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Treatment Approach for Type 2 Diabetes

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University of North Dakota

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Abstract

The growing prevalence and pervasiveness of type 2 diabetes (DMII) constitutes a global health crisis. The current guideline-based treatment strategies for DMII feature a stepwise titration and addition of oral and/or injectable agents to assist in improving glycemic parameters while minimizing the development of common complications. However, this strategy leaves relatively unopposed the pathophysiological processes that underlie DMII – beta-cell dysfunction and insulin resistance. There is a gathering research effort dedicated to the development and refinement of a novel disease-modifying treatment that alters the natural history of DMII through rapid resolution of hyperglycemia, reversal of insulin resistance, and restoration of beta-cell secretory function. This treatment is called short-term intensive insulin (STII) therapy and involves subjecting patients to 2-3 weeks of insulin administration to bring about a rapid return to normoglycemia. A collection of 16 pertinent studies that address and investigate this novel treatment modality was assembled during a comprehensive literature search utilizing several academic literature search databases. After scrutiny of methodology and synthesis of findings, it was concluded that STII therapy is a superior alternative to current treatment approaches with respect to the following outcomes: improvement of beta-cell function, reversal of insulin resistance, attainment of glycemic control, achievement and maintenance of drug-free glycemic remission, and safety. In addition, investigators have identified several patient factors that increase the likelihood of achieving remission. Although more research is certainly warranted, this novel therapy is positioned to be embraced and employed by providers and specialty organizations that publish DMII practice guidelines.

Early Short-term Intensive Insulin Therapy: A Disease-modifying

Treatment Approach for Type 2 Diabetes

The following is an all-too-familiar scenario that plays out on a daily basis in primary care offices everywhere: A moderately-overweight middle-aged patient presents to the clinic for a routine visit to monitor type 2 diabetes management. She was diagnosed two years ago and has made little, if any, progress toward achievement and maintenance of normoglycemia despite lifestyle modification and escalation of oral antidiabetic drug therapy. She has known neurovascular complications and comorbid hypertension and hyperlipidemia. As medication doses are increased and the addition of other agents is considered, the provider longs for the existence of a disease-modifying therapy that could alter the natural history of DMII by reversing the two pathophysiologic processes at the heart of DMII – beta-cell dysfunction and insulin resistance. Fortunately, there is currently underway a research movement with a goal to make this wish a reality for patients like the one mentioned above.

Type 2 diabetes (DMII) represents a global health crisis in demand of urgent intervention. Arising out of an interplay of both non-modifiable and modifiable risk factors, DMII is a chronic health problem that is exploding in worldwide prevalence and exacting an ever-increasing toll on health, quality of life, and economic and healthcare resources. The International Diabetes Federation reports that the worldwide prevalence of DMII in 2013 was around 340 million (or 8.5% of those individuals over 18 years of age) with that number expected to grow to 530 million by 2035 (Saisho, 2014). DMII is a leading cause of blindness, kidney failure, heart attack, stroke, and lower extremity amputation worldwide, with diabetic complications directly implicated in anywhere between 2.2 million and 5.1 million deaths per year (Saisho, 2014). Further, it is estimated that treatment of DMII and its complications account for 10.8% of total

worldwide healthcare expenditures (Saisho, 2014). It is imperative that this be addressed before it becomes a global health catastrophe.

The current treatment approach for DMII typically involves starting with a trial of lifestyle modifications with the hope that euglycemia can be restored in a non-pharmacological manner. If not successful, this is usually followed by addition of an oral antidiabetic drug (most often metformin) with subsequent escalation of the dose until satisfactory glycemic control is achieved. If this is not achieved, the stepwise addition of other oral medications from other classes and/or injectable agents (either GLP-1 agonists or insulin) takes place until Hgb A1c reaches the treatment goal. This strategy, although successful in reestablishing short-term glycemic control in many cases, simply corrects hyperglycemia while the underlying pathophysiological processes of DMII continue in the background. This permits the disease to advance insidiously, which is reflected by the need for progressive intensification of therapy and the eventual necessity of exogenous insulin administration.

DMII develops after an individual, due to the interplay of modifiable and non-modifiable risk factors, experiences a sustained level of hyperglycemia that reinforces and amplifies itself by directly inhibiting pancreatic beta-cell function (both through the phenomenon of glucotoxicity and by increasing secretory workload) and by contributing to the development of tissue-level insulin resistance. As insulin sensitivity deteriorates, hyperglycemia becomes more pervasive, beta-cell function and mass decline further, hyperglycemia intensifies, DMII complications develop, and treatment begins to demand continual escalation until exogenous insulin is required due to total secretory failure of beta-cells.

Therapy failure, much like that illustrated in the presented case, is too often experienced using current guideline-based management approaches. In fact, it is believed that fewer than 50%

of those with a high Hgb A1c are receiving treatment that would be considered optimized

(Weng, 2017). Further, when metformin is started as a sole agent at DMII diagnosis, a 17% per

year treatment failure rate is noted (Weng, 2017). Many believe that this is the case because the

underlying pathophysiological features of DMII – beta cell dysfunction and insulin resistance –

continue to worsen despite the use of conventional treatment strategies (Weng, 2017)

It has been posited that some level of beta-cell dysfunction is present up to 12 years

before the diagnosis of DMII, and insulin sensitivity and secretion are already detectably

abnormal 3-6 years before diagnosis (Hanefeld, 2014). Further, obese individuals with DMII

have been found on autopsy to have 65% less beta-cell mass than those without DMII, and beta-

cell function may have already decreased by 80% by the time impaired glucose tolerance is first

noted (Saisho, 2014). It is not surprising, then, that many researchers assert that treatment is

started too late in the process and that, when treatment is started, it should center on the reversal

of beta-cell damage / death and the restoration of beta-cell secretory function. There is a belief,

based on scientifically-generated evidence, that the use of insulin for a short period (2-3 weeks)

near the time of DMII diagnosis can help restore beta-cell function and insulin sensitivity in such

a dramatic way that there is, after the short-term intensive insulin (STII) period, a real possibility

of experiencing a drug-free remission period during which normoglycemia can be maintained

with lifestyle modification alone (Weng et al., 2015).

Even though its addition is usually inevitable (usually at an average of 9 years after DMII

diagnosis), insulin is typically one of the final introductions to currently-used therapy regimens.

Newer research evidence tends to suggest that insulin is added far too late, with the average Hgb

A1c at insulin initiation being 9.5% (Home et al., 2014). At that point, about 90% of patients

have experienced at least one DMII-related complication, and fewer than 10% of beta-cells are

even functional (Home et al., 2014). Because of these findings, there has been a growing interest in utilizing a short burst of intensive insulin therapy at the time of diagnosis in order to achieve these effects and alter the natural history of DMII. This paper will attempt to critically evaluate and formulate a synthesis of the research literature that addresses the novel DMII treatment modality that is known as short-term intensive insulin (STII) therapy. Specifically, the role of STII will be investigated as it relates to the following parameters: beta-cell function, insulin resistance, glycemic control, rates of drug-free remission, incidence of hypoglycemia, and predictors of glycemic remission versus relapse.

Case Report

A 45-year-old female presented to her primary care provider's office at the prompting of her diabetes educator due to patient reports of high morning home blood glucose readings. She was diagnosed with type 2 diabetes (DMII) two years earlier and has struggled with her glycemic control having implemented lifestyle modifications (including weight loss attempt, healthier diet, increased aerobic activity, and diabetes education) in addition to taking 1000 mg of metformin daily. Her initial A1c upon diagnosis was 9.6%, and her fasting plasma glucose was 267 mg/dL. She elected to solely try lifestyle modifications at that time, but after failing to lower her glycemic parameters by 3- and 6-month follow-up appointments, she agreed to begin taking 1000 mg daily of metformin. During the subsequent 1.5 years, she has continued monthly appointments with the diabetes educator and has tried unsuccessfully to make lasting weight, diet, and activity modifications. She has been reluctant to escalate her pharmacologic therapy despite never having lowered her A1c to below 8.2% during the past 2 years. She sees an eye provider for diabetic eye exams every year and reports no issues. Her kidney function has

remained acceptable thus far. However, she has been experiencing symptoms of progressive peripheral neuropathy in her lower extremities since before her diagnosis.

In addition to metformin, she also takes the following daily medications: aspirin 81 mg, lisinopril 20 mg, atorvastatin 20 mg, and a daily multivitamin. Her blood pressure has been well-controlled up to this point with the ACE inhibitor, but her lipid profile has never reached satisfactory status for someone with DMII (LDL >130). She has no history of other significant medical problems. Her mother, maternal grandmother, and paternal grandfather all suffer from DMII, and her maternal grandmother has had a myocardial infarction. She is married, has two school-aged children, and works outside of the home as a cook.

During the visit, her physical exam was unremarkable with the exception of marked reduction of sensation bilaterally in her feet during a 10-point monofilament exam. Her review of symptoms revealed no vision changes, nausea, vomiting, polyuria, chest pain, shortness of breath, or changes in level of consciousness. Her labs during the visit were as follows: A1c 8.5% (previous 8.3%), FPG 178 (previous 145), TSH 6.4, Free T4 0.8, total cholesterol 187, HDL 43, LDL 133 (previous 128), triglycerides 180 (previous 195), serum creatinine 0.69 (previous 0.72), urine albumin-to-creatinine ratio 16 mg albumin/gram creatinine (previous 17). Her weight is stable (BMI 28), and the only abnormal vital sign during her visit was blood pressure, which was 148/98 mmHg. Qualitatively, her history, exam, vital signs, and lab studies demonstrate continued poorly-controlled DMII with peripheral neuropathy (though without renal or retinal complications) in the setting of less-than-ideal serum lipid levels (specifically LDL and triglycerides) and elevated blood pressure.

At the conclusion of this visit, after all the available history, exam, and laboratory data had been reviewed and synthesized, the following treatment plan was formulated and

implemented by the patient and provider: 1) Greater effort would be assigned to weight loss, eating a healthier diet, and increasing activity level to feature 150 minutes a week of semi-vigorous exercise, 2) Double the daily dose of metformin to 2000 mg, 3) Double the daily dose of atorvastatin to 40 mg, 4) Double the daily lisinopril dose to 40 mg, and 5) Return in 3 months to evaluate progress toward achieving control of glycemic profile, lipid levels, and blood pressure with the anticipation of escalating DMII therapy.

Literature Review

A comprehensive literature search was conducted utilizing CINAHL, PubMed, and the Cochrane Library. A search of Google Scholar was also included with the goal of returning guidelines and other grey literature that may not be unearthed in a formal search of the bibliographic databases. CINAHL was searched first with the following limits applied to the search strategy: "English language," "peer-reviewed," and "publishing dates 2010-2018." With these filters in place, a search was performed utilizing the CINAHL Headings *Diabetes, Type 2,* and *Insulin* in combination with the keywords *intensive* OR *short-term*. Sixty-six citations were returned, and after title and abstract review, it was determined that 6 of these articles directly addressed the clinical phenomenon at hand. The remaining studies were not pertinent and were discarded.

The Cochrane Library was searched next with results limited to articles published between 2010 and 2018. In the first search, the MeSH Term *Insulin* was combined with the MeSH Term *Diabetes, Type 2*. This yielded 2,767 citations, so the keyword *intensive* was added to the search strategy, and this yielded a more-manageable queue of 78 citations. After title and abstract review, 8 pertinent citations remained, which included one systematic review and 7 trials. Various combinations of the MeSH Term *Diabetes Mellitus, Type 2* with the keywords

intensive, insulin, and *diagnosis* were searched, yielding several citations, the most pertinent of which being duplicates of those yielded in the initial Cochrane search.

Finally, PubMed was searched with the following limits applied to the search strategies: "English," "human subjects," "free full text," and "published in the last 5 years." The first search involved combining the MeSH Terms *Insulin* and *Diabetes, Type 2* with the terms *intensive*, *new* and *diagnosis*, which returned 22 citations, 2 of which were kept after title and abstract review and after accounting for duplicates from the Cochrane and CINAHL searches. The second search combined the keywords *intensive*, *insulin*, and *Type 2 Diabetes*, which produced 136 results, 5 of which were kept after title and abstract review and after accounting for duplicates from all previous searches. The third search combined the keywords *intensive*, *insulin*, *therapy*, *Type 2 Diabetes*, and *diagnosis*, which returned 103 citations, 2 of which were kept after title and abstract review and after accounting for duplicates from all previous searches. This brought the total number of relevant citations from PubMed to 9.

In total, twenty-three articles deemed germane to the clinical topic in question were obtained during the comprehensive literature search of CINAHL, PubMed, and the Cochrane Library. Additionally, a search of Google Scholar unearthed two sets of professional clinical practice guidelines that had not yet been yielded by the aforementioned database searches. This brought the total number of relevant manuscripts for this literature review to 25. Sixteen of these were analyzed and evaluated on their merit as evidence to support the recommendation to implement STII therapy early in DMII.

Summary of Findings

To evaluate the quality of the evidence yielded in the literature search and grade the strength of the practice recommendation based on it, the Strength of Recommendation

Taxonomy (SORT), which was developed by the American Academy of Family Physicians, was utilized (Ebell et al., 2004). Table 1, which can be found at the end of this paper, presents a list of the 16 included articles, each with a practice recommendation, respective SORT evidence level assignment, and strength of recommendation grade. Below is a synthesis and discussion of the evidence as it pertains to the effects of STII therapy on beta-cell function, insulin resistance, and glycemic control (disease-oriented outcomes), as well as the patient-oriented outcomes of safety, drug-free remission incidence, and predictive factors of remission.

Eleven manuscripts mentioned STII favorably in terms of preserving and improving beta-cell function in DMII (H. Chen, Wu, & Kuo, 2014; Chon et al., 2017; Hanefeld, 2014; Harrison, Adams-Huet, Li, Raskin, & Lingvay, 2014; Kramer, Zinman, & Retnakaran, 2013; Kramer, Choi, Zinman, & Retnakaran, 2013; J. Liu et al., 2013; Presswala & Shubrook, 2011; Retnakaran & Zinman, 2012; Weng et al., 2015; Zhang, Chen, Yang, Wang, & Li, 2016). Notably, Kramer et al. (2013) found in their meta-analysis that STII contributed to a 13% improvement in beta-cell function, with one-third of the study subjects having experienced > 25% improvement after STII therapy. Zhang et al. (2016) determined that beta-cell secretory function actually increased 8-fold after a brief period of STII therapy in subjects experiencing glycemic remission. Further, Harrison et al. (2014) noted that the beta-cell preservation effects attributed to STII therapy are still detectable 6 years after therapy. These studies are highly suggestive that STII therapy exerts a direct positive effect on the secretory capacity of beta-cells.

Seven studies demonstrated improvement in insulin resistance after STII therapy (H. Chen et al., 2014; Q. Cheng et al., 2015; Kramer, Choi et al., 2013; Kramer, Zinman et al., 2013; J. Liu et al., 2013; Weng et al., 2015; Zhang et al., 2016). Of note, in their meta-analysis, Kramer, Zinman, et al. (2013) reported a 43% reduction of insulin resistance after STII, and

Zhang et al. (2016) found that insulin sensitivity was increased by 100% in those subjects who achieved drug-free remission after STII therapy. Q. Cheng et al. (2015) also reported a significant improvement in the Matsuda Index (a surrogate for insulin resistance) after a short period of STII therapy. These data make a strong case for the beneficial effects of STII therapy on insulin sensitivity by direct reversal of mechanisms responsible for insulin resistance.

Both short- and long-term glycemic control were found to be positively affected by STII therapy in 10 studies (H. Chen et al., 2014; Q. Cheng et al., 2015; Chon et al., 2017; Hanefeld, 2014; Harrison et al., 2014; Kramer, Zinman et al., 2013; J. Liu et al., 2013; Presswala & Shubrook, 2011; Retnakaran & Zinman, 2012; Weng et al., 2015). In their RCT featuring a 6-year follow-up, Harrison et al. (2014) reported a dramatic decrease in subjects' A1c from 10.8% to 5.9% after 3 months of STII therapy, and after 6 years of conventional oral antidiabetic (OAD) therapy post-STII, 69% of patients still exhibited a Hgb A1c < 7%. An 8-study review conducted by Hanefeld (2014) also revealed long-lived significant reductions in A1c and FPG in those subjects who underwent STII therapy. Retnakaran and Zinman (2012) also reported that significantly more individuals who took part in STII therapy early in DMII achieved and maintained euglycemia (demonstrated by A1c and FPG) at 1 year post-intervention than those who were managed via standard OAD therapy. Finally, in a case report, Presswala and Shubrook (2011) described a patient who initially exhibited a Hgb A1c that was too high to be measured who was subjected to a basal-bolus STII therapy for 15 weeks, after which his Hgb A1c was measured at 6.4%. Without any further pharmacologic intervention, his Hgb A1c was 6.0% at 1 year and 6.7% after 27 months post-STII (Presswala & Shubrook, 2011). The above studies illustrate the ability of STII therapy to rapidly achieve (and often maintain) glycemic control.

The induction of drug-free glycemic remission, which is arguably the most exciting potential benefit associated with STII therapy, was reported in 11 of the papers returned during the literature search (H. Chen et al., 2014; Chon et al., 2017; Hanefeld, 2014; Kramer, Zinman et al., 2013; Kramer, Zinman, Choi, & Retnakaran, 2016; J. Liu et al., 2013; L. Liu et al., 2015; Presswala & Shubrook, 2011; Retnakaran & Zinman, 2012; Weng et al., 2015; Zhang et al., 2016). Hanefeld (2014) found that 66.2% of individuals enjoyed drug-free remission (A1c < 7%) at 3 months post-STII therapy, and 42% of these were still in remission at 24 months. Kramer, Zinman et al. (2013) reported a 56% remission rate at 48 weeks post-STII, while Zhang et al. (2016) reported that 50% of their study subjects remained in remission at 1 year post-STII therapy. Similarly, Retnakaran and Zinman (2012) found that 44.9% of those who underwent brief STII therapy were in remission at 1 year versus only 26.7% of those who underwent intensive therapy with OAD during the same time period. Chon et al. (2017) also compared STII therapy with OAD in terms of remission and reported that significantly more subjects in the STII group achieved and maintained remission, with the STII group enjoying 52.2% less risk of relapse at 2 years post-STII therapy (Chon et al., 2017).

One potential barrier to widespread use of STII therapy is fear of exogenous insulin-related hypoglycemia. Eight of the manuscripts returned during the literature search featured study of this, with all of the investigators reporting that STII therapy is a safe modality if properly administered. (H. Chen et al., 2014; Q. Cheng et al., 2015; Chon et al., 2017; Harrison et al., 2014; Kramer, Choi et al., 2013; L. Liu et al., 2015; Presswala & Shubrook, 2011; Weng et al., 2015). H. Chen et al. (2014) reported zero episodes of hypoglycemia in their study, while Chon et al. (2017), L. Liu et al. (2015), Presswala and Shubrook (2011), and Weng et al. (2015) reported a very low incidence of hypoglycemic events (and none of a serious nature) during the

course of STII therapy. This array of evidence seems to support the safety of using STII therapy in an outpatient setting, as long as patients are prepared and deemed capable of managing their regimen.

Much of the research that has addressed STII therapy has found, unfortunately, that not all type 2 diabetic individuals respond favorably to the same degree after STII therapy. For instance, even though initial improvements in glycemic control, beta-cell function, and insulin sensitivity are generally seen in all patients after STII therapy, these effects vary in magnitude and duration. Furthermore, because it is felt that the amelioration of these pathophysiological components of DMII is what permits the development of drug-free remission, it is no surprise that not all subjects experience remission, and in those who do, their remission periods vary in length. It would be helpful, therefore, to identify any patient factors that may make remission more or less likely to occur and persist.

The literature search identified 8 manuscripts that reported discovery of patient factors predictive of remission (A. Chen et al., 2012; L. Cheng et al., 2016; Kramer, Choi et al., 2013; Kramer, Zinman et al., 2013; Kramer et al., 2016; J. Liu et al., 2013; L. Liu et al., 2015; Zhang et al., 2016). Kramer, Zinman et al. (2013) and Kramer et al. (2016) found that lower baseline Hgb A1c, higher baseline BMI, and lower baseline FPG were independently predictive of achieving and maintaining glycemic remission after STII. L. Cheng et al. (2016) reported that a shorter time interval between STII initiation and achievement of glycemic goal is also prognostic of achievement of drug-free remission. Zhang et al. (2016) directly measured acute glucagon response (AGR) during STII and found that a greater magnitude of reduction was noted in those who ultimately achieved remission. A. Chen et al. (2012) demonstrated that positive attitude, higher educational attainment, and patient compliance and self-care ability are factors found

more often in those who experience remission. Kramer et al. (2016) concluded that the patient

factor most influential in terms of predictive value of remission is duration of DMII, with less

than 2 years since onset seemingly being the ideal timeframe.

Limitations of Evidence and Barriers to Implementation

The evidence presented in the 16 included studies is unequivocally complimentary of the

beneficial effects of STII therapy in early DMII. However, despite the therapeutic promise of this

modality, there are some criticisms of the evidence that warrant discussion. First, several of the

early studies that investigated the benefits of STII on the natural history of DMII were small,

single arm intervention studies (no control group) that were conducted at a few centers in China.

Methodological issues like lack of randomization, no control groups, and small study size may

justifiably call into question the validity of some of the resulting data. Another criticism of the

evidence touted by early studies is that some of them required hospitalization of study subjects

for the duration of STII therapy, which calls into question the practicality of this form of

treatment. Additionally invoked as a criticism of earlier evidence is lack of consistency regarding

the choice of insulin delivery mode utilized for STII therapy (i.e. some studies used continuous

subcutaneous infusion and others used basal-bolus injection protocols).

Although these criticisms and limitations are all valid, their merit has been fading

recently as more studies have been conducted that look at multi-ethnic populations in the

outpatient setting with results that seem to mimic the earlier studies. Further, a handful of the

newer multi-center studies have featured larger numbers of enrolled subjects in addition to the

investigators' implementation of more rigorous methodological standards. The array of returned

manuscripts used in this literature review reflect this progressive evolution of study quality, as

shown by the distribution of SORT evidence levels assigned to the studies. That being said, there

continues to be a need for more and larger outpatient-based, multi-ethnic RCTs that use multiple daily injections (instead of continuous subcutaneous infusion) as the STII delivery mode of choice when investigating the benefits of this therapy.

Looking past the ever-improving issues related to evidence limitations, there are other barriers to widespread adoption of STII therapy as a disease-modifying therapy in early DMII. These barriers can be broken down into two categories: patient factors and provider factors. Patient factors representing barriers include cost (insulin, needles, home meters, follow-up provider visits), fear and/or unpalatability of needles/self-injection, need for high degree of compliance and reliability, the health belief or perception that insulin signifies the presence of advanced disease, potential for insulin-related weight gain, and the necessity to be prepared and equipped to recognize and treat hypoglycemic episodes (Home et al., 2014; Weng, 2017). Considerable effort by provider and patient will likely be necessary to overcome these barriers.

From a provider barrier standpoint, the term "clinical inertia" has been applied in this instance by Home et al. (2014) to describe the phenomenon where providers are reluctant to adopt a progressive treatment modality due to comfort and ease in employing the current established treatment. For example, due to the nature of STII therapy and its dissimilarity with current treatment guidelines, there may be a perception by primary care providers that it is aggressive, foreign, and not within their capacity to manage. As pervasive as this inertia is, it is intensified when providers do not experience pressure from guideline-publishing authorities to espouse the new treatment. Based on the DMII practice guidelines published by the American Diabetes Association and the American Association of Clinical Endocrinologists / American College of Endocrinology (neither of which mentions STII therapy as a treatment option), the hesitation of U.S. providers to adopt STII therapy in their primary care practices is not

unexpected (Garber et al., 2017; Rhinehart et al., 2017). Slightly more liberal is the joint position statement published by the ADA and the European Association for the Study of Diabetes that prescribes a patient-centered approach to DMII management permitting prompt reversal of hyperglycemia using insulin when a patient presents initially with ketosis, catabolic features, or very deranged glycemic profiles (Inzucchi et al., 2015). The most progressive guideline found in the literature search was published by the Israeli National Diabetes Council. The authors described how short-term insulin use has been shown to abolish glucotoxicity, and, ultimately, preserve beta-cell function (Mosenzon, Pollack, & Raz, 2016). They suggested that STII be considered for any individual who presents with an A1c > 9%, with or without symptoms of DMII. Given what is known about the disease-modifying benefits of STII, its absence of mention within American-based DMII treatment guidelines is a mystery. As new evidence of high quality emerges in favor of implementation of STII therapy, appropriate changes to practice and management guidelines should ideally come to reflect this with the appropriate adoption by primary care providers to follow.

Conclusion

Based upon the review of available and current literature, there is a compelling indication to implement early and aggressive STII therapy in DMII. STII therapy leads to rapid resolution of hyperglycemia, which mitigates the negative effects of gluco- and lipotoxicity on beta-cell function, directly reverses insulin resistance, reduces beta-cell secretory stress (i.e. provides beta-cell "rest"), and diminishes the acute glucagon response. The overall result of the action of STII therapy on beta-cell function and insulin sensitivity is an evidence-substantiated safe promotion of normoglycemia that has the potential to lead to short- or even long-term drug-free glycemic remission. Patient factors that make this remission more likely to occur and persist are higher

BMI, lower baseline fasting plasma glucose and A1c, faster time to glycemic goal after STII

initiation, positive attitude, greater self-care ability and compliance, higher educational level

attained, and, most importantly, a shorter duration of DMII. As DMII continues to devastate the

lives of more patients with each passing year, there is a need to identify and implement new

disease-modifying treatment modalities that are successful in stalling and even reversing the

progression of the key pathophysiological features of this disease. STII therapy seems to hold

much promise in serving as such a treatment.

Learning Points

- When implemented early in DMII, STII therapy, which usually consists of 2-3 weeks of daily

  insulin administration, has been shown to safely alter the natural history of type 2 diabetes by

  quickly restoring normoglycemia, reversing insulin resistance, improving beta-cell function,

  and blunting the acute glucagon response.

- The positive effects of short-term intensive insulin therapy on insulin resistance, beta-cell

  function, and the acute glucagon response have been shown to safely facilitate the

  achievement of drug-free glycemic remission in up to 65% of individuals, with this remission

  persisting in about 50% of subjects at one year and 42% of subjects at 2 years.

- Some patient factors that have been found to predict achievement and maintenance of drug-

  free remission are as follows: higher baseline BMI, lower baseline Hgb A1c and FPG, shorter

  duration of DMII, positive attitude, greater compliance and self-care ability, and higher

  educational level attained.

- Providers and guideline-publishing groups have been slow to adopt STII therapy as a

  treatment option. More studies are needed to solidify its place and clarify issues such as ideal

  length of STII therapy and how to dose multiple daily injection regimens.

Table 1.

Level of Evidence and Strength of Recommendation for each of the 16 articles reviewed. Determinations were formulated utilizing the Strength of Recommendation Taxonomy (SORT), which was developed and published by the American Academy of Family Physicians (Ebell et al., 2004).

Paper / Study	Recommendation Based on Results	Level of Evidence (based on AAFP SORT)	Strength of Recommendation
Retnakaran & Zinman, 2012	STII therapy should be considered at DMII diagnosis in certain patients as a means to improve glycemic profiles, beta-cell function, and insulin sensitivity in the hope that drug-free remission can be induced.	Level 1 Evidence – Systematic Review of several trials that addressed remission, beta-cell function, glycemic parameters, and predictors of remission after STII therapy	A
Kramer, Zinman, & Retnakaran, 2013	STII therapy should be initiated at diagnosis to improve underlying pathophysiology of DMII and alter its natural history. Remission can be predicted based on baseline patient characteristics.	Level 1 Evidence – Systematic Review and Meta-analysis of 7 studies that addressed beta-cell function, insulin resistance, remission, and predictors of remission after STII	A
Harrison et al., 2014	Initiate insulin-based short-term intensive therapy early in DMII, as it can generate improvements in beta-cell function and glycemic control that last for at least 6 years.	Level 1 Evidence – RCT with 6 year follow up looking at beta-cell function and glycemic control in insulin-based vs. triple oral therapy after STII therapy	A
Chen, Wu, & Kuo, 2014	Institute STII therapy early in the course of DMII. After the initial STII period, the continued use of insulin glargine (instead of standard COAD) extends glycemic benefit.	Level I Evidence – RCT of high quality that compared COAD versus continuing insulin after 10-14 days STII therapy on long term glycemic control	A
Hanefeld, 2014	Utilize STII therapy early in DMII. It can improve beta-cell function, insulin sensitivity, and glycemic control, as well as potentially induce drug-free remission. Reduction in major CV events are likely a benefit of early intensive glycemic control.	Level I Evidence – Systematic Review and Meta-analysis of 5 studies addressing beta-cell recovery, 7 studies addressing remission, and 8 studies addressing glycemic control after STII	A
Chen et al., 2012	Positive attitude, higher educational level attained, self-care adherence and ability, lower insulin resistance at baseline, and greater improvement of acute insulin response are independent predictors of remission after STII	Level 2 Evidence -Case control that addressed baseline characteristics of those who achieved remission after STII	B
Liu et al., 2013	Fasting plasma glucose at end of STII is an independent predictor of relapse. (Higher = greater risk of relapse)	Level 2 Evidence - Case Control that addressed fasting plasma glucose as risk factor for relapse after STII	B
Kramer, Choi, Zinman, & Retnakaran, 2013	Reduction of insulin resistance was an independent predictor of greater improvement of beta-cell function. Can be used to predict who will experience remission vs. relapse.	Level 2 Evidence - Case control that addressed insulin resistance change as predictor of remission vs. relapse after STII	B

Note. STII - Short-term intensive insulin; COAD – combined oral anti-diabetic drug therapy; OAD – oral anti-diabetic drug therapy; TTG = Time to (glycemic) goal

Table 1.
Continued

Paper / Study	Recommendation Based on Results	Level of Evidence (based on AAFP SORT)	Strength of Recommendation
Liu et al., 2015	The degree of decrease in total daily dose of insulin needed to hold euglycemia during the two weeks after STII was predictive of relapse vs. remission. (greater decrease = greater chance of remission).	Level 2 Evidence – Case Control that addressed change in total daily dose (TDD) of insulin needed to maintain glycemic target after STII and how this predicts relapse vs. remission	B
Cheng et al., 2015	STII therapy is able to improve glycemic control and beta-cell function at diagnosis of DMII. After that point, it doesn't matter whether insulin is continued or OAD is initiated in terms of these parameters.	Level 2 Evidence – Randomized trial but no control group. Compared continuing insulin vs. COAD after STII	B
Zhang et al., 2016	STII can improve beta-cell function and insulin sensitivity to the point of inducing drug-free remission. Greater drop in acute glucagon response is predictive of remission.	Level 2 Evidence – Single arm intervention. Small sample. No control. Looked at beta-cell function, insulin resistance, and remission after STII	B
Kramer, Zinman, Choi, & Retnakaran, 2016	STII can induce a long-term drug-free remission. Lower baseline A1c, better baseline beta-cell function, and shorter duration of DMII (less than two years) are predictive of remission.	Level 2 Evidence – Case Control looking at predictors of remission at 48 weeks after STII	B
Chon et al., 2018	OAD therapy and STII can equally achieve short-term glycemic control, but beta-cell function, insulin sensitivity, and the likelihood of achieving and maintaining drug-free remission are better in STII group.	Level 2 Evidence – Randomized trial but no control group. Compared oral anti-diabetic drug therapy vs. STII in terms of remission, beta-cell function, and glycemic control.	B
Presswala & Shubrook, 2011	2-3 weeks of STII can lower very high A1c values (down to 6.6% at one year post-STII), as well as induce remission that is still active at one year in about 50% of patients.	Level 3 Evidence – Case series describing drug-free remission (i.e. "Legacy Effect") associated with STII therapy.	C
Weng et al., 2015	Guidelines should be amended to reflect the success of STII in inducing DMII remission via its improvement of beta-cell function, insulin resistance, and glycemic control.	Level 3 Evidence – Review paper by expert panel that addresses compelling evidence to suggest use of STII therapy.	C
Cheng et al., 2016	Fast time to glycemic goal during STII therapy has implications in disease-oriented outcomes (i.e. fast TTG = better improvement in insulin sensitivity and slower TTG = better beta-cell function improvement.	Level 3 Evidence – Case control addressing how beta-cell function and insulin sensitivity (disease-oriented outcomes) correlate with time to glycemic goal during STII therapy.	C
		Totals: (5) Level 1 (8) Level 2 (3) Level 3	Final Strength of Recommendation Grade: **A**

Note. STII - Short-term intensive insulin; COAD – combined oral anti-diabetic drug therapy; OAD – oral anti-diabetic drug therapy; TTG = Time to (glycemic) goal

Table 2.

Breakdown of the 16 included papers based on noted improvements in patient-oriented and disease-oriented parameters. Also included is number of papers addressing predictors of glycemic remission versus relapse.

		Number of Included Papers that Measured and Reported Improvement in the Following Parameters / Outcomes after STII
Patient-Oriented Outcomes	Drug-Free Remission Incidence	11
	Safety (low incidence of hypoglycemia)	8
	Predictors of DMII Remission	7
Disease-Oriented Outcomes	Glycemic Control (Hgb A1c and/or FPG)	10
	Beta-cell Function	11
	Insulin Resistance / Sensitivity	7

Note. STII – Short-term intensive insulin; DMII – Type 2 Diabetes Mellitus; Hgb A1c – Glycosylated hemoglobin; FPG – Fasting Plasma Glucose

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