

APT Insulin Selection in Type 2 Diabetes Mellitus with Different Comorbid Conditions

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ABSTRACT

In the current scenario, treatment of diabetes has become individualized and patient centric with customization of therapy being the key. Selection and adoption of insulin therapy now is driven by many factors like patient preference, co-morbid conditions, patient education and availability of insulin and cost of therapy [1]. This review attempts to discuss the rational use of different types of insulins in different situations.

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A decline in pancreatic beta-cell function has been defined as a key contributing factor to the progression of type 2 diabetes mellitus (T2DM). As β -cell dysfunction progresses over time, a large number of patients on oral agents, fail to achieve or maintain adequate glycemic control. In order to maintain sustained glycemic control, therapy needs to be directed towards protection of the beta cells [2]. Clinical inertia about insulin initiation and titration when clinically indicated exposes patients to prolonged hyperglycemia and increased risk of diabetes-related complications. In spite of several guidelines providing rational directions for the initiation and intensification of therapy, insulin therapy remains a major challenge across the globe [3]. Various international and national guidelines differ in their opinion on the selection of the type of insulin. Also most guidelines do not specifically describe the patient characteristics that should be the basis of choosing a particular insulin regimen [4].

In case a premixed insulin is chosen then the doses must be so adjusted so as to take care of both basal and prandial hyperglycemia if once daily dose of premixed insulin does not control prandial sugar then twice or must be adjusted accordingly [5, 6]. In patients are inadequately controlled on basal insulin then basal one plus or basal two plus or basal bolus regimen may be initiated based on the glycemic profile of the patient.

Comorbid Conditions and Insulin Selection Newly Diagnosed Diabetes

In newly diagnosed T2DM oral hypoglycemic agents are generally initiated but if the HbA1c is $> 9.0\%$ then dual therapy including insulin may be started. Timely early initiation of insulin therapy can rapidly correct the metabolic imbalance and thereby reverse the deleterious effects of glucotoxicity and lipotoxicity on β -cell function [7]. Hyperglycemia leads to increased production of reactive oxygen species and oxidative stress, which results in diminished insulin gene expression in glucotoxic β -cells a

condition which is reversible with reinstatement of euglycemic conditions [8]. Improvement in insulin sensitivity and β -cell function after correction of hyperglycemia with early intensive insulin therapy has been demonstrated [9]. After glycemic and metabolic control is achieved with insulin, patients may be shifted to oral hypoglycemic agents [10].

Cardiovascular Disease

Several studies have observed that higher insulin levels are associated with an increased risk of cardiovascular disease triggering concerns to whether exposure to high levels of exogenous insulin also increases the risk of cardiovascular disease in diabetic patients. Insulin use has been associated with weight gain, recurrent hypoglycemia and iatrogenic hyperinsulinemia. Over-insulinization by exogenous insulin may predispose to inflammation, atherosclerosis, hypertension, dyslipidemia, heart failure, and arrhythmias [11]. In prospective follow-up studies increased doses of insulin were proportional to increased risks of cardiovascular disease. However clinical studies examining the cardiovascular safety of insulin therapy have been reassuring. In the DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) Study in patients with diabetes and myocardial infarction, the improvement in glycaemia control obtained with intensified insulin therapy had led to a significant reduction in mortality [12]. In a 20 year follow up of DIGAMI a long-lasting beneficial effect of intensive intensive glycemic control on longevity was established [13]. The ORIGIN trial done with insulin glargine on patients with recent-onset type 2 diabetes or pre-diabetes and high cardiovascular risk, with an appropriate sample size of 12 537 and follow-up of 6.2 years suggested a neutral effect of the basal insulin [14]. Ultra-long-acting insulin analogs like insulin degludec are non-inferior to insulin glargine in terms of cardiovascular outcomes [15]. The choice of insulin regimen should be individualized and based upon considerations of hypoglycemia [16, 17].

Impaired Renal Function

Chronic kidney disease is associated with several alterations in the metabolism of insulin and carbohydrate metabolism. With the advancement of renal failure insulin clearance decreases, thus requiring a dose reduction of insulin. The reduction in insulin clearance is initially compensated for by an increase in insulin uptake by proximal tubular cells and an increase in insulin resistance, thereby at times causing requirement of large amount of insulin [18]. Basal plus, basal bolus or premix insulin can be used depending on the individual levels but glycemic monitoring and dose adjustment should be done carefully [19].

Impaired Liver Function

Insulin therapy is considered as the safest and most effective therapy for diabetes in patients with liver dysfunction. The major site of metabolism for circulating insulin is the liver. Hyperinsulinemia and peripheral insulin resistance are often demonstrated in advanced liver cirrhosis due to higher insulin secretion rate and reduced hepatic clearance. Reduced capacity for gluconeogenesis and reduced hepatic breakdown of insulin may also be seen. Due to such varied factors insulin requirement may vary in decompensated liver disease patients. Short-acting insulins are preferred because the duration of action may vary in such situations [20]. The choice should be regimens with low risk of hypoglycemia [21]. Insulin analogs may offer equivalent glycemic control compared to standard insulin with a lower risk for hypoglycemia. There is no clinically significant impact of hepatic impairment on the pharmacokinetics of insulin as part but because they can be given just after meals they may be of benefit too many patients with advanced hepatic impairment having nausea and reduced appetite [22]. Ultra-long pharmacokinetic properties of insulin degludec have been found to be preserved in patients with hepatic impairment without any meaningful differences in absorption or clearance. [23] while another case study found detemir to be less efficacious in achieving glycemic control in such situations [24].

Pregnancy & Lactation

Diabetes mellitus during pregnancy is associated with multiple complications like polyhydramnios, intrauterine fetal death, macrosomia and stillbirths etc. Glycemic targets during pregnancy are stringent. Insulin remains the agent of choice in the treatment of diabetes during pregnancy. Placental anti-insulin hormones, increased maternal cortisol level, weight gain and reduced exercise in pregnancy may cause a rise in insulin requirements. In the first trimester, there is a slight drop in insulin requirement from the pre-conception requirement of ~0.8 units/kg weight to ~0.7 units/kg maternal weight. In early pregnancy, the placental passage of glucose and a transient drop in progesterone levels decrease the insulin requirement in the later part of the first trimester. There is a propensity of a low-fasting and high-postprandial blood glucose level pattern in this period. With the advancing of pregnancy, placenta produces increasing amounts of anti-insulin hormones, leading to progressive increase in insulin needs to ~0.9–1.0 units/kg pregnant weight [25]. Insulin requirements may decrease again closer to term, because of transfer of maternal glucose to fetus. Morbidly obese woman and those with twin pregnancies may need ~1.5–2.0 units/kg to overcome the combined insulin resistance of pregnancy and obesity. Either multiple daily insulin injections with basal bolus or premix can be used. Recent data suggest no significant difference between premix insulin analogues and premix human insulin in terms of glycemic control or fetal outcome. Basal-bolus regimen of regular insulin and NPH is widely used. However this combination does not mimic the

physiological insulin kinetics and may make aggressive glycemic control difficult with an increase in the risk of hypoglycemia. Lispro has been found to be associated with lower hypoglycemic episodes, lower postprandial hyperglycemia and better reduction in HbA1c levels in pregnancy in comparison to regular human insulin with no differences seen in rates of cesarean sections, preterm delivery, pre-eclampsia, or other neonatal morbidities [26]. Glargine in pregnancy is not approved in pregnancy. Detemir is currently the only basal insulin analog with an FDA pregnancy category B classification. Premixed insulin aspart 30 (BIAsp 30) has been demonstrated to be equivalent to premixed human insulin 30, producing comparable fetal outcomes [27].

Fasting

Fasting may have detrimental consequences for a patient on insulin. Prolonged fasting poses a risk of hypoglycemia, hyperglycemia, ketoacidosis, dehydration and thrombosis [28]. Fasting may be undertaken only if the patient is stable, otherwise healthy, is aware about hypoglycemia and its management and well compliant. The duration of the fast as well as the type of insulin used can help guide insulin treatment during the fasting period. For short term or half a day fasting short-acting insulin before meals has to be stopped till the time the patient has a meal. The basal insulin dose may need to be reduced by one half or one third. During the period of fast self-monitoring of blood glucose and adherence to therapy is very important. If premix is used, analogues are preferred over human insulin, considering the lower risk of hypoglycemia. Insulin glargine and Insulin detemir can be safely used but their doses have to be adjusted accordingly.

Elderly

When insulin therapy is required in elderly patients, particularly the ones with advanced complications and /or life-limiting coexisting illnesses, once-daily basal insulin injection therapy is preferred to multiple daily injections as the latter may be too complex for them. Self-monitoring of blood glucose (SMBG) at home is highly recommended in older patients [29].

Conclusion

Timely and selective introduction of insulin therapy in type 2 diabetes mellitus can facilitate the achievement and maintenance of euglycemia. The choice of insulin could vary depending on the individual and the associated comorbid conditions.

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