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SECOND (NEW) GENERATION INSULIN THERAPY IN GERIATRIC POPULATION

Geriatrics

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ABSTRACT

Insulin analogues play an effective role in the management of type 2 diabetes. However, there are several behavioural barriers to appropriate early initiation of insulin therapy, despite compelling evidence supporting the benefits of this strategy in those patients for whom oral anti-diabetes agents provide insufficient control. The development of second-generation insulin analogues (insulin glargine 300 U/mL and insulin degludec) has provided physicians with agents that can provide comparable glycaemic control to first-generation insulin but with a reduced risk of hypoglycaemia and modes of action suited to once-daily regimens. Therefore, these features may help both patient and physician to overcome their concerns about early insulin use for the management of the disease [1]. This article is aimed to understand management of T2DM based on ultra-long-acting second-generation basal insulin analogues over the geriatric population and also why is it beneficial over first-generation insulin analogues.

KEYWORDS

INTRODUCTION:

The number of adults (>65 years) are affected by diabetes keeps increasing with increasing age of a general population. It is estimated that almost 33% of adults over the age of 65 are diabetic which makes them more prone to risk of developing diabetes-related complications such as hypoglycaemia, kidney failure, and several heart-related disorders [3]. Here insulin therapy comes as a rescuer by replacing the insulin normally produced by the body. People suffering from type 1 diabetes must take insulin every day. Whereas, people with T2DM are given insulin when the oral antidiabetic drug therapy fails to control the optimal blood sugar levels. T2DM being a progressive disease, it is necessary to intensify the management from oral anti-diabetes agents to insulin therapy in majority of the patients. Currently, basal insulin therapy has shown promising results in management for patients with T2DM, especially for those who do not achieve glycaemic control even after intensification of oral anti-diabetic agents. The second-generation insulin analogues provide physicians with new treatment options for achieving targeted glycaemic control. Being more stable and having an ultra-long duration of action, the newer insulin treatment options provide additional clinical benefits besides providing similar efficacy in lowering HbA1c to first-generation insulin analogues which also enables it to administer once daily with flexibility in daily injection time along with a lower risk of hypoglycaemia [2].

Diabetes in geriatric patients:

Today an aging population is growing worldwide where people above the age of 60 years accounts for almost 15% and that above 65 years accounts for almost 33% of the entire population are estimated to be diabetic which is estimated to be around 7.5 billion. This population has a potentially higher risk of developing diabetes-related complications like hypoglycaemia (low blood sugar), kidney failure, and several heart-related disorders compared to the younger population which is diabetic [4,2,3]. The primary cause of diabetes in the elderly is the resistance to insulin with age. Moreover, T2DM is typically silent and is often diagnosed as an incidental laboratory finding [2,13].

The risk factors include:

- Carbohydrate-rich diet.
- Chronic stress disorder
- Decreased muscle mass (sarcopenia)
- Hypertension
- Obesity
- Significant family history
- Have or have had high blood sugar levels during pregnancy.
- PCOS

The thirst mechanisms are impaired in the elderly because the renal threshold for glucose increases with age, hence the typical semiology or the cardinal signs for T2DM i.e., polyuria, polydipsia and polyphagia is usually lacking in old people. Consequently, common symptoms leading to T2DM diagnosis are complications such as neuropathy or nephropathy, heart, and vascular problems, and/or recurrent UTI and skin problems. Sometimes signs and symptoms like fatigue, hypotension, incontinence, cognitive impairment or functional decline, depression, and dementia which might be the first manifestations of the disease are usually wrongly attributed to signs of aging. [5,2,4,13].

Insulin therapy in the elderly:

Patients with T2DM with acute illness or surgery, pregnancy, glucose toxicity, contraindications to or failure to achieve desired glycaemic targets with oral anti-diabetic medications, are indicated for exogenous insulin therapy [6]. The patient must be diagnosed for diabetes or hyperglycaemia and should be confirmed before ordering, dispensing, or administering insulin. Insulin therapy stands as the primary treatment in all patients diagnosed with type 1 diabetes mellitus (T1DM). These patients typically require initiation with multiple injections on daily basis at the time of diagnosis which are usually short-acting insulins or rapid-acting insulin analogues which are given 0 to 15 min before meals together with one or more daily separate injections of intermediate or long-acting insulin. We can also use two or three premixed insulin injections on daily basis.

The target is chosen to aim at minimizing hyperglycaemia, severe hypoglycaemia, and hypoglycaemic unawareness, and to reduce the likelihood of development of long-term complications [2,6,4]. Many elderly patients who have a poor glycaemic control and weight loss will benefit from insulin even if they do not achieve this HbA1c target, since insulin therapy is usually associated with weight gain of around 4-5 kg.

The insulin therapy included 3 major categories based on their duration of action, which were: short-acting, intermediate-acting, and long-acting. Under short-acting came two more subtypes: Regular insulin (soluble) and Seme-Lente insulin. Unter intermediate also came two more subtypes: Neural Protamine Hagedorn (NPH) and Lente insulin. There is only one type of long-acting which is Ultra-Lente insulin a Zinc insulin suspension that was used as intermediate insulin and later came with 2 types called Seme-Lente and Ultra-Lente.

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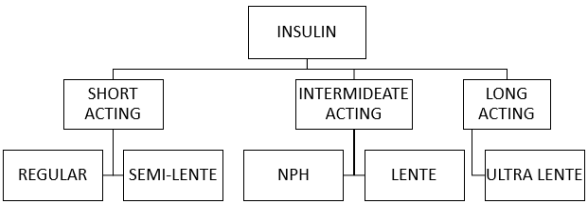
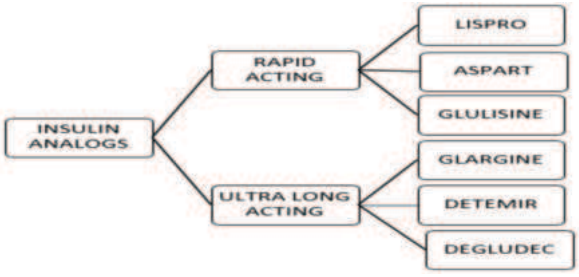


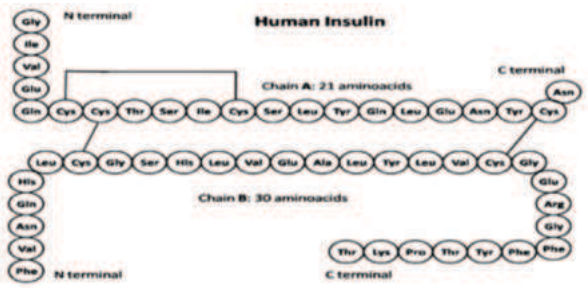
Currently, basal insulin analogues are used instead of insulin itself. These are further classified into rapid-acting, and ultra-long-acting based on their duration of action. The rapid acting insulin analogues are of three types: Glulisin, Lispro, and Aspart among which the Lispro and Aspart comes under the Second-generation insulin analogues. Under the class of ultra-long-acting insulin analogues come 3 subtypes: Glargine, Detemir, and Degludec, among which Degludec is the longest-acting second-generation insulin [8,9,10].



An individualized strategy is required to manage the diabetes in elderly population that takes age-related changes in function and cognition under consideration and also recognizes that life expectancy may be limited by non-diabetes-related disease. Patients with T2DM, especially who are elderly, insulin therapy is a safe choice, provided that a multidisciplinary team of physicians and diabetologists starts it carefully with proper monitoring of the blood sugar levels with defined glycaemic target along with controlling the risk or signs of hypoglycaemia [7].

Insulin therapy may be part of the initial management of myocardial infarction, acute illness, hyperosmolar coma, and major surgery for T2DM patients in a hospital setup. Insulin may also be indicated in the acute management of stroke. For patients those who seek advice on outpatient basis, the usual reason for insulin therapy is poor glycaemic control that manifests with symptoms of hypoglycaemia, non-specific poor health with malaise that sometimes accompanied by weight loss [7]. It is necessary to review the glycaemic goals and regimen with aging and the onset of cognitive impairment or frailty. Insulin therapy might fail if the patient or carers are unable to cope with the injections or if hypoglycaemia is complicated [6,7,13].

The molecular structure of human insulin in general has two long amino acid chains. The A chain has 21 amino acids and the B chain has 30 amino acids that runs from N- terminal to C-terminal. Two disulfide bridges (residues A7 to B7, and A20 to B19) covalently connect the chains, and chain A contains an internal disulfide bridge (residues A6 to A11). In this study we will understand the ultra-long-acting insulin analogues.



First-generation insulin analogues:
The first-generation insulin analogues were developed by recombinant DNA technology where the amino acid sequence of human insulin was altered to create the desired effects. Insulin Glargine 100 units/mL (Gla-100) was first of these basal insulin analogues that became available in the year 2000 which was soon followed by insulin Detemir (IDet) that was available in the year 2005 [11].

GLA-100: Gla-100 was developed by replacing the asparagine in A-21 chain by glycine, and two arginine residues were added to B30 chain of the human insulin. These modifications increased the isoelectric point of the insulin analogues which made it soluble in acidic conditions (prior to injection), but when it was injected to the higher physiologic pH of the human subcutaneous space, the micro-precipitates form in the injection depoted. This made the monomers of Gla-100 slowly get released into the circulation from the micro-precipitate of the injection depot. As this process is dependent on the surface area of the injection depot, it protracts the PK profile of insulin glargine [11,10].

IDET: In IDet, the insulin analogues were developed by altering the amino acid sequence of the human insulin as well as adding a 14-carbon myristoyl fatty acid to the B29-lysine residue [11]. This made the insulin soluble that self-associates into di-hexamers in the subcutaneous space. This di-hexamer then uses a fatty acid linker molecule to reversibly binds to albumin, allowing for a slower and an extended release of monomeric free insulin [10,11].

Second-generation insulin analogues:
The second-generation basal insulin analogues were introduced in the year 2015. These were insulin Glargine 300 units/mL (Gla-300) and insulin Degludec (Ideg).

GLA-300: Gla-300 delivers the same dosage of insulin as Gla-100 but in one-third of the volume. The Gla-300 is a different formulation of glargine, whereby the insulin is delivered in about one-third volume of liquid. This altered the PK profile of the insulin with even longer effect than Gla-100 [11]. Moreover, this gave a flatter curve than the Gla-100. This results in reduced surface area of the injection depot, ultimately resulting in a slower and more gradual release of monomers of Gla-300 as compared with Gla-100 [10,11]

IDEG: IDEG exists as di-hexamers in solution. When injection into the subcutaneous space, the phenol component removes and allows for self-association into multi-hexamer chains [11]. The zinc in IDeg dissociates over time and the hexamers are released and then dissociate into monomers that enter the circulation in a more prolonged time, making it the longest acting insulin analogues. [11].

Comparative study between both the generations:
The second-generation insulin analogues happen to have prolonged duration of action compared to the NPH and first-generation insulin analogues with more fatter PK/PD profile that has the least chances of hypoglycaemia which makes it safer for use. Where the NPH shows an inadequate duration of action, Degludec happens to be the longest-acting insulin [2,11,10].

Taken together, it would appear that the two second-generation insulin analogues are effective ones with similar glycaemic efficacy and similar hypoglycaemia. Comparatively less hypoglycaemia was observed with Gla-300 during the titration period in insulin-naive individuals with T2DM. Similar hypoglycaemia was seen during the maintenance phase among those individuals. Therefore, the more important clinical interpretation of these data is that second-generation analogues are better than their first-generation counterparts and should be used preferentially. The choice of which second-generation analogues to use should be based on practical differences like cost, access, devices etc [11].

The above-mentioned table shows a generalized comparison of different forms of insulin therapies based on their rate of absorption safety and duration of action where we can see that the most promising results are shown by the second-generation analogues.

Safety and side effects:
There are neither any studies based on the relationship of age and the effects of insulin degludec injection that's appropriately been performed in the geriatric population, nor any geriatric-specific problems have been noticed or documented till date. However, elderly patients usually have age-related hypoglycaemia, that might require adjustments and precautions in the dosing for patients receiving insulin degludec [12, 10].

Some side effects of Glargine-300 may include hypoglycaemia, unexplained weight gain, swelling in arms, legs, face, feet, or ankles (edema), tingling of the hands or feet, hypokalemia, reactions at the injection site where some symptoms may include: lipoatrophy i.e.,

increase or decrease in fatty tissue under the skin from too much using the injection site [11, 2, 8, 10].

CONCLUSION

The second-generation basal insulin analogues provide physicians with new treatment options for achieving targeted glycaemic controls by providing similar efficacy in lowering HbA1c compared to first-generation insulin analogues. The second- generation insulin therapy provides additional clinical benefits like more stability, ultra-long duration of action that makes the dosing easy by enabling once-daily administration with flexibility in daily injection time, along with a lower risk of hypoglycaemia [2].

Finally, we can conclude:

- Second-generation insulin has comparable glycaemic efficacy with less hypoglycaemia compared to first-generation BI analogues.
- Less hypoglycaemia with second-generation insulin may be particularly helpful in vulnerable populations.
- Less hypoglycaemia in older adults, those with renal impairment, obesity, cardiovascular disease, and long duration of insulin use and may represent a safer option to achieve glycaemic control while minimizing hypoglycaemia by the use of second-generation insulin

More data are required in other vulnerable populations, such as those with cognitive impairment, severe renal disease, or malignancy, and in different settings, such as acute hospital, perioperative, and long-term care.

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