Giving Insulin Is Not a Guessing Game: Insulin Replacement Therapy in Type 2 Diabetes Mellitus

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ABSTRACT

In 2021, 537 million adults were living with diabetes. Being a progressive disease, there would eventually be failure of oral hypoglycemic agents (OHA) to maintain good glycemic control and a majority will require insulin. However, optimal glycemic control has not been satisfactory in a significant proportion of patients who were on insulin therapy. Patient factors (eg, awareness, compliance, socioeconomic) have been identified but physician-related factors are as important. These include incorrect choice and inappropriate combination of insulin therapy which could be corrected by making the treatment physiologic. The purpose of this article is to improve management decisions in type 2 diabetes by reviewing its pathophysiology and identifying the optimum insulin regimen that could mimic such. Since eventual beta cell failure is central to its pathophysiology, it is but reasonable to replace insulin by mimicking its physiologic secretion. Hence, the term Insulin Replacement Therapy (IRT) should be utilized. This could be provided by the combination of premix insulin (ie, NPH + regular insulin) and rapid-acting insulin which has been reported to provide an initial 17.5% HbA1c reduction and even 18% reduction on 5-year follow-up providing sustainable control. A stepwise approach is an effective tool for insulin intensification. Hypoglycemia in insulin therapy could be prevented with an appropriate dietary regimen through automatic snacking.

Keywords: Insulin replacement therapy, type 2 diabetes mellitus, pathophysiology

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INTRODUCTION

Several risk factors contribute to the pathophysiology of type 2 diabetes mellitus (DM). There are about 130 genetic variants associated with this disease. It has a strong inheritable genetic pattern—a patient may have approximately 40% lifetime risk of acquiring type 2 diabetes if one parent has it. Moreover, environmental factors (eg, obesity, sedentary lifestyle, dietary factors, cigarette smoking, microbiome) also play a vital role in the pathophysiology of diabetes as the prevalence catches up with genetic variations globally. Both genetic and environmental factors affect the natural history by contributing to generalized inflammation and metabolic stress, subsequently affecting beta cell mass and function. This leads to defective insulin secretion, a concept that is central to the pathophysiology of disease. Ultimately, beta cell secretion of insulin over time will not be enough to respond to the demands (ie, beta cell failure) and will not be able to overcome

the already ongoing insulin resistance in type 2 diabetes.[1,2]

Evidences also show the role of alpha-cell dysfunction in the pathophysiology of type 2 DM which leads to a rise in glucagon and hepatic glucose levels during the fasting state which are not suppressed by meals.[2] With all these interplays of pathogenesis, pharmacologic therapies and eventual insulin therapy may be required to achieve normal blood glucose levels to prevent the occurrence of diabetes complications.[3]

In 2021, it was estimated that 537 million adults aged 20 to 79 years are living with diabetes.[4] Being a progressive disease, there would eventually be failure of oral hypoglycemic agents (OHA) to maintain good glycemic control and a majority of patients will require insulin. The rate of such was 44% after six years of diabetes according to the United Kingdom Prospective Diabetes Study [UKPDS].[5]

Approximately 47% (6-7 million) of type 2 diabetes patients in the United States (US) were on insulin therapy.[6] In 2016, 8.6% or 21.0 million adults in the US were diagnosed with type 2 diabetes based on the registry of patients on insulin.[7] In the Southeast Asian region, type 2 diabetes has significant disease burden (ie, early onset of disease, rapid occurrence of diabetes complications) with a high prevalence of 9.3%. In contrast with the Western population where insulin resistance predominates, Southeast Asian phenotype of type 2 diabetes have lower body mass index and a defect in insulin secretion plays a bigger role in the pathophysiology of diabetes. Hence, early insulin replacement is usually needed in the Asian population.[8]

Optimal glycemic control has been reported to not achieve HbA1c goal even on a significant proportion of patients who were placed on insulin therapy—only 35-45% of type 2 diabetes patients prescribed with insulin were able to reach the target HbA1c goal of <7%. Moreover, some literatures even reported a higher HbA1c on patients treated with insulin as compared to oral drug therapy.[9] In a more recent cross-sectional study, 83.5% of insulin-treated patients with diabetes had HbA1c above 7% at baseline, a finding that was comparable with earlier literatures. Noteworthy, combination therapy with OHA and insulin was not significantly associated with HbA1c level. In the Southeast Asian region, premixed insulin is the most popular choice for insulin therapy. However, the usual insulin practices are not efficient in achieving good glycemic control (ie, HbA1c<7%): only 41% in Malaysia (mean HbA1c 7.8 ± 2.2%), 32.1% in Indonesia (mean HbA1c 8.2 ± 2.0%), 23.1% in Bangladesh (mean HbA1c 8.6 ± 2.0%) and 29.7 to 41.3% in Thailand.[8] With all these evidences, there could be factors that we should consider on how to utilize insulin as an ultimate approach in reaching the target HbA1c goal in type 2 diabetes patients.

Insulin therapy plays an important role in achieving optimal glycemic control in order to prevent complications. Several literatures showed evidence that many patients on insulin are still not able to reach individualized glycemic targets. Hence, the purpose of this article is to review the physiologic secretion of insulin and correlate it with the eventual abnormality that leads to the development of type 2 diabetes, identify some factors on why there are still patients with type 2 diabetes who have poor glycemic control in spite of insulin therapy and provide recommendations to reach optimal glycemic control.

Physiologic Insulin Secretion in Response to Meals

Figure 1 shows the physiologic insulin secretion of normal beta cells of the pancreas. Basal insulin is continuously secreted at low levels in order to counteract hepatic gluconeogenesis. On the other hand, prandial insulin is secreted intermittently in response to glycemic excursions after meals.[10] An average person consumes three major meals—breakfast, lunch and dinner. There are two phases of insulin secretion in response to meals. The first phase sets in within seconds of food ingestion, peaks in 1-2 minutes and may last for 10 minutes. This phase of insulin secretion represents the release of pre-formed insulin and serves to suppress glucose output from the liver, limit postprandial glycemic surges and stimulate phase 2 of insulin secretion. The second phase is the release of newly synthesized insulin which lasts for about 1-2 hours until the glycemic level is brought to normal.[10,11]

The insulin secretion is deranged in patients with type 2 diabetes. The phase 1 is significantly affected among these patients and eventually absent. The phase 2 of insulin secretion will be affected usually by more than 50% as the disease progresses.[10]
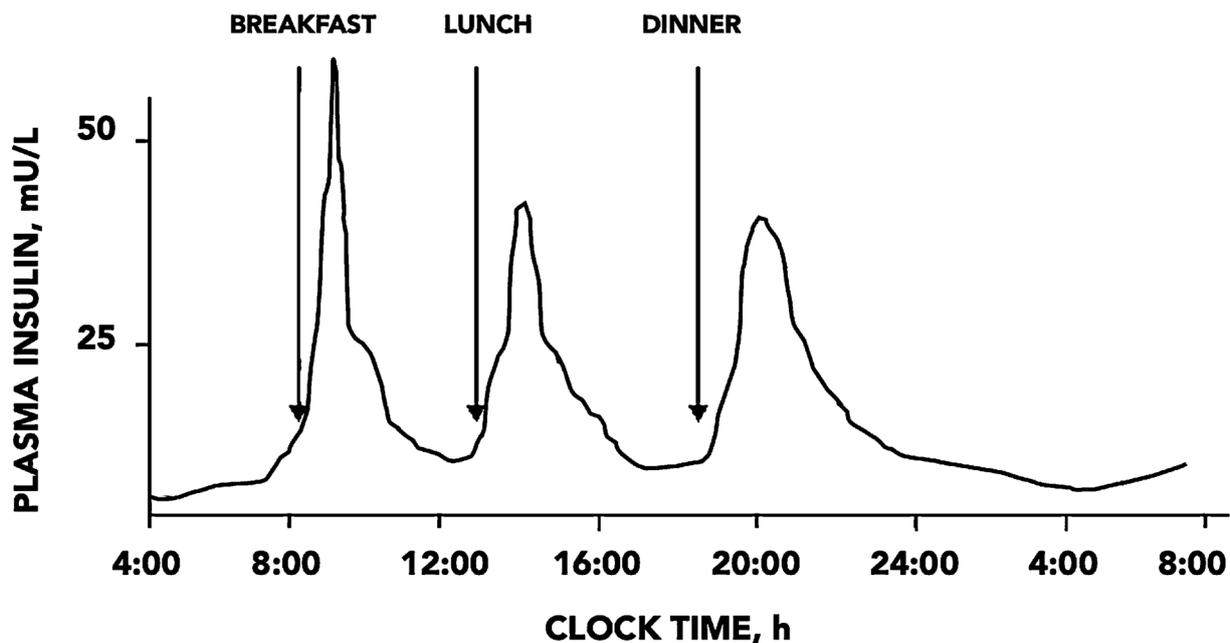
Figure 1: Physiologic insulin secretion of a healthy pancreas. *Thompson R, Christie D, Hindmarsh PC. The role for insulin analogs in diabetes care. Current Pediatrics 2006;117–22 [cited 2022 April 06] [12]; Adapted with modifications.*
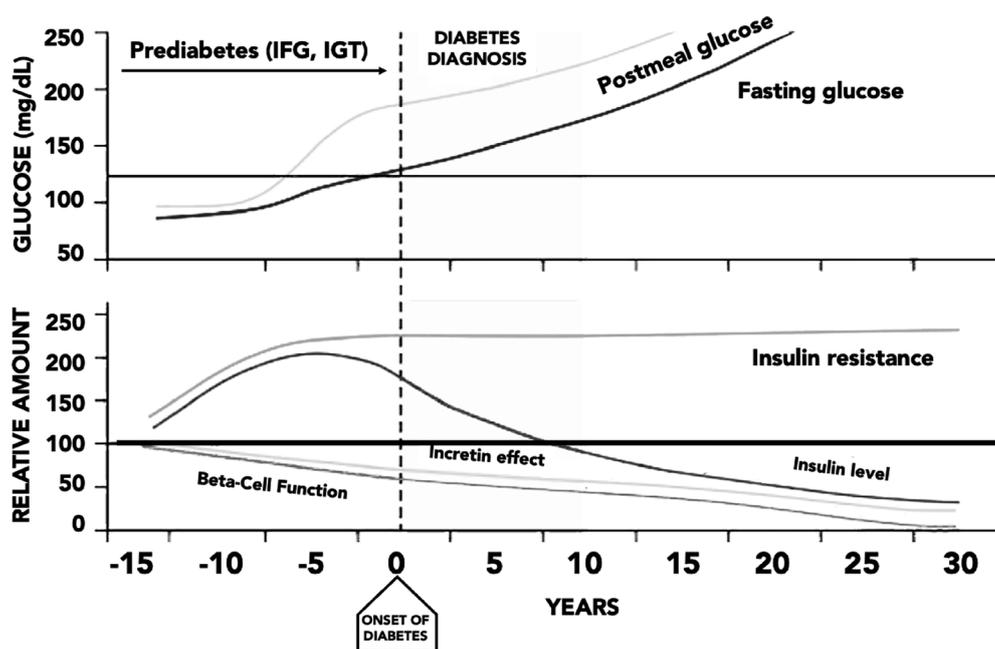
Natural History of Type 2 Diabetes Mellitus

Central to the understanding of the natural history of type 2 diabetes is the concept of beta cell mass and function. As with type 1 diabetes, beta cell mass is also reduced in type 2 diabetes leading to insulin insufficiency that is continuous and progressive over time. Hyperglycemia induces stress response which contributes to beta cell apoptosis.[1]

Insulin resistance begins the pathogenesis of classic type 2 diabetes. This increases the demand on beta cells for insulin secretion.[13] Insulin secretion varies depending on the level of insulin sensitivity in order to maintain normal glucose levels.[1] The compensatory increase in insulin secretion (ie, pre-IGT) would be able to maintain normoglycemia in a majority of patients. Nevertheless, this compensatory increase will eventually fail resulting in pre-diabetes. As shown in Figure 2, even in the earliest stages, there is already an underlying loss of beta cell function and mass (through apoptosis). [13,14] In the pre-diabetes stage, blood glucose levels are already elevated but not enough to reach the diabetes range. Persistently elevated glucose and lipid levels lead to more inflammation as well as oxidative and endoplasmic reticulum (ER) stress subsequently leading to further damage of beta cell function and mass, beyond this, these people progress to hyperglycemia (fasting and postmeal) and overt diabetes. At the time of diagnosis, around 40-50% of beta cells are lost and followed by a 4-5%

loss per year. Further into the continuum, persistent hyperglycemia leads to diabetic complications. [13,14]

Disposition index (ie, relationship between insulin secretion and insulin sensitivity) is decreased in type 2 diabetes as the beta cells could not adequately increase insulin secretion to overcome insulin resistance.[1] The first phase of insulin secretion in response to glucose level is markedly impaired in type 2 diabetes.

The transition to diabetes as shown in Figure 1 results from continuous beta cell function that is unable to compensate for persistent insulin resistance. Several models for beta cell failure were reported: (a) reduction in beta cell number (approximately 60%) during period of persistent hyperglycemia, especially among patients with genetically or environmentally induced low beta cell mass, (b) exhaustion of beta cells due to oxidative stress brought about by abnormal glucose metabolism, and (c) dedifferentiation of beta cells into other type of cells because of constant high metabolic load leading to gene expression loss. Recent reports mentioned that beta cell mass and functions are both deranged in people with type 2 diabetes.[13] C-peptide, a surrogate marker of beta cell function, is shown to be decreased as early as the first three years of diagnosis with further decline in patients with diabetes duration of 16-18 years (decreased to 0.6 pmoL/mL). Beyond 21 years, beta cell loss is

Figure 2: Natural History of Type 2 Diabetes. *IFG, impaired fasting glucose, IGT, impaired glucose tolerance. Wysham C, Shubrook J. Beta-cell failure in type 2 diabetes: mechanisms, markers, and clinical implications. Postgrad Med. 2020 Nov;132(8):676–86 [Cited with modification 2022 April 06] [13] Adapted with modifications.*

stable and no further decline is observed.[13] It is at this important stage that timely initiation of insulin therapy must be done. Knowledge of this concept is important in giving insulin replacement therapy (IRT).

Insulin Treatment in Type 2 Diabetes

Due to the progressive nature of this disease, many patients will be requiring insulin therapy after failure of oral medications. Customarily, type 2 diabetes mellitus (DM) upon reaching the stage of insulin treatment due to its progressive nature is eventually called insulin-requiring or insulin-dependent type 2 DM.[15] The appropriate timing of initiation of insulin may prevent worsening of diabetes [Outcome Reduction With Initial Glargine Intervention (ORIGIN) study] by protecting residual beta cell functions from the stress brought by glucotoxicity and lipotoxicity. This is important for patients who had type 2 diabetes for 10 to 15 years in whom the residual beta cell function is critically deranged. Unlike most OHA which needs an estimated minimum beta cell function of 15% to 20%, insulin can be used at any stage of the disease.[15]

The timely insulin replacement may likewise reduce diabetic complications. Early addition of insulin to OHA was able to reduce the risk of complications [UKPDS]. Noteworthy, there was a significant reduction in the occurrence of chronic kidney disease (strongest observation on the reduction of microalbuminuria) and retinopathy among those with baseline HbA1c of 6.4% [ORIGIN]. Intensive insulin therapies are able to correct hyperglycemia within 1 to days of initiation and able to achieve near normoglycemia for over three to six years (shown for insulin glargine and degludec).[15]

There are various distinct indications of the initiation of insulin therapy. Basal and/or basal-bolus insulin may be initiated among (a) patients on dual or triple OHA but still with HbA1c >10%, (b) more than 2% above the individualized target, or (c) patients with HbA1c >11% with clinical presentation of catabolism and sarcopenia. Newly diagnosed patients with signs and symptoms of glucotoxicity may be initiated on insulin for urgent glycemic control. This may apply on patients presenting with hyperglycemic crisis, dehydration or infection. Furthermore, patients presenting with severe insulin deficit (eg, elevated postprandial glucose rises and/or microvascular complications upon diagnosis) may preferably be placed on insulin.[15]

The goal of therapy, according to the American Diabetes Association, is HbA1c of <7% (fasting plasma glucose 80-130 mg/dL, postprandial plasma glucose <180 mg/dL) in majority of patients who are otherwise healthy; <8% in patients who are at higher risk of developing hypoglycemia, shorter life expectancy and significant comorbidities. Among

type 2 diabetes patients who were not able to reach glycemic targets on OHA, insulin replacement lowers HbA1c by 1.2-1.5% (at 0.2 units/kg or 10 units daily) by suppressing hepatic gluconeogenesis. Prandial insulins are usually added if there is an adequate fasting glucose control but still with elevations later in the day and persistently elevated HbA1c—a state of beta cell failure. At this point, exogenous insulin is being given as replacement. [16,17] In order to achieve adequate control and prevention of further complications in the state of beta cell failure, physicians must be able to provide appropriate insulin replacement tailored to the individual needs of type 2 diabetes patients. In this light, the knowledge on several insulin preparations is very important.

Insulin Preparations

Several insulin preparations are available: (a) short-acting regular insulin, (b) rapid-acting insulin analogs, (c) intermediate-acting insulin (NPH), and (d) long-acting basal insulins. The short- and rapid-acting insulins are used for prandial/bolus insulin replacement while the latter two are used for basal insulin coverage.

Short-Acting Regular Insulin: This type of insulin is mainly used to blunt postprandial rises in glucose levels. It has a delayed onset of action of 30-60 minutes due to the formation of hexamers after reaching the subcutaneous space slowing the absorption. Regular insulins peak at 2-4 hours and have duration of action of 6-8 hours.[16]

Rapid-Acting Insulin Analogs: These analogs results from substitution in the amino acid sequence of the human insulin leading to decrease in hexamer formation after injection into the subcutaneous space. Because of this, they have a rapid onset of action (5-15 minutes), peak (1 hour) and shorter duration of action (4 hours). Available rapid-acting insulin includes insulin aspart, glulisine, and lispro. There are no significant clinical differences amongst different insulin analogs.[16] Because of their pharmacokinetic profile, insulin analogs offer the advantage of optimum reduction in postprandial hyperglycemia and lead to lesser late postprandial hypoglycemia as compared to the regular insulins.

Neutral Protamine Hagedorn (NPH) Insulin: NPH insulin is an intermediate-acting insulin with more prolonged effects due to the addition of protamine. Its onset of action is 2 hours, peak effect of 6-14 hours and duration that lasts for 10-16 hours. This pharmacokinetic property gives NPH insulin a basal property when given at bedtime and may serve as basal and prandial insulin if given in the morning.

Long-Acting Insulin Analogs: These insulin analogs serve to provide basal coverage. The main function is to inhibit hepatic gluconeogenesis providing fasting normoglycemia. Available basal insulin analogs are detemir, glargine and degludec (differences in pharmacodynamics are shown in Table 1). In contrast with NPH, there is a lower occurrence of hypoglycemic events.

Pre-mixed Insulins: These are fixed combinations of regular or rapid-acting analogs with intermediate-acting insulin or protaminated rapid-acting

Table 1: Insulin Pharmacodynamics

Insulin	Onset (hr.)	Peak (hr.)	Duration (hr.)	Appearance
Insulin Lispro	within 15 min	~ 1	3-5	Clear
Insulin Aspart	within 15 min	1-3	3-5	Clear
Insulin Glulisine	0.25-0.5	0.5-1	4	Clear
Regular	~ 1	2-4	5-8	Clear
NPH	1-2	4-10	14+	Cloudy
Insulin Detemir	3-4	6-8 (though relatively flat)	up to 20-24	Clear
Insulin Glargine	1.5	Flat	24	Clear
Insulin Degludec	1	9	42	Clear
Lispro Mix 50/50	0.25-0.5	0.5-3	14-24	Cloudy
Lispro Mix 75/25	0.25-5	0.5-2.5	14-24	Cloudy

Donner T, Sarkar S. Insulin – Pharmacology, Therapeutic Regimens, and Principles of Intensive Insulin Therapy. [Updated 2019 Feb 23; cited 2022 April 06].

insulin analogs. This combination of two distinct insulin pharmacodynamics allows for both basal and prandial coverage. A newer fixed dose co-formulation available in the market is a combination of insulin degludec and aspart resulting in insulin action that reflects the individual profile of the two insulins. It has a more rapid onset of action (aspart) providing prandial coverage and a prolonged peakless duration of action (degludec) that may last beyond 24 hours.

Common Practices of Insulin Therapy

Several insulin replacement strategies are used based on the needs of individual patients. However, there has not been a consensus on the most effective and optimal insulin regimen for type 2 diabetes despite advances in pharmacotherapy and technology.[17]

Once-Daily Insulin Injection: This regimen is usually given among type 2 diabetes patients with OHA. Basal insulins (eg, NPH, insulin glargine, detemir, degludec) are given once a day usually at night; however, they may be given at any time of the day. Once daily premixed insulin may also be given prior to dinner for patients who consume a large proportion of carbohydrates for dinner.[16]

Twice-Daily Insulin Regimen: Split-mixed insulin regimen typically gives two-thirds of the total insulin dose before breakfast and the remaining third before dinner. In this regimen, pre-mixed insulin or a mixture of short- and intermediate-acting insulin can be used.[16]

Multiple Daily Injection Regimen: This is the basal bolus insulin regimen combining long-acting insulin and short/rapid-acting insulin. This regimen may be given in any of the following forms: (a) once-daily long-acting insulin analog and regular or rapid-acting insulin analog before meals, or (b) twice-daily NPH and rapid-acting insulin analogs before meals. [16]

Identified Factors Why HbA1c Goal Is Not Achieved During Insulin Therapy

Despite the benefits of insulin and its outstanding safety profile, the sad reality is that adequate glycemic control has not improved for years. Based on recent evidences, the average HbA1c among diabetes patients on insulin in the US and Europe is 8.5% with a third at 9% or even higher.[17] Several factors are associated with poor glycemic control among patients with type 2 diabetes. In a study by Fekadu, et al. of 154 type 2 diabetes patients, patient factors contributed to inadequate glycemic control—poor compliance to dietary requirement (67.5%), inadequate physical activity (84.6%), lack of self-monitoring of blood sugar (32.5%), constant smoking (6.6%) and alcohol drinking (13.2%). Patient knowledge is also vital in achieving good control. Most patients had no proper knowledge on target glucose levels and mainly depend on their physicians for the management of diabetes.[18] Other factors affecting glycemic control are BMI, central obesity, dyslipidemia and self-care practices. [19]

Factors affecting inadequate glycemic control were studied by Tong, et al. specifically, among type 2 diabetes patients on insulin therapy. Four major themes were identified: (a) challenges in adherence to lifestyle recommendations (eg, inability to control eating habits, misleading dietary recommendations and health factors prohibiting optimum physical activity), (b) psychosocial and emotional aspects which includes lack of motivation, (c) diabetes treatment-related factors and (d) lack of knowledge. [20]

Most importantly, physician-related factors contribute significantly to poor glycemic control among patients on insulin. In one cross-sectional study, 40% claimed to have given inadequate insulin therapy education. Also, a similar percentage reported that HbA1c results were not able to provide guidance in diabetes management. Lack of access to rapid-acting insulins and other insulin analogs was also identified as one barrier.[21] An important factor that contributes to the inability to reach glycemic targets in almost half of type 2 diabetes patients is therapeutic inertia. Practitioners often are willing to tolerate periods of minimal hyperglycemia that often delays treatment intensification by almost 3 years.[22]

Focusing more closely on physician-related factors, the following identified factors could significantly impact the difficulty of achieving good glycemic control despite insulin therapy:

A. *The type of insulin is incorrect:* This results due to inadequate knowledge on available insulin preparations and their respective pharmaco-dynamic properties (as discussed above) and
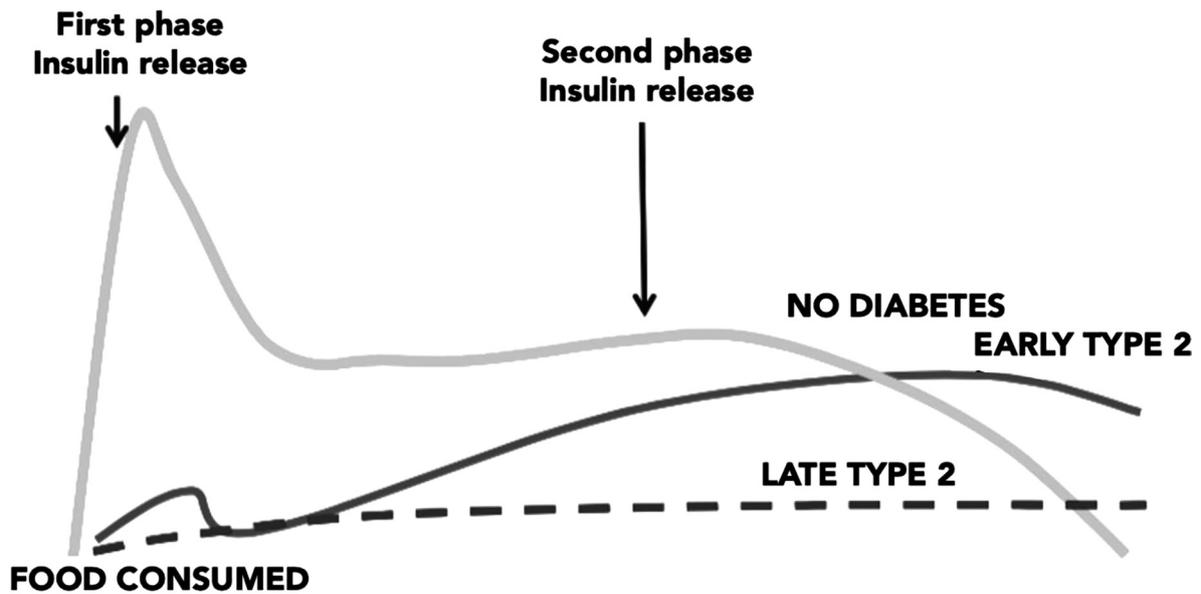
Figure 3: Phases of insulin secretion of a healthy pancreas compared with patients with type 2 diabetes. *Diabetes Educators [Internet]. Pathophysiology of Diabetes Mellitus Type 2. [Updated 2022; cited 2022 April 06] Available from: Diabeteseducatorscalgary.ca [23]*

insufficient comprehension of the physiology of insulin secretion. This could lead to erroneous dosing and frequency which subsequently results in both hyperglycemia and hypoglycemia.

B. *Combination of insulin is incorrect:* Combination therapy would be needed in a majority of type 2 diabetes patients (especially in intensive insulin therapy) in order to achieve the HbA1c target. However, improper combination could lead to the direction of poor glycemic control.

C. *Approach is not physiologic:* A very important aspect that is most commonly missed by most physicians in prescribing insulin is the knowledge of the pathophysiology of diabetes. Understanding and mimicking the normal physiologic insulin secretion in response to a meal would guide physicians in giving the best and optimum insulin regimen that would lead to a targeted HbA1c level. Factors A and B could be addressed better by making diabetes decision-making on insulin therapy a physiologic one as well.

Insulin Replacement Therapy (IRT): The Physiological Approach

As endocrinologists, a majority of the cases we see entails either excess or deficiency of a hormone. As with hormonal deficiencies, an endocrinologist must be able to adequately replace appropriate hormone with an appropriate dose.[17] How are we going to do proper replacement? One must always go back to the basics—the pathophysiology. Adequate replacement means giving exogenous hormones by mimicking the physiological state. This is true with IRT.

Based on previously mentioned evidences and this current discussion, we emphasized that insulin therapy is initiated among type 2 diabetes patients who already lack significant pancreatic insulin secretion. Since eventual beta cell failure (ie, lack of insulin secretion) is central to the pathophysiology of type 2 diabetes, it is but reasonable to replace insulin by mimicking its physiologic secretion. Hence, we should utilize the term IRT. Such terminology will serve as a constant guide and reminder on the very vital reason of giving the insulin—to simulate insulin physiology. In this light, making the treatment physiologic is equivalent to providing definitely effective diabetes care and treatment that will ultimately improve the patient's quality of life.

In a normal pancreas, basal insulin is constantly secreted to counteract the hepatic glucose production and prevent ketogenesis between meals and overnight. Basal requirements are usually 50% of the total daily dose. Moreover, the beta cells release insulin in response to postprandial glycemic excursions. As a replacement, prandial insulin is about 50-60% of the total requirement. Basal bolus regimens provide replacement that closely mimics the normal insulin secretion. Insulin given once or twice daily does not mimic physiologic insulin secretion. This may work well on patients with

less severe beta cell failure.[16] Achieving a more physiologic insulin replacement, therefore, requires more frequent insulin injections which eventually puts greater reliance on short-acting insulins. Noteworthy, postprandial glucose control becomes more significant as glycemic status closes to the target goals.[10]

One regimen that mimics physiologic insulin secretion is a combination of premix insulin (ie, NPH + regular insulin) and rapid-acting insulin. Pharmacodynamics of this regimen demonstrate that rapid-acting insulin acts during the first 5-15 minutes (peak 1 hour and duration of action 3-5 hours) while the onset of action of premix insulin sets in at 30 minutes and peaks at 2-12 hours (ie, 2-4 hours for the regular insulin, 4-12 hours for the NPH insulin). In a study by Laplano, et al., glycemic control and sustainability were measured among a total of 218 patients on insulin 70/30 with lispro and insulin 70/30 alone (outcomes were measured as reduction in HbA1c and postprandial CBG). Both were combined with metformin 1 g twice daily. Although the premixed insulin regimen alone produced significant reduction (33%; mean reduction of 42.3 mg/dL) in postprandial CBG, there is an even larger significant decrease among patients on premixed insulin and lispro (45%; mean reduction of 93.6 mg/dL). This regimen shows how the lispro covers the first phase of postprandial insulin secretion while the premix insulin covers for the second phase of insulin secretion and for basal requirement. Serial HbA1c levels showed a decreasing trend from an initial 17.5% reduction (mean duration of 7 months) to an even sustained 18% reduction of further follow-up proving reliable glycemic control.[24] With good glycemic controls, there would be reduction in the development of microvascular complications in type 2 diabetes [UKPDS].

The next question would be—how sustainable would this kind of physiologic regimen be? In a study by Laplano and Mercado-Asis, 138 patients were able to reach target after a mean interval of 6.7 months. Further extension of follow-up for more than five years still showed a durable adequate glycemic control (mean HbA1c of 6.6%) showing a 32% reduction in the level of HbA1c from baseline (9.7% to 6.6%). The patients included in the study had chronic duration (mean >8 years) of poorly controlled diabetes (baseline HbA1c >9%)

representing an already significantly decreased beta cell function.[25]

The former two studies are important especially among regions in the world that uses premixed and co-formulation insulin most popularly such as in the Southeast Asian countries.[8] Understanding the pathophysiology now would help one in determining the optimum management. For example, prescribing premix insulin before breakfast and before dinner clearly demonstrate a lack of coverage for the glycemic excursion at lunch.

Stepwise Approach to Insulin Treatment

Not all individuals progress in the course of beta cell failure at the same time and patients may be in different stages of deficiency of the pancreatic insulin reserve.[13] Hence, a stepwise approach is logical in transitioning from oral (ie, some insulin reserve) to insulin therapy (ie, beta cell failure). We mimic physiologic insulin secretion once patients advance to the stage of insulin lack.

In a retrospective study of Lopez, et al., a stepwise insulin treatment approach has been demonstrated in achieving the desired HbA1c goals (Figure 4). Majority of the patients ended up in regimen D (55%) and regimen E (17%) in order to achieve good and sustainable glycemic control. A stepwise approach may be an effective tool for insulin intensification as this could significantly bring down the levels of HbA1c with minimal occurrence of hypoglycemia and insignificant weight gain.[26] This could guide physicians in using a more complex insulin regimen that would cater to the natural course of type 2 diabetes.

With all these regimens, individual patient profile should still be considered (eg, BMI, age, duration of diabetes, socioeconomic factors and support system). Clinical evidences of insulin resistance should be considered even prior to initiating any treatment regimen for type 2 diabetes. Insulin resistance coupled with progressive failure of beta cells are likely to end up in treatment failure with oral antidiabetic medications. The aging process also contributes to peripheral insulin resistance due to a possible post-receptor defect mechanism.[26] One must remember that in prescribing insulin, one size fits all does not apply—dose and frequency may vary patient per patient but guides given above would help a physician in achieving desired targets.
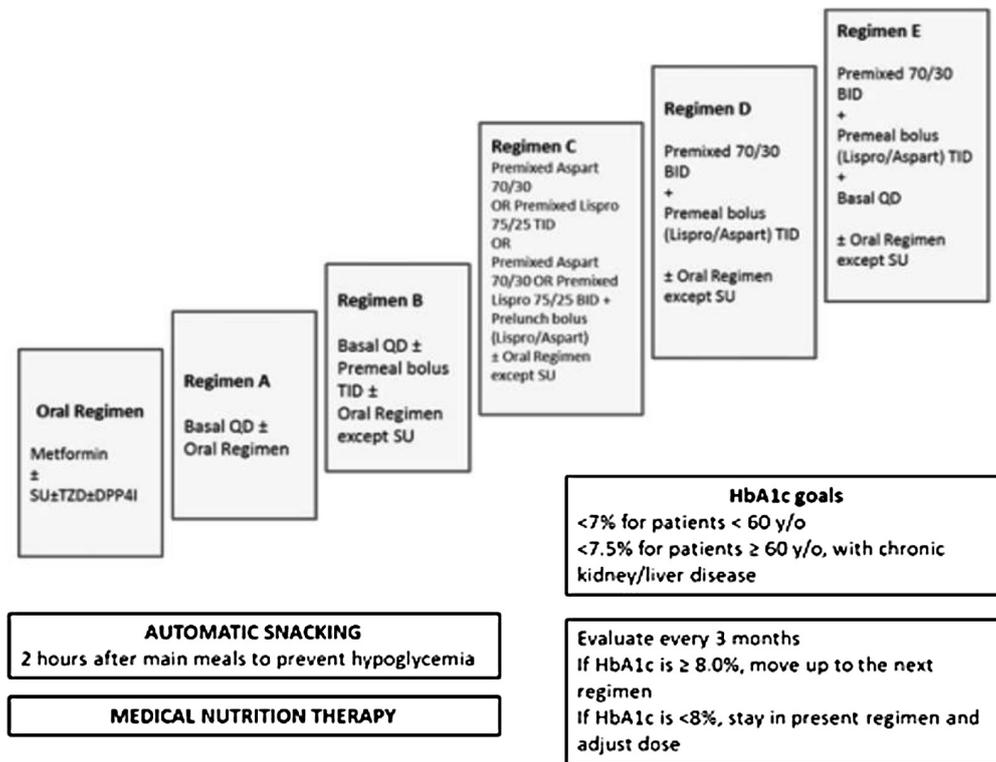
Figure 4: Stepwise Insulin Combination Treatment Algorithm. *Lopez, AA, Mendoza, ES, Valdez, VU and Mercado-Asis, LB. Treatment Outcomes with the Use of a Stepwise Insulin Combinations Algorithm Among Type 2 Diabetic Patients. 2016. Philippine Journal Internal Medicine 2016. Volume 54 Number 2. [cited 2022 April 6]*

Medical Nutrition Therapy (MNT) Through Automatic Snacking: Approach to Prevent Hypoglycemia During Intensive Insulin Therapy

As shown above, there are several barriers to insulin therapy—risk of hypoglycemia, weight gain and inexperience by the physician, all of which may lead to treatment inertia.[26] Among these, the risk of hypoglycemia restricts most physicians in using insulin despite its limitless capacity and effectiveness to reduce and normalize HbA1c.[9] Previous literatures showed that severe hypoglycemia is associated with increased cardiovascular outcome (eg, myocardial infarction, heart failure and stroke) and all-cause mortality.[27] This was supported by the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study Group wherein patients on intensive therapy group (ie, HbA1c 6.4%) had higher occurrence of nonfatal myocardial infarction, nonfatal stroke or death from cardiovascular causes.[28] Rates of hypoglycemia and cardiovascular complications (specifically coronary heart disease) and mortality significantly increase as the age advances.[29] These are the reasons why this intensive insulin treatment regimen has been abandoned by many practitioners across age groups including the elderly.[30] On the other hand, poor glycemic control is also associated with higher frequency of cardiovascular risk factors and events. Among the elderly, chronic high glucose levels (higher A1c) may even be associated with lower cognitive function. [31] Nevertheless, long-term follow-up (median 12 years, range 7-22 years) among type 2 diabetes patients on intensive insulin replacement with therapy by Valdez MNR and Mercado-Asis LB in the outpatient setup showed that the rate for acute coronary event (0.001 per person-year), stroke (0.009 per person-year) and even dialysis (0.002 per person-year) were all negligible. Blindness and amputation were likewise not observed.[32] With all these recent evidences, the better way to go is towards a safe intensive IRT by preventing patients to experience hypoglycemia.

An effective way to prevent hypoglycemia even in intensive therapy among patients with type 2 diabetes has been shown through MNT with automatic snacking.[24-26,30] In automatic snacking, the total caloric requirement was computed on the basis of physical activity. Caloric prescription are as follows: 60% carbohydrates, 15% proteins, 25% fats. The intake per day is divided into three major meals and three snacks per day with the snacks advised to be taken automatically two hours after each major meal even in the absence of hunger.[30]
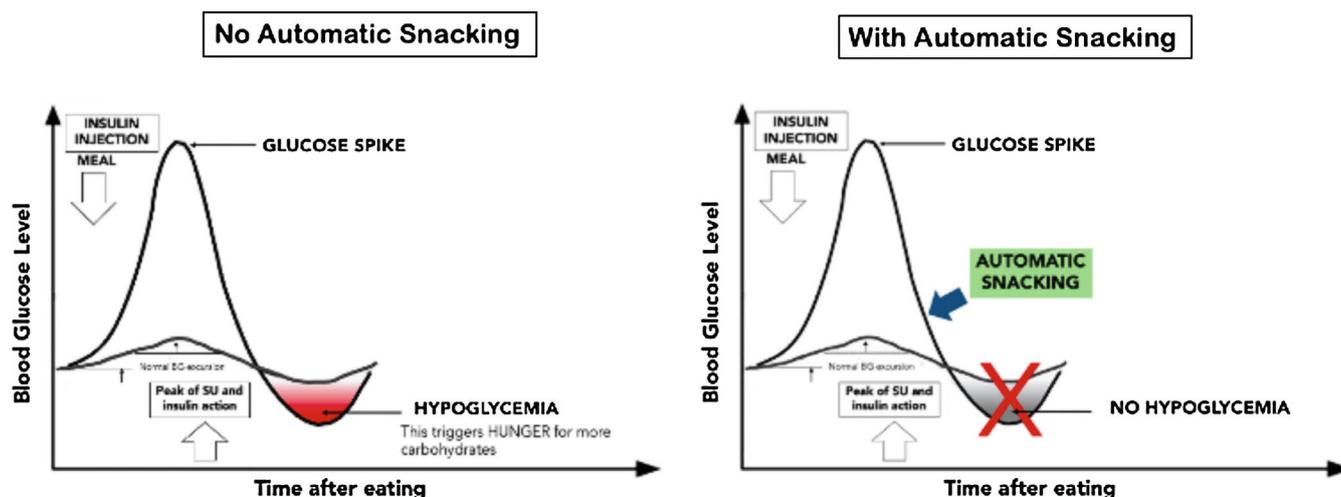
Figure 5: Schematic diagram depicting when automatic snacking is instituted to prevent hypoglycemia in type 2 diabetes mellitus patients on sulfonylurea (SU) and insulin therapy. *Mercado-Asis LB and Lorenzo-Redoblado ZG. Cardiovascular Adverse Outcomes as Challenges on Glycemic Variability Among Patients with Type 2 Diabetes on Intensive Insulin Therapy: The Role of Medical Nutrition Therapy with Automatic Snacking. Series Endo Diab Met. 2021;3(2):59–68. [Cited with similar figure title 2022 April 06]*

In the study of Lorenzo and associates, both in the outpatient and inpatient setting, goal of glycemic control has been achieved early and satisfactorily. It is important to note that no one of these patients experienced significant hypoglycemia. Hence, automatic snacking is an efficient way of preventing hypoglycemia while achieving glycemic control with intensive insulin therapy.[24-26,30] Lastly, Mercado-Asis and Lorenzo-Redoblado demonstrated that automatic snacking effectively reduced glycemic variability (ie, fluctuations of blood glucose in terms of daily blood glucose and HbA1c mean levels). Glycemic variability is associated with increased occurrence of macrovascular and microvascular complications. Hence, MNT with automatic snacking among patients on intensive IRT is associated with negligible hypoglycemia and reduced glycemic variability both leading to the attainment of good glycemic control.[33]

Summary and Recommendations

Insulin resistance begins the pathogenesis of type 2 diabetes. Along with this, beta cell mass and function progressively decline in type 2 diabetes leading to insulin insufficiency. In time, the beta cell insulin secretion will not be able to cope up with the increase in demand brought about by the ongoing insulin resistance. Patients may be diagnosed in any part of this diabetes pathophysiology spectrum and oral medications may be effective only during the early stages where there are still some insulin reserves. Majority of the patients will progress to beta cell failure and will be needing insulin therapy. However, there are several barriers into achieving good glycemic control on insulin therapy. Patient-related factors such as poor education and awareness, compliance and socioeconomic status have been identified. Moreover, physician-related factors are equally important. These include incorrect choice and inappropriate combination of insulin therapy which could be corrected by making the treatment physiologic. Hence, with the available evidences, we formulated the following recommendations:

A. *Individualization of insulin therapy.* Progression of type 2 diabetes starts in different stages. Individualization of management is still the key approach. Individual patient profiles should be considered upon initiation, modification or intensification of diabetes management. One type of regimen may provide adequate glycemic control to certain patients but not to the others.

B. *Timely initiation of insulin.* As shown earlier, patients would usually be prescribed with OHA early in the course of therapy. Nevertheless, as the disease progresses, the majority would eventually need IRT. Patients with persistently elevated HbA1c levels (ie, ≥8%) on three determinations despite being on maximum doses of oral medications shall be put on insulin therapy. With appropriate timing of insulin initiation, diabetes

complications could be prevented early in the disease.

C. *Follow the stepwise insulin combination treatment algorithm.* Initiating insulin therapy is one thing, proper insulin combination treatment is another. The stepwise algorithm by Lopez, et al. serves as a guide in transitioning from oral to insulin therapy and combining insulins based on the natural history of the disease. This has proven to provide glycemic levels at target.

D. *Use of dietary regimen through automatic snacking.* Hypoglycemia is one of major factors why most physicians and patients hesitate to use and continue insulin therapy. This could be prevented among patients on IRT with automatic snacking enabling the physician to reach and sustain glycemic targets and control.

E. *Make the treatment physiologic.* All of the recommendations boil down to the basic—the physiology. Making the treatment physiologic allows one to choose the proper type of insulin and appropriate combination and timing of injection. We must always take into consideration that insulin therapy is a replacement therapy. This could be provided by the combination of premix insulin (ie, NPH + regular insulin) and rapid-acting insulin which has been reported to provide efficient and sustainable glycemic control.

CONCLUSION

Giving insulin is not a guessing game. As with all other diseases, management decisions in the treatment of type 2 diabetes should be based on the pathophysiology—progressive failure of beta cells that is unable to cope up with ongoing insulin resistance. With this in mind, insulin therapy should be given as replacement in order to mimic the physiologic insulin secretion, specifically in the advanced stage of insulin lack in patients with type 2 DM. Combination of premix insulin and a rapid-acting insulin with or without basal insulin would cover for the defects in insulin secretion and would provide a physiologic, sustainable glycemic control over years. This may be achieved using a stepwise approach in insulin replacement. Hypoglycemia, a significant barrier in the initiation and intensive treatment with insulin could be prevented by the implementation of appropriate dietary management through automatic snacking.

REFERENCES

1. Skyler JS, Bakris GL, Bonifacio E, Darsow T, Eckel RH, Groop L, et al. Differentiation of diabetes by pathophysiology, Natural History, and Prognosis. Diabetes. 2017;66(2):241–55. Available from: http://dx.doi.org/10.2337/db16-0806

2. Olokoba AB, Obateru OA, Olokoba LB. Type 2 diabetes mellitus: a review of current trends. Oman Med J. 2012;27(4):269–73. Available from: http://dx.doi.org/10.5001/omj.2012.68

3. Artasensi A, Pedretti A, Vistoli G, Fumagalli L. Type 2 diabetes mellitus: A review of multi-target drugs. Molecules. 2020;25(8):1987. Available from: http://dx.doi.org/10.3390/molecules25081987

4. International Diabetes Federation. [Updated 2021 September 12; cited 2022 April 03]. Available from: https://idf.org/aboutdiabetes/what-is-diabetes/facts-figures.html.

5. Wong J, Yue D. Starting insulin treatment in type 2 diabetes. Aust Prescr. 2004;27(4):93–6. Available from: http://dx.doi.org/10.18773/austprescr.2004.075

6. DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. JAMA. 2003;289(17):2254–64. Available from: http://dx.doi.org/10.1001/jama.289.17.2254

7. Bullard KM, Cowie CC, Lessem SE, Saydah SH, Menke A, Geiss LS, et al. Prevalence of diagnosed diabetes in adults by diabetes type - United States, 2016. Morb Mortal Wkly Rep. 2018;67(12):359–61. Available from: http://dx.doi.org/10.15585/mmwr.mm6712a2

8. Kalra S, Thai HQ, Deerochanawong C, Su-Yen G, Mohamed M, Latt TS, et al. Choice of insulin in type 2 diabetes: A southeast Asian perspective. Indian J Endocrinol Metab. 2017;21(3):478–81. Available from: http://dx.doi.org/10.4103/ijem.IJEM_82_17

9. Chen S-Y, Hsu H-C, Wang R-H, Lee Y-J, Hsieh C-H. Glycemic control in insulin-treated patients with type 2 diabetes: Empowerment perceptions and diabetes distress as important determinants. Biol Res Nurs. 2019;21(2):182–9. Available from: http://dx.doi.org/10.1177/1099800418820170

10. Blonde L, Aschner P, Bailey C, Ji L, Leiter LA, Matthaei S, et al. Gaps and barriers in the control of blood glucose in people with type 2 diabetes. Diab Vasc Dis Res. 2017;14(3):172–83. Available from: http://dx.doi.org/10.1177/1479164116679775

11. Normal Glucose Metabolism. [Updated 2022; cited 2022 April 6] Available from: https://www.diabeteseducatorscalgary.ca/other/diabetes-overview/pathophysiology-of-diabetes.html#sppb-tab2-3.

12. Thompson R, Christie D, Hindmarsh PC. The role for insulin analogues in diabetes care. Curr paediatr. 2006;16(2):117–22. Available from: http://dx.doi.org/10.1016/j.cupe.2005.12.011

13. Wysham C, Shubrook J. Beta-cell failure in type 2 diabetes: mechanisms, markers, and clinical implications. Postgrad Med. 2020;132(8):676–86. Available from: http://dx.doi.org/10.1080/00325481.2020.1771047

14. Phillips LS, Ratner RE, Buse JB, Kahn SE. We can change the natural history of type 2 diabetes. Diabetes Care. 2014;37(10):2668–76. Available from: http://dx.doi.org/10.2337/dc14-0817

15. Hanefeld M, Fleischmann H, Siegmund T, Seufert J. Rationale for timely insulin therapy in type 2 diabetes within the framework of individualised treatment: 2020 update. Diabetes Ther. 2020;11(8):1645–66. Available from: http://dx.doi.org/10.1007/s13300-020-00855-5

16. Donner T, Sarkar S. Insulin - Pharmacology, Therapeutic Regimens, and Principles of Intensive Insulin Therapy. [Updated 2019 Feb 23; cited 2022 April 06]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK278938/

17. Hodish I. Insulin therapy for type 2 diabetes – are we there yet? The d-Nav® story. Clin Diabetes Endocrinol . 2018;4(1):1–11. Available from: http://dx.doi.org/10.1186/s40842-018-0056-5

18. Fekadu G, Bula K, Bayisa G, Turi E, Tolossa T, Kasaye HK. Challenges and factors associated with poor glycemic control among type 2 diabetes mellitus patients at Nekemte Referral Hospital, western Ethiopia. J Multidiscip Healthc. 2019;12:963–74. Available from: http://dx.doi.org/10.2147/JMDH.S232691

19. A Kakade A, R Mohanty I, Rai S. Assessment of factors associated with poor glycemic control among patients with Type II diabetes mellitus. Integr Obes Diabetes. 2018;4(3):1–6. Available from: http://dx.doi.org/10.15761/iod.1000209

20. Tong WT, Vethakkan SR, Ng CJ. Why do some people with type 2 diabetes who are using insulin have poor glycaemic control? A qualitative study. BMJ Open. 2015;5(1):e006407. Available from: http://dx.doi.org/10.1136/bmjopen-2014-006407

21. Motial S. Physician related barriers towards insulin therapy at primary care centres in Trinidad: a cross-sectional study. BMC Fam Pract. 2020;21(1):197. Available from: http://dx.doi.org/10.1186/s12875-020-01271-1

22. Freeman JS. Insulin analog therapy: improving the match with physiologic insulin secretion. J Am Osteopath Assoc. 2009;109(1):26–36. PMID: 19193822.

23. Diabetes Educators [Internet]. Pathophysiology of Diabetes Mellitus Type 2. [Updated 2022; cited 2022 April 06] Available from: Diabeteseducatorscalgary.ca

24. Laplano NE, Quiambao DA, Uy J, Mercado-Asis LB. Combination Insulin Therapy with Pre-Mixed Intermediate/Rapid-Acting Insulin (70/30) and Insulin Lispro Mimicking Physiologic Insulin Secretion: Optimal Glycemic Treatment with Sustainability of Control in type 2 Diabetic Patients. Philippine Journal Internal Medicine. 2009;47:93–7. Available from: doi 10.3860/PJIM.V47I3.1650

25. Laplano NE, Asis LM. Sustainable Glycemic Control with Combination Insulin Therapy of Biphasic Insulin Plus Rapid-Acting Insulin Mimicking Physiologic Insulin Secretion in Type 2 Diabetes. Philippine Journal Internal Medicine 2012;50. Available from: DOI:10.1210/endo-meetings.2011.PART2.P10.P1-536

26. Lopez AA, Mercado-Asis LB. Treatment Outcomes with the Use of a Stepwise Insulin Combinations Algorithm Among Type 2 Diabetic Patients. Philippine Journal Internal Medicine. 2016;54. Available from: https://www.researchgate.net/publication/306147033

27. Yun J-S, Park Y-M, Han K, Cha S-A, Ahn Y-B, Ko S-H. Severe hypoglycemia and the risk of cardiovascular disease and mortality in type 2 diabetes: a nationwide population-based cohort study. Cardiovasc Diabetol. 2019;18(1):103. Available from: http://dx.doi.org/10.1186/s12933-019-0909-y

28. Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study Group, Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med.

2008;358(24):2545–59. Available from: http://dx.doi.org/10.1056/NEJMoa0802743

29. Huang ES, Laiteerapong N, Liu JY, John PM, Moffet HH, Karter AJ. Rates of complications and mortality in older patients with diabetes mellitus: the diabetes and aging study: The diabetes and aging study. JAMA Intern Med. 2014;174(2):251–8. Available from: http://dx.doi.org/10.1001/jamainternmed.2013.12956

30. Lorenzo ZG, Mercado-Asis LB. Automatic Snacking Prevents Hypoglycemia Among Outpatient Type 2 Diabetic Patients on Intensive Insulin Therapy. Philippine Journal Internal Medicine. 2011;49(2). Available from: https://www.researchgate.net/publication/290613381

31. Cukierman-Yaffe T, Gerstein HC, Williamson JD, Lazar RM, Lovato L, Miller ME, et al. Relationship between baseline glycemic control and cognitive function in individuals with type 2 diabetes and other cardiovascular risk factors: the action to control cardiovascular risk in diabetes-memory in diabetes (ACCORD-MIND) trial. Diabetes Care. 2009;32(2):221–6. Available from: http://dx.doi.org/10.2337/dc08-1153

32. Valdez MNR, Mercado-Asis LB, Faculty of Medicine and Surgery, University of Santo Tomas, Manila, Philippines. Long term evaluation of intensive insulin therapy in patients with type 2 diabetes mellitus. Series Endo Diab Met. 2021;2(3):88–94. Available from: http://dx.doi.org/10.54178/jsedmv2i3002

33. Mercado-Asis LB, Section of Endocrinology and Metabolism, Department of Medicine, Faculty of Medicine and Surgery, University of Santo Tomas, Manila, Philippines.

Cardiovascular adverse outcomes as challenges on glycemic variability among patients with type 2 diabetes on intensive insulin therapy: The role of medical nutrition therapy with automatic snacking. Series Endo Diab Met. 2021;3(2):59–68. Available from: http://dx.doi.org/10.54178/jsedmv3i2004