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ROLE OF INSULIN THERAPY IN MANAGEMENT OF TYPE 2 DIABETES MELLITUS: LITERATURE REVIEW

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Abstract:

Background: *The number of type 2 diabetes (T2D) patients is rapidly growing. This alarming figure is a result of the aging population. Prevention of long-term complications is the ultimate goal of diabetes management. This is achieved by improvement and maintenance of glycemic control over time. Insulin is the most effective therapy in lowering blood glucose by allowing the body to maintain glucose within a normal range.*

Objective: *In this review, we will discuss the role of insulin in management of T2D and evaluate its efficacy and safety.*

Method: *A comprehensive search was done using biomedical databases; Medline, and PubMed, for studies concerned with assessment of role of insulin in management of type 2 DM. Keywords used in our search through the databases were as; "Type 2 DM Pathophysiology", "Type 2 DM Management", and "Insulin".*

Conclusion: *Guidelines for initial insulin therapy indicate that addition of a long-acting basal insulin to oral therapy is the first step for most patients. Many patients require intensification of insulin therapy later, with the addition of rapid-acting insulin before one or more meals. In order to prevent or delay the long-term complications of diabetes, the goal of glycemic control is an HbA1c of 7.0% or less unless hypoglycemia ensues. Adherence to insulin therapy for people with diabetes is vital, in order to reduce the risks of future complications. Adherence to therapy is poor with many patients omitting or altering their insulin doses. Better communication with patients can improve patient engagement with therapy. Healthcare professionals may need to make their patients aware of improvements in insulin therapies and delivery devices, in terms of reducing other adverse effects, including injection pain and weight gain, and increasing dosing flexibility.*

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INTRODUCTION:

The number of type 2 diabetes (T2D) patients is growing rapidly. It has been estimated in 2017 that almost 425 million adults worldwide were diagnosed with diabetes. This number is expected to increase to 628 million by year 2045 (1). This alarming figure is a result of the aging population. Elderly are more likely to develop T2D especially with the worldwide lifestyle changes. Also, the fact that T2D is being diagnosed earlier can be a reflection of increasing number. Moreover, patients nowadays are living longer due to the advances in management strategies (2).

Prevention of long-term complications is the ultimate goal of diabetes management. This is achieved by improvement and maintenance of glycemic control over time. Unfortunately, this is not an easy task because T2D is a progressive disease in nature, which requires timely optimization of treatment. This will lead to insulin therapy in the majority of cases (3).

Insulin is the most effective therapy in lowering blood glucose by allowing the body to maintain glucose within a normal range (4). Therefore, in this article, we will review the insulin therapy in managing type 2 diabetes.

METHODOLOGY:

Sample: We performed comprehensive search using biomedical databases; Medline, and PubMed, for studies concerned with evaluation of Type 2 DM published in English language. Keywords used in our search through the databases were as; "Type 2 DM Pathophysiology", "Type 2 DM Management", and "Insulin". More relevant articles were recruited from references lists scanning of each included study.

Analysis: No software was used, the data were extracted based on specific form that contain title of the study, name of the author, objective, summary, results, and outcomes.

DISCUSSION:

In the beginning of 20th century, and before the discovery of insulin, physicians Allen and Joslin endorsed fasting and calorie-restricted diets for diabetes (5). This led to an improvement of glucosuria and acidosis, decreased coma, and delayed death among children with diabetes. All diabetics were instructed to decrease their sugar and dietary starch intake, and those who were obese were advised to lose weight. Later, insulin, which is pancreatic crude extract, was discovered in 1922. This discovery was a major breakthrough in medicine. It gave hope to patients with diabetes mellitus. The later development of precisely engineered insulin analogs, improved diabetes control and reduced or delayed complications. Insulin continues to be the cornerstone of the therapy (6).

Insulin is a protein synthesized in the beta cells of the pancreas in the form of preproinsulin, which is the ultimate precursor and gene for the same is located on chromosome 11 close to that for insulin like growth factor-2 (IGF-2). Nowadays, human insulin is produced by recombinant DNA technology. The principle behind it, is to introduce human insulin or proinsulin gene into organisms like E.coli or Yeast that keep on multiplying which lead to producing insulin or proinsulin which is converted to insulin by enzymatic cleavage (7).

Type 2 diabetes is characterized by progressive beta-cell failure, but the natural history of beta-cell decline is variable and assessment of beta-cell function is difficult. The commonly accepted explanation is that when insulin secretion can no longer compensate for the underlying metabolic disturbance, type 2 diabetes develops (3). It is understood that most people with type 2 diabetes will eventually require insulin therapy as secretory capacity progressively declines with time (8).

The UK Prospective Diabetes Study (UKPDS) showed that early and continued glucose control can reduce microvascular complications. They also improve cardiovascular prognosis in the long-term (9). In addition, studies on insulin in type 1 diabetes support the beneficial effect of insulin therapy. It is apparent that both micro- and macro-vascular protection is achieved if insulin therapy is used effectively to induce early glycemic control (10). Achieving HbA1c 7.0% is a difficult task. However, even if the HbA1c target is not achieved, improvement of glycemic control with insulin is associated with improved patient well-being (11). An oral agent without insulin can prominently lower blood glucose at the time of diagnosis, especially when accompanied with lifestyle modifications such as starting exercise and proper diet.

Although some patients may manage T2D with oral medications, most will eventually need to use insulin to achieve glycemic control because T2D is a progressive disease (2). In cases when patients are no longer meeting glycemic targets on combination therapy using oral drugs, insulin treatment is usually initiated. Moreover, it is recommended to be initiated

when a glycated hemoglobin A1c (HbA1c) level of 9.0% with symptomatic hyperglycemia (12).

Guidelines for initial insulin indicate that addition of a long-acting basal insulin to oral therapy is the first step for most patients. This step is to achieve control of fasting plasma glucose (FPG) levels. Insulin analogs are favored over neutral protamine Hagedorn (NPH) insulin because of their better hypoglycemic profile due to their flat pharmacokinetic curve (13). Nevertheless, NPH insulin has also its advantage, which is significant lower costs. This advantage keeps NPH widely used in some resource-limited countries (14).

These regimens will successfully help most of the patients achieve and maintain glycemic control. However, sometimes basal insulin alone can be insufficient and the disease may progress to the point these patients will require additional therapeutic support to control postprandial glucose (PPG) levels. Managing patients who do not achieve glycemic goals despite uptitration of basal insulin provides a particular challenge, with a number of available options.

In order to prevent or delay the long-term complications of diabetes, the goal of glycemic control is an HbA1c of 7.0% or less unless hypoglycemia ensues (15). In patients at increased risk of hypoglycemia, glycemic targets should be higher. They also should be higher in those with decreased life expectancy, cardiovascular disease, comorbidities, diminished resources, or insurmountable psychological barriers. Many patients require intensification of insulin therapy later, with the addition of rapid-acting insulin before one or more meals. Nevertheless, a single injection of long-acting insulin added to oral hypoglycemic agents often achieves glucose control for several years. A number of patient and clinician barriers often need to be overcome, such as patient costs, despite proven overall cost-effectiveness of treatment. This was the recommended strategy for intensifying insulin therapy. It was by the addition of rapid-acting insulins (RAIs) to the treatment regimen as mentioned earlier, either as additional prandial injection or as part of a premixed insulin formula. Nevertheless, combining a GLP-1 Receptor Agonists with basal insulin has been recently shown to provide equal or slightly superior efficacy to the addition of prandial insulin, with a beneficial effect on weight and less hypoglycemia events, as well as reduced regimen complexity which results in better compliance (15-16). Based on the finding, the most recent 2018 recommendations from the American Diabetes Association found that compared with basal-plus insulin, basal insulin plus GLP-1 RAs are associated with less hypoglycemia and with weight loss instead of weight gain but may be less tolerable and have a greater cost (13). (Jerry Meece)(2) paper provided an excellent algorithm for combination injectable therapy for type 2 diabetes (figure 1).

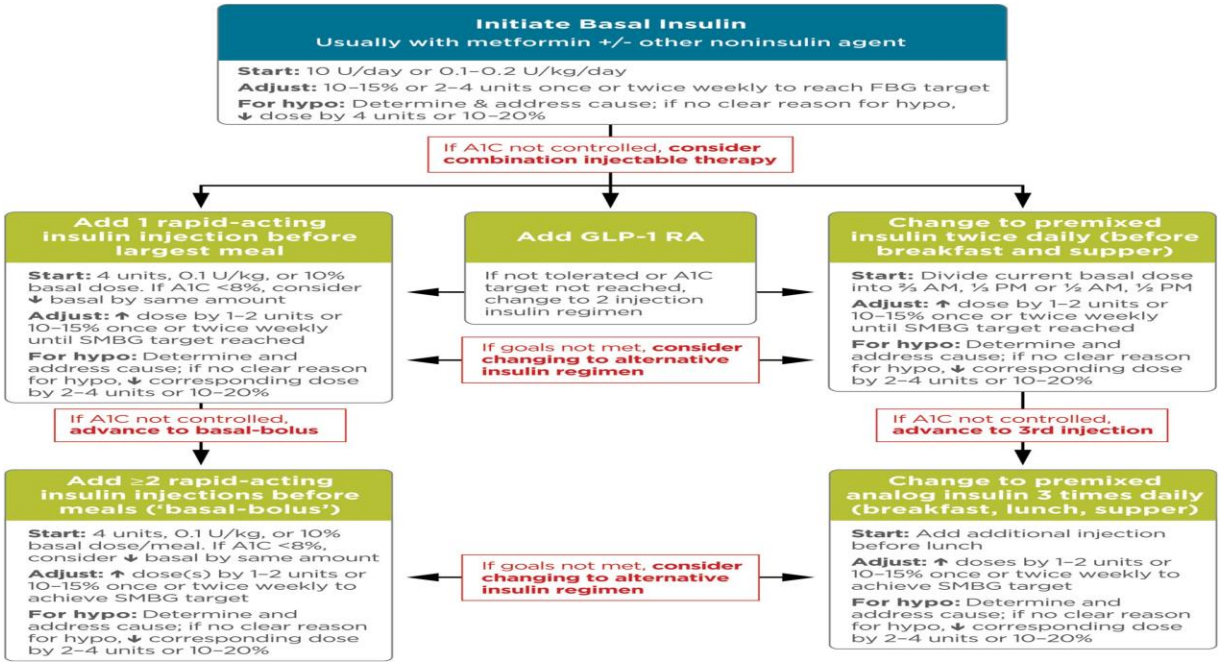

Figure 1: *Combination injectable therapy for type 2 diabetes. Adapted from American Diabetes Association 2017 guidelines.*

The outcomes are affected by patient preferences, adherence, cost and the diversity of treatment plans (17). Unfortunately, not every diabetic patient achieve appropriate glycemic control and cardiovascular risk factor target. This fact increases the need for proven methods that improve care in real life (18-19). (Patrick et al.)(20) found among a large cohort of commercially insured patients with diabetes that there are significant departures from guideline-recommended insulin therapies and a lack of insulin intensification. Insulin is frequently initiated in a manner that is inconsistent with the ADA/EASD guidelines. The co-prescribing of insulin secretagogues with short-acting insulin places patients at an increased risk of hypoglycemia. In addition, the majority of patients had no evidence of treatment intensification, and a quarter of patients discontinued insulin following initiation. The reasons for delayed initiation and intensification of insulin should be examined and the factors affecting psychological insulin resistance should be looked at in both health care professionals and patients (21-22). Due to the many negative beliefs about insulin among people, up to one-third of patients report being unwilling to start insulin if recommended (23). Furthermore, adherence to insulin (60%-80%) is lower than adherence to OHAs and is lower in patients with frequent dosing schedules (25). Factors affecting adherence include regimen comprehension, perception of benefits, adverse effects, regimen costs (insulin, syringes, glucose strips), regimen complexity, and emotional well-being (25). Although the benefits of insulin initiation and intensification economically and clinically have been shown, patient costs may lead the decision-making. The concerns about insulin injections, adverse effects, maintenance of glycemic control, and hypoglycemia avoidance are raised mostly by the patients with no prior experience with insulin. Patients with prior insulin experience had fewer concerns (26-27).

Syringes are available in varying capacities 0.3, 0.5, 1 and 2 ml. Different syringes are available for use with 40U and 100U vials, differing in markings, though both may be of 1 ml capacity. Regular insulin is preferred to be administered on an average 30 min prior to meals. If rapid acting insulin was used, the time lag should not exceed 30 min and can be given immediately prior to or even just after meals. Similar instructions should be given to the patient who is using regular or rapid acting insulin mixed with other insulins. These intervals may need to be individualized in some patients depending on several factors such as the site of injection, food type, and exercise. Intermediate acting insulin is preferable given at bedtime in order to avoid late night hypoglycemia that can be associated with predinner administration (7).

Insulin may be injected into the subcutaneous tissue of the upper arm and the anterior and lateral aspects of the thigh, buttocks, and abdomen. Injection site rotation is recommended to prevent lipohypertrophy or lipoatrophy. The abdomen has the fastest rate of absorption, followed by the arms, thighs, and buttocks. Exercise increases the rate of absorption from injection sites. Areas of lipohypertrophy usually have slower absorption (7).

Various regimens are available for insulin initiation in a diabetic patient. The choice of the proper regimen depends on the diagnosis, glycemic status, patient compliance and physicians choice. Patients with T2D have defects in both insulin secretion and insulin action. The impairments in insulin secretion are manifest in at least three ways which are blunted or absent first-phase insulin response to glucose, so that insulin secretion is delayed and fails to restore prandial glycemic excursions in a timely manner, decreased sensitivity of insulin response to glucose, such that hyperglycemia may fail to trigger an appropriate insulin response, or decreased overall insulin secretory capacity, progressive in nature with more prolonged and therefore more severe T2D.

The AACE/ACE guidelines recommend basal insulin, in combination with metformin or other glucose-lowering agents, as initial therapy for patients with an entry HbA1c level >9% who have symptoms of hyperglycemia and in other patients as an add-on option for dual- or triple-combination therapy (28). Specifically, basal insulin is suggested for use in patients with T2DM receiving 2 oral glucose-lowering agents who have an HbA1c >8% or long-standing T2DM. Likewise, the ADA recommends basal insulin as 1 of 6 options for dual combination therapy, for example, for step-up from monotherapy or initial dual therapy when HbA1c is 9% (13). For newly diagnosed patients with T2D, the ADA suggests initiating combination injectable therapy, such as, basal insulin plus prandial insulin, basal insulin plus a GLP-1 RA, or a premixed insulin in patients who have an HbA1c 10%, a blood glucose level 300 mg/dL, or marked symptoms (13).

Insulin initiation and intensification are often delayed because of a number of factors, despite proven efficacy as a treatment option for people with T2D. Moreover, adherence to therapy is poor with many patients omitting or altering their insulin doses. Adherence to insulin therapy for people with diabetes

is vital, in order to reduce the risks of future complications and financial burden for both the healthcare systems and the patients as individuals. Adherence can be improved by several factors, in particular, practical approaches based on better communication with patients can be made to improve patient engagement with therapy. This approach will result in potentially better adherence to their insulin regimens. One of the best approaches is involving patients in decision-making process in terms of their treatment plans and choosing regimens that are well tolerated and as simple and flexible for the patients as possible are likely to improve adherence to treatment (29). This is advised to be done by encouraging patient's self-titration and providing the patient the support of a diabetes healthcare professional if necessary. Patients benefit the most from their healthcare professionals educating them, and their family members about the efficacy of insulin therapy and emphasizing on how much improved insulin therapies along with decreased risks of hypoglycemia. Healthcare professionals may need to make their patients aware of improvements in insulin therapies and delivery devices, in terms of reducing other adverse effects, including injection pain and weight gain, and increasing dosing flexibility. Working to improve the knowledge of patients with diabetes and healthcare professionals regarding the benefits of insulin therapy may lead to earlier initiation and intensification of insulin regimens. Determining a treatment regimen that fits a patient's lifestyle and takes patient's concerns regarding insulin therapy into consideration may improve treatment satisfaction and compliance, with the ultimate goal of improving glycemic control (29).

CONCLUSION:

Guidelines for initial insulin therapy are clear. The addition of a long-acting basal insulin to oral therapy is the first step for most patients. Many patients require intensification of insulin therapy later, with the addition of rapid-acting insulin before one or more meals. In order to prevent or delay the long-term complications of diabetes, the goal of glycemic control is an HbA1c of 7.0% or less unless hypoglycemia ensues. Adherence to insulin therapy for people with diabetes is vital, in order to reduce the risks of future complications. Adherence to therapy is poor with many patients omitting or altering their insulin doses. Better communication with patients can improve patient engagement with therapy. Healthcare professionals may need to make their patients aware of improvements in insulin therapies and delivery devices, in terms of reducing other adverse effects, including injection pain and weight gain, and increasing dosing flexibility.

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