporting a reaction. This is because kids are taught about drug detection, testing, comprehension, and prevention to some extent in their curriculum. The questionnaire-based survey included 20 questions separated into five phases: basic understanding of pharmacovigilance, basic knowledge of adverse drug reactions, reporting of ADRs, and reporting of ADRs. Personal views of pharmacists based on awareness.

The poll included a total of 20 medical stores, which were individually visited for one-on-one interactions with the respective Pharmacists. The Pharmacist completed and signed the paperwork, which was then only collected. This survey provided insight into the chemist's knowledge of Adverse Drug Reactions (ADRs) and Pharmacovigilance.

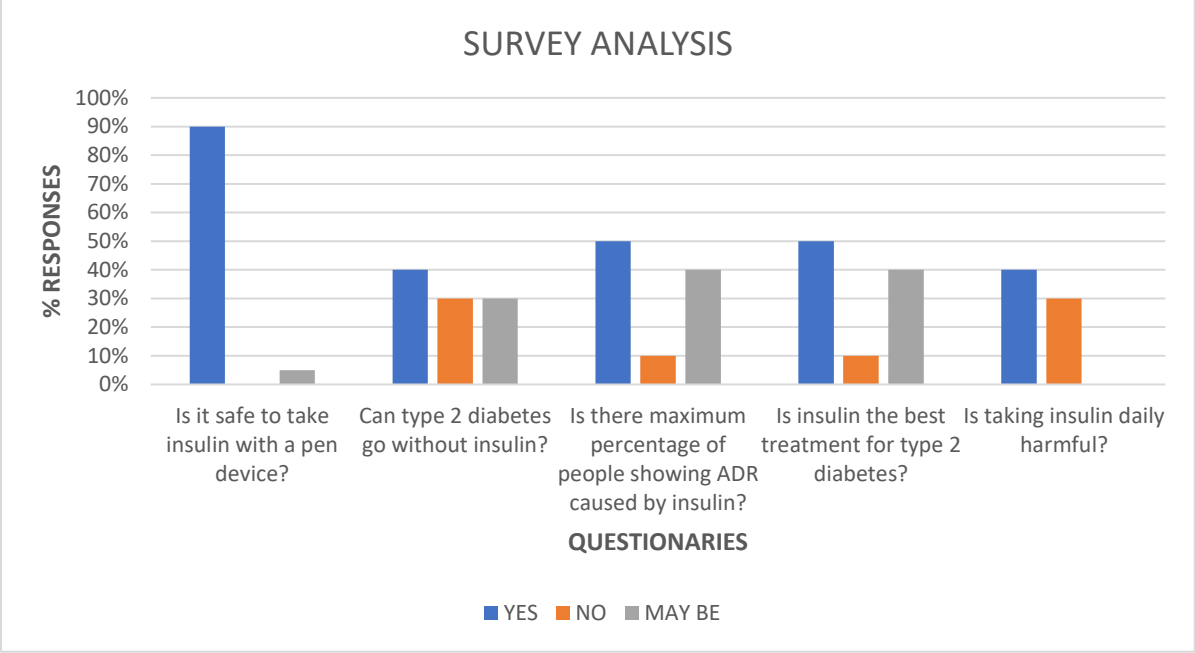

Table no 3 Survey Analysis

During the survey, it was discovered that some pharmacists were unaware and lacked basic information about reporting an ADR, whereas others were found to be aware and knowledgeable about the process of reporting an ADR and to be cooperative in nature and willing to share their views and information based on their experience. Pharmacists who were unfamiliar were given basic information regarding ADR reporting and encouraged to report an ADR. During the survey, we also encountered the following difficulties with Pharmacists:

- Pharmacists' refusal to cooperate.
- Being hesitant owing to a lack of knowledge.
- Failing to reveal one's identify.
- Making excuses like a lack of time.
- Avoiding questions about demographics.

5. CONCLUSION:

The paper has used survey data to assess the perception of risk for developing adverse drug reactions (ADRs) of insulin after administration and to investigate the effect of being a member of a patient organization for insulin on these factors, in comparison with other patients. Additionally, the paper has used information on the physiology of insulin-producing cells and the options for second-line insulin therapy.

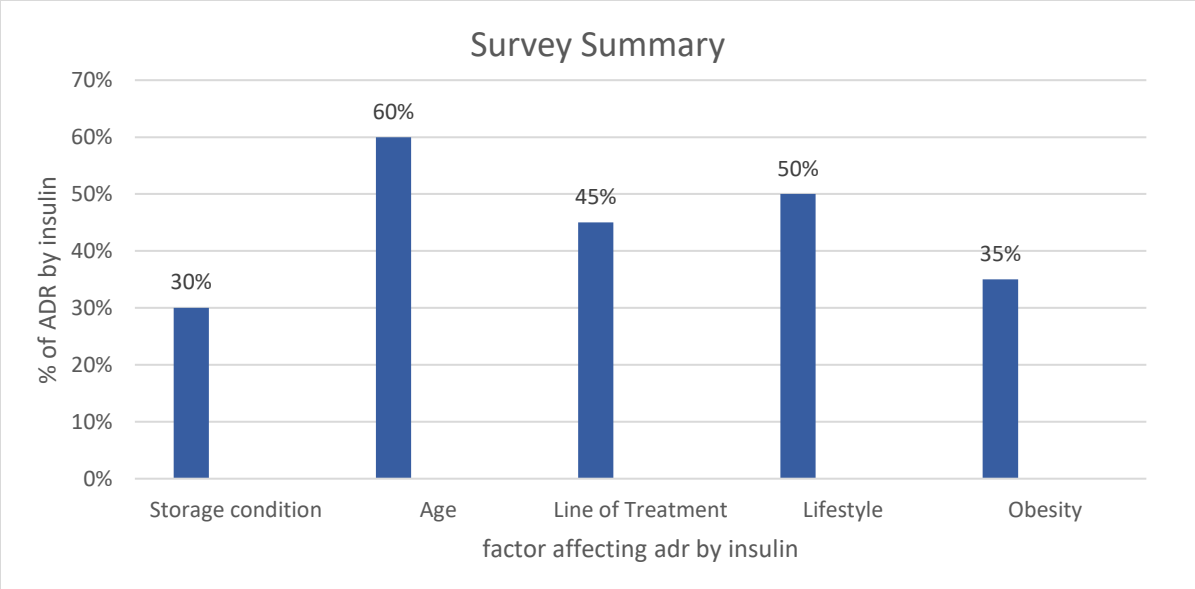

Table no 4 Survey Summary

The conclusions drawn from the paper are that age is a significant factor contributing to adverse drug reactions (ADRs) caused by insulin, with 60% of the survey respondents indicating age as a major factor for ADRs. The study suggests that to minimize ADRs, second-line treatment is available, and precautions such as avoiding self-medication, polypharmacy, and glucose monitoring can be effective measures to minimize ADRs caused by insulin. The paper emphasizes the importance of patient education and awareness regarding insulin use and ADRs. The study also highlights the need for updating pharmacists on counseling expertise and encouraging reporting of ADRs and patient-oriented services to pharmacists to have a positive influence on the healthcare system.

6. REFERENCES:

1. M. S. Rahman *et al.*, "Role of insulin in health and disease: An update," *Int. J. Mol. Sci.*, vol. 22, no. 12, pp. 1–19, 2021, doi: 10.3390/ijms22126403.
2. R. Khursheed *et al.*, "Treatment strategies against diabetes: Success so far and challenges ahead.," *Eur. J. Pharmacol.*, vol. 862, p. 172625, Nov. 2019, doi: 10.1016/j.ejphar.2019.172625.
3. A. Chaudhury *et al.*, "Clinical Review of Antidiabetic Drugs: Implications for Type 2 Diabetes Mellitus Management.," *Front. Endocrinol. (Lausanne).*, vol. 8, p. 6, 2017, doi: 10.3389/fendo.2017.00006.
4. V. R. A/L B Vasanth Rao, S. H. Tan, M. Candasamy, and S. K. Bhattamisra, "Diabetic nephropathy: An update on pathogenesis and drug development.," *Diabetes Metab. Syndr.*, vol. 13, no. 1, pp. 754–762, 2019, doi: 10.1016/j.dsx.2018.11.054.
5. K. Papatheodorou, M. Banach, M. Edmonds, N. Papanas, and D. Papazoglou, "Complications of Diabetes.," *Journal of diabetes research*, vol. 2015. England, p. 189525, 2015. doi: 10.1155/2015/189525.
6. S. Kalra *et al.*, "Consensus Recommendations on Sulfonylurea and Sulfonylurea Combinations in the Management of Type 2 Diabetes Mellitus - International Task Force.," *Indian J. Endocrinol. Metab.*, vol. 22, no. 1, pp. 132–157, 2018, doi: 10.4103/ijem.IJEM_556_17.
7. S. Padhi, A. K. Nayak, and A. Behera, "Type II diabetes mellitus: a review on recent drug based therapeutics.," *Biomed. Pharmacother.*, vol. 131, p. 110708, Nov. 2020, doi: 10.1016/j.biopha.2020.110708.
8. C. Matos, F. van Hunsel, R. Tavares Ribeiro, D. Nascimento do Ó, and J. F. Raposo, "Diabetes patient's pharmacovigilance knowledge and risk perception: the influence of being part of a patient organisation.," *Ther. Adv. drug Saf.*, vol. 11, p. 2042098620953935, 2020, doi: 10.1177/2042098620953935.
9. G. Durrieu, C. Hurault, V. Bongard, C. Damase-Michel, and J. L. Montastruc, "Perception of risk of adverse drug reactions by medical students: influence of a 1 year pharmacological course.," *Br. J. Clin. Pharmacol.*, vol. 64, no. 2, pp. 233–236, Aug. 2007, doi: 10.1111/j.1365-2125.2007.02882.x.
10. P. Comtex, N. Network, and N. Biod, "Biodel Inc . Announces VIAject (TM) Data at Oral Presentation at the American Diabetes Association Meeting," 2007.
11. Z. Fu, E. R. Gilbert, and D. Liu, "Regulation of

insulin synthesis and secretion and pancreatic Beta-cell dysfunction in diabetes.," *Curr. Diabetes Rev.*, vol. 9, no. 1, pp. 25–53, Jan. 2013.
12. J. Boucher, A. Kleinridders, and C. R. Kahn, "Insulin receptor signaling in normal and insulin-resistant states.," *Cold Spring Harb. Perspect. Biol.*, vol. 6, no. 1, Jan. 2014, doi: 10.1101/cshperspect.a009191.
13. X. Huang, G. Liu, J. Guo, and Z. Su, "The PI3K/AKT pathway in obesity and type 2 diabetes.," *Int. J. Biol. Sci.*, vol. 14, no. 11, pp. 1483–1496, 2018, doi: 10.7150/ijbs.27173.
14. P. Wee and Z. Wang, "Epidermal Growth Factor Receptor Cell Proliferation Signaling Pathways.," *Cancers (Basel).*, vol. 9, no. 5, May 2017, doi: 10.3390/cancers9050052.
15. D. Schröder and H. Zühlke, "Gene technology, characterization of insulin gene and the relationship to diabetes research.," *Endokrinologie*, vol. 79, no. 2, pp. 197–209, Jun. 1982.
16. W. T. Cefalu, "Insulin resistance: cellular and clinical concepts.," *Exp. Biol. Med. (Maywood).*, vol. 226, no. 1, pp. 13–26, Jan. 2001, doi: 10.1177/153537020122600103.
17. F. Kulozik and C. Hasslacher, "Insulin requirements in patients with diabetes and declining kidney function: differences between insulin analogues and human insulin?," *Ther. Adv. Endocrinol. Metab.*, vol. 4, no. 4, pp. 113–121, Aug. 2013, doi: 10.1177/2042018813501188.
18. H. Of *et al.*, "INDICATIONS AND USAGE HUMULIN R U-500 is a concentrated human insulin indicated to improve glycemic control in adult and pediatric patients with diabetes mellitus requiring more than 200 units of insulin per day.
19. Rubino, L. J. McQuay, S. C. Gough, M. Kvasz, and P. Tennis, "Delayed initiation of subcutaneous insulin therapy after failure of oral glucose-lowering agents in patients with Type 2 diabetes: a population-based analysis in the UK.," *Diabet. Med.*, vol. 24, no. 12, pp. 1412–1418, Dec. 2007, doi: 10.1111/j.1464-5491.2007.02279.x.
20. G. A. Nichols, Y. H. Koo, and S. N. Shah, "Delay of insulin addition to oral combination therapy despite inadequate glycemic control: delay of insulin therapy.," *J. Gen. Intern. Med.*, vol. 22, no. 4, pp. 453–458, Apr. 2007, doi: 10.1007/s11606-007-0139-y.
21. H. Yki-Järvinen *et al.*, "Effect of obesity on the response to insulin therapy in noninsulin-dependent diabetes mellitus.," *J. Clin. Endocrinol. Metab.*, vol. 82, no. 12, pp. 4037–4043, Dec. 1997, doi: 10.1210/jcem.82.12.4460.
22. M. J. Alomar, "Factors affecting the development of adverse drug reactions (Review article).," *Saudi Pharm. J. SPJ Off. Publ. Saudi Pharm. Soc.*, vol. 22, no. 2, pp. 83–94, Apr. 2014, doi: 10.1016/j.jsps.2013.02.003.
23. A. Barnett, A. Begg, P. Dyson, M. Feher, S. Hamilton, and N. Munro, "Insulin for type 2 diabetes: choosing a second-line insulin regimen.," *Int. J. Clin. Pract.*, vol. 62, no. 11, pp. 1647–1653, Nov. 2008, doi: 10.1111/j.1742-1241.2008.01909.x.
24. J. Rosenstock, M. Davies, P. D. Home, J. Larsen, C. Koenen, and G. Schernthaner, "A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes.," *Diabetologia*, vol. 51, no. 3, pp. 408–416, Mar. 2008, doi: 10.1007/s00125-007-0911-x.
25. R. G. Bretzel, U. Nuber, W. Landgraf, D. R. Owens, C. Bradley, and T. Linn, "Once-daily basal insulin glargine versus thrice-daily prandial insulin lispro in people with type 2 diabetes on oral hypoglycaemic agents (APOLLO): an open randomised controlled trial.," *Lancet (London, England)*, vol. 371, no. 9618, pp. 1073–1084, Mar. 2008, doi: 10.1016/S0140-6736(08)60485-7.
26. L. Monnier, H. Lapinski, and C. Colette, "Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA(1c).," *Diabetes Care*, vol. 26, no. 3, pp. 881–885, Mar. 2003, doi: 10.2337/diacare.26.3.881.
27. R. R. Holman *et al.*, "Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes.," *N. Engl. J. Med.*, vol. 357, no. 17, pp. 1716–1730, Oct. 2007, doi: 10.1056/NEJMoa075392.
28. M. J. Calvert, R. J. McManus, and N. Freemantle, "Management of type 2 diabetes with multiple oral hypoglycaemic agents or insulin in primary care: retrospective cohort study.," *Br. J. Gen. Pract. J. R. Coll. Gen. Pract.*, vol. 57, no. 539, pp. 455–460, Jun. 2007.
29. O. Gawa, :"»„,°„˝ß `I„‰ 1 ¡¡ » (1," vol. 17. 2007.
30. "1. Promoting Health and Reducing Disparities in Populations.," *Diabetes Care*, vol. 40, no. Suppl 1, pp. S6–S10, Jan. 2017, doi: 10.2337/dc17-S004.