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The Effect of Insulin vs. Metformin or Sulfonylurea Treatment on β-Cell Function in Newly Diagnosed Type 2 Diabetes Patients

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The Effect of Insulin vs. Metformin or Sulfonylurea Treatment on β-Cell Function in Newly Diagnosed Type 2 Diabetes Patients

Abstract
Background: Type 2 Diabetes Mellitus (T2DM) is a chronic, progressive incurable disease affecting over 23.6 million people in the US. This disease involves the deterioration of β-cell function, which causes hyperglycemia. Early diagnosis and treatment of diabetes is essential and helps prevent long-term medical complications such as neuropathy, nephropathy and retinopathy. Treatment begins with diet, exercise and weight loss and then progresses to oral hypoglycemic agents (OHAs), combination OHAs, and finally to insulin therapy. Initial treatment with insulin may improve β-cell function, reduce glucotoxicity and increase insulin secretion when compared to the usual course of OHA treatment.

Hypothesis: What effect does insulin treatment have on β-cell function in newly diagnosed T2DM patients?

Methods: Exhaustive search of available medical literature from 1998 to present, for studies regarding newly diagnosed T2DM patients, treated with insulin as compared to metformin and/or a sulfonylurea, which included the evaluation of β-cell function. The four studies reviewed evaluated β-cell function by measuring fasting c-peptide, insulin and proinsulin levels, post-prandial c-peptide levels, HOMA B, HOMA IR or proinsulin-to-insulin ratios.

Results: Newly diagnosed T2DM patients treated with insulin had increased c-peptide, insulin, HOMA B and post-prandial c-peptide levels, and decreased proinsulin, HOMA IR and proinsulin-to-insulin ratios, all of which indicate improved β-cell function. This improvement was measured over durations of 6, 12, and 24 months, and after that point a decline was seen. Treatment with OHAs showed a similar pattern, however, insulin treatment showed greater improvement which lasted for longer periods of time.

Conclusion: Optimal improvement in β-cell function of T2DM patients is seen with early, intensive, short-term treatment with insulin vs. metformin or a sulfonylurea. Increase in β-cell function helps to improve metabolic control, increase insulin secretion, increase acute insulin response to glucose and decrease PI/IRI ratios. Due to the progressive nature of T2DM, this improvement in β-cell function deteriorates gradually with time.

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The student authors attest that this work is completely their original authorship and that no material in this work has been plagiarized, fabricated or incorrectly attributed.
Andrea Moore is a long time resident of Oregon where she majored in Biology and minored in Chemistry at Willamette University (WU) in 1999. While working on her undergraduate degree, she worked in Imaging at Emanuel Hospital in Portland, Oregon and at Salem Hospital in Salem, Oregon. When she took microbiology in college, she was hooked, and pestered the Assistant Lab Director for a job until she was hired to work weekends in the Microbiology lab. After graduation, she continued working part-time in the lab and also worked full-time as a research assistant at WU. She performed numerous experiments, collected data and was contributing author on five published papers. Before the grant-funded research position ended, she went to work full-time in the lab, was cross-trained in multiple departments and promoted to lead lab assistant. When boredom set in, she took Medical Laboratory Technologist classes, aced her first year and reached an important conclusion: Working with instruments is pretty darned cool, but working with patients is far more challenging. After her two daughters successfully completed high school and college, she decided to pursue her life-long dream of practicing medicine and applied to PA school. Before submitting her application to Pacific University, she made a leap of faith, returned to work at Legacy Emanuel Hospital and moved to Hillsboro, Oregon. Much to her astonishment, the stars and planets aligned, and she was accepted into the Class of 2009 at Pacific University. It is with great pleasure that she submits this paper in partial satisfaction of the requirements of her Master of Science Degree in Physician Assistant Studies.
**Abstract**

**Background:** Type 2 Diabetes Mellitus (T2DM) is a chronic, progressive incurable disease affecting over 23.6 million people in the US. This disease involves the deterioration of β-cell function, which causes hyperglycemia. Early diagnosis and treatment of diabetes is essential and helps prevent long-term medical complications such as neuropathy, nephropathy and retinopathy. Treatment begins with diet, exercise and weight loss and then progresses to oral hypoglycemic agents (OHAs), combination OHAs, and finally to insulin therapy. Initial treatment with insulin may improve β-cell function, reduce glucotoxicity and increase insulin secretion when compared to the usual course of OHA treatment.

**Hypothesis:** What effect does insulin treatment have on β-cell function in newly diagnosed T2DM patients?

**Methods:** Exhaustive search of available medical literature from 1998 to present, for studies regarding newly diagnosed T2DM patients, treated with insulin as compared to metformin and/or a sulfonylurea, which included the evaluation of β-cell function. The four studies reviewed evaluated β-cell function by measuring fasting c-peptide, insulin and proinsulin levels, post-prandial c-peptide levels, HOMA B, HOMA IR or proinsulin-to-insulin ratios.

**Results:** Newly diagnosed T2DM patients treated with insulin had increased c-peptide, insulin, HOMA B and post-prandial c-peptide levels, and decreased proinsulin, HOMA IR and proinsulin-to-insulin ratios, all of which indicate improved β-cell function. This improvement was measured over durations of 6, 12, and 24 months, and after that point a decline was seen. Treatment with OHAs showed a similar pattern, however, insulin treatment showed greater improvement which lasted for longer periods of time.

**Conclusion:** Optimal improvement in β-cell function of T2DM patients is seen with early, intensive, short-term treatment with insulin vs. metformin or a sulfonylurea. Increase in β-cell function helps to improve metabolic control, increase insulin secretion, increase acute insulin response to glucose and decrease PI/IRI ratios. Due to the progressive nature of T2DM, this improvement in β-cell function deteriorates gradually with time.

**Keywords:** Type 2 diabetes mellitus, insulin, metformin, sulfonylurea, beta-cell function
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Table 2: Summary of study results for reviewed articles.

List of Abbreviations

ADA.................................................................American Diabetes Association
CSII..............................................................Continuous Subcutaneous Insulin Infusion
FBG.............................................................Fasting Blood Glucose
FPG.............................................................Fasting Plasma Glucose
HbA1C.............................................................Hemoglobin A1C
HOMA............................................................Homeostasis Model Assessment
HOMA B.........................................................Homeostasis Model Assessment Basal insulin secretion
HOMA IR.........................................................Homeostasis Model Assessment Insulin Resistance
MDI.............................................................Multiple Daily Injections
NIDDM..........................................................Non-Insulin Dependent Diabetes
OHA.............................................................Oral Hypoglycemic Agents
PI/IRI ratio......................................................Proinsulin-to-Immunoreactive Insulin ratio
T2DM.............................................................Type 2 Diabetes Mellitus
TX.................................................................Treatment
THE EFFECT OF INSULIN VS. METFORMIN OR SULFONYLUREA TREATMENT ON β-CELL FUNCTION IN NEWLY DIAGNOSED TYPE 2 DIABETES PATIENTS

Introduction

Barely a day goes by without mention in the news of the increasing number of patients being diagnosed with Type 2 Diabetes Mellitus (T2DM). In a recent study conducted in China, 44% of newly diagnosed T2DM patients treated with intensive insulin therapy went into remission, and normoglycemia was maintained for up to one year with diet and exercise. Remission was attributed to early intervention with intensive glycemic control, reducing glucotoxicity and enabling pancreatic β-cell rest and recovery of function. Most patients with T2DM are treated with diet and lifestyle changes first, and then with oral medications. Initial treatment of T2DM with insulin therapy and the resulting induction of remission was a novel concept. Further reading on this subject matter lead to the development of the clinical question: What effect does insulin treatment have on β-cell function in newly diagnosed T2DM patients?

Background

Diabetes mellitus is a progressive, chronic, incurable disease that involves either the lack of insulin production in Type 1 diabetes, or insulin resistance in Type 2 diabetes. Insulin is a hormone produced by β-cells of the pancreas, in the islets of Langerhans. The body requires insulin to change sugar, carbohydrates and other food into the energy necessary to sustain life. Diabetes was first described in 1552 BC, by an Egyptian physician, Hesy-Ra, as “the passing of too much urine,” but it was not named until 1425 AD, when ‘diabete’ first appeared in the Middle English language. Diagnosis made by the presence of sugar in urine was established in 1776, by an
English physician, Matthew Dobson, and medical treatment was first prescribed by John Rollo, a physician in Scotland, in 1797. Pancreatic islet cells were discovered by a German medical student, Paul Langerhans in 1869. Research by Dr. Frederick Banting, lead to the discovery of endogenous insulin in 1921, shortly after which insulin was mass produced by Eli Lilly in 1922. It was not until 1959, that the differences between Type 1 and Type 2 diabetes were recognized.5

Today, diabetes affects over 23.6 million adults and children in the United States (US). An estimated 5.7 million of these people have the disease and are under diagnosed, and the number of individuals with the disease is increasing in epidemic proportions: From 1990 to 2005, prevalence rates doubled, and from 2005-2007, the number of patients diagnosed with diabetes increased by 13.5%. In the US, 5-10% of patients diagnosed have Type 1 diabetes, treated with daily insulin injections and dietary control.3,6

Type 2 diabetes is the most common form of this disease, and typically occurs in obese adults over the age of 40, however, as the general population becomes more obese, this disease is being seen more frequently in children and adolescents.7 This disease is characterized by hyperglycemia, caused by insulin resistance, reduced insulin secretion and increased hepatic glucose production.8 People with T2DM produce insulin, but it does not convert sugar into energy.3,4 Blood glucose and insulin levels increase, causing hyperglycemia.7 In response to elevated blood glucose, β-cells in the pancreas become overworked and gradually lose the ability to function. Disease progression leads to β-cell deterioration and to reduced secretion of insulin.8,9 In later stages of the disease, combination treatment with oral medications
and insulin is required to maintain glycemic control. Early diagnosis and treatment of diabetes is essential to reducing hyperglycemia, slowing the loss of β-cell function, and to reducing the added complications of dyslipidemia, hypertension, hypercoagulability and obesity. Improved glycemic control also helps prevent the long term complications of neuropathy, nephropathy and retinopathy.4,7

Based on standards established by the American Diabetes Association (ADA), diagnosis of T2DM is made when fasting plasma glucose (FPG) levels are 126 mg/dL and above. Fasting plasma glucose levels below 100 mg/dL are considered normal, and levels of 100-125 mg/dL indicate impaired glucose tolerance or pre-diabetes. Two-hour plasma glucose tolerance testing with levels from 140-199 mg/dL indicate pre-diabetes, and a level of 200 mg/dL or above is diagnostic for T2DM.11 New recommendations made by a panel of experts to the ADA include using hemoglobin A1C levels (HbA1C) over 6.5% to diagnose T2DM in children and adults.12

Once a patient is diagnosed with T2DM, treatment typically begins with dietary changes, weight loss and exercise.3 Weight loss and exercise are critical components of successful treatment. Numerous chemicals released by adipose cells alter insulin receptors in the tissue, contributing to insulin resistance and reduced insulin sensitivity.4,7 A loss of 5-10 pounds can significantly reduce the risk of diabetes, reverse chemically related changes and, in some patients, induce remission.13,14,15 The ultimate goal of diabetes treatment is glycemic control, which is defined by the ADA as a HbA1C of 7% or less.11 When glycemic control is not achieved with dietary changes and exercise, then monotherapy with an oral hypoglycemic agent (OHA), either metformin or a sulfonylurea is started. A
sulfonylurea, such as gliclazide, glibenclamide or glyburide, is recommended for initial treatment, however, metformin is more commonly prescribed because it has the beneficial side effect of weight loss. If monotherapy fails, then combination OHA therapy with metformin and a sulfonylurea is used. Doses are adjusted until glycemic control is achieved. Insulin is added as a last resort, after combination therapy with maximum doses of OHAs fails to maintain glycemic control. Progressive deterioration of glycemic control and hyperglycemia is characteristic in T2DM patients, even with combination therapy using different medication classes.

Beta-cell dysfunction is present early in T2DM, long before diagnosis is made. By the time hyperglycemia occurs, β-cell secretory ability has already decreased by an estimated 50-75%. Several mechanisms for causing β-cell dysfunction have been proposed. Elevated glucose and lipid levels may be toxic and desensitize β-cells. Increasing insulin resistance and relative insulin deficiency may place a high secretory demand on the β-cell, cause exhaustion and lead to cell failure. Patients with T2DM may have some defect in their islet cells or, β-cell mass reduction and increased islet amyloidal buildup may contribute to the decline in function.

Beta-cell function may be evaluated several ways. One method involves measuring plasma levels of proinsulin, the precursor molecule to insulin, which is processed by cleaving off the c-peptide chain, forming a mature insulin molecule available for use by the body. Individuals with T2DM often have elevated levels of proinsulin and proinsulin-to-insulin ratios, which suggest incomplete insulin processing and reduced secretory capacity, and serves as a marker for increased β-cell
dysfunction. C-peptide levels are a strong measure of insulin secretion, but do not measure insulin action or sensitivity. Another commonly accepted method for measuring β-cell function and estimating insulin sensitivity is the Homeostasis Model Assessment (HOMA), which uses fasting plasma glucose, insulin, and c-peptide levels for calculations. HOMA B levels measure the basal rate of insulin secretion, while HOMA IR measures insulin resistance. In healthy individuals, insulin and c-peptide levels increase in response to elevated levels of glucose, while patients with T2DM will have a delayed or absent response. The HOMA B level is higher, and HOMA IR level lower in healthy patients as compared to T2DM patients.

Materials and Methods

A comprehensive literature search was performed using combinations of the keywords: Type 2 diabetes, Type 2 diabetic, NIDDM, insulin, glycemic control, beta-cell, β-cell, metformin, sulfonylurea, randomized, c-peptide, HOMA, and remission, on Ovid-Medline, CINAHL and PubMed-Medline databases. Literature from 1998 to the present was reviewed by title and abstract. Relevant articles were compiled, analyzed and cross-referenced, using a cited reference search on the Web of Science database, for other pertinent literature. Reference sections from relevant articles were also reviewed for literature pertaining to the subject matter. The inclusion criteria were all clinical studies in the English language, published after 1998 that were a minimum of six months in length and involved: 1) treatment of newly diagnosed T2DM patients with insulin monotherapy or with OHAs, metformin and/or a sulfonylurea, and 2) evaluation of β-cell function. Preference was given to
randomized studies. Exclusion criteria were articles published before 1998, non-English language works, studies less than six months in duration, articles without evaluation of β-cell function, studies which combined insulin and oral hypoglycemic medications, used oral medications other than metformin or sulfonylurea, or included patients which were not newly diagnosed.

Results

A total of five articles comparing insulin treatment with oral hypoglycemic medications were published, that included evaluation of β-cell function. One study began treatment with monotherapy, and when that failed, insulin and OHA combination therapy was used, and the study was excluded.10 Study criteria for the relevant articles are summarized in Table 1. These articles address the effectiveness and remission rates between insulin treatment as compared to oral hypoglycemic treatment of patients, and the effect of treatment on β-cell function and metabolic control.

Chandra et al, studied 60 subjects in India, treated with either insulin or gliclazide, to compare the effectiveness and remission rate between groups.20 Patients with a mean of three fasting blood glucose (FBG) levels > 200 mg/dL, were included in the study. Treatment was chosen by the patient and groups were equal in size. All subjects in the study received diabetes education regarding lifestyle changes, nutrition and the monitoring of FBG levels, which was reinforced during each follow-up visit. Subjects monitored FBG levels and discontinued treatment when levels remained less than 90 mg/dL for at least one week in gliclazide treated patients, and when FBG levels remained less than 100 mg/dL for over one week or
when hypoglycemia occurred in insulin treated patients. Fasting plasma glucose levels normalized within two to six weeks for both groups. Subjects in the insulin group were treated an average of 3 months before remission was induced. At six months, 3.3% of gliclazide subjects and 80% of insulin subjects were in remission. At twelve months, 5% of gliclazide subjects and 62.5% of insulin subjects remained in remission. Post-prandial c-peptide levels evaluating β-cell function were measured at baseline and six months. No other testing was performed to evaluate β-cell function. Treatment was withdrawn 24 hours prior to testing. C-peptide levels increased from 3.2 to 5.8 ng/mL, in the insulin subjects, and levels remained unchanged in the gliclazide subjects, from 3.4 to 3.8 ng/mL, with a significant difference between groups (p = 0.0003). C-peptide levels were not measured at twelve months. Hemoglobin A1C levels measured at baseline and six months decreased from 10.4 to 6.2% in both groups. Thirty subjects enrolled in each group, all 60 completed six months of follow-up, and 36 completed twelve months of follow-up. Two patients in the insulin group were lost to follow-up at nine months; both were in remission at their last visit.20

Weng et al, studied 382 subjects in China, treated with insulin, metformin, gliclazide, or metformin with gliclazide, to compare the effect of treatment on β-cell function and remission rate. All subjects had a FPG level of 7.0-16.7 mmol/L (126-300 mg/dL) and started with 3-7 days of dietary treatment before randomization into one of three groups treated with either, a continuous subcutaneous insulin infusion pump (CSII), multiple daily insulin injections (MDI) or an oral hypoglycemic agent (OHA), metformin and/or gliclazide. A target glycemic goal established for all
subjects was a FBG level less than 110mg/dL, or two hour post-prandial blood-glucose level less than 144 mg/dL. Body-mass index was calculated for all subjects, and obese patients in the OHA group started treatment with metformin and non-obese patients started with gliclazide. Combination OHAs were used if the subject failed to attain glycemic control on monotherapy. Subjects continued treatment for two weeks after the glycemic target was met, and at that point, treatment was discontinued and the subjects only used diet and exercise for glycemic control. If glycemic control was not reached, the subject was dropped from the study. Glycemic control was reached in 92.1% of all subjects in 7.9 days, 97.1% of CSII subjects in 4.0 days, 95.2% of MDI subjects in 5.6 days, and 83.5% of OHA subjects in 9.3 days. Statistical differences were found between OHA and CSII groups (p < 0.0001) and between OHA and MDI groups (p = 0.01). Prior to treatment, all groups had similar β-cell function, as measured by acute insulin response to glucose, HOMA B, HOMA IR, and proinsulin-to-immunoreactive insulin (PI/IRI) ratios. Acute insulin response was absent in all groups before treatment. After treatment, acute insulin response and HOMA B significantly increased in all subjects (p < 0.0001), while HOMA IR and PI/IRI ratios both significantly decreased (p < 0.0001). There was no statistical difference seen in HbA1C levels, measured before and after treatment, and a comparable reduction in HbA1C level was seen in all groups.¹

After one year, 42.0% of all subjects who reached glycemic control remained in remission, which included 51.1% of the CSII group, 44.9% of the MDI group and 26.7% of the OHA group. Remission rate was significantly higher in the insulin treated groups than in the OHA treated group (p = 0.0012). Acute insulin response at
one year remained increased in the insulin treated groups and decreased in the OHA treated groups, with a significant difference between the CSII and OHA groups (p = 0.006), and no difference between MDI and OHA groups (p = 0.097). Patients lost to follow-up, included 23 subjects who did not achieve glycemic control, 7 who withdrew from the study due to gastrointestinal side effects from metformin, and 21 who dropped out of the study due to immigration issues or were lost to follow-up.1

Alvarsson conducted a four-year study in two parts.21,22 Results for the first two years are published in Alvarsson 2003, where 51 subjects in Sweden were studied, to determine whether metabolic control and β-cell function improves with insulin or glibenclamide treatment.21 The glycemic goal for treatment was a HbA1C level $\leq 1\%$ above the normal level, however, “normal level” was never defined. At the time of publication, the ADA standard for a normal HbA1C was $< 6.5\%$. Subjects included in the study had FPG levels from 7.0-12.0 mmol/L (126-216 mg/dL), and were excluded from the study if pharmacologically treated for more than six months. All subjects in the study were screened for T2DM during a 30 day period of dietary treatment before randomization to two groups. Beta-cell function was evaluated during treatment and after short-term withdrawal of treatment, and all measurements were made at baseline and yearly during the study. Fasting c-peptide, insulin and proinsulin levels were measured during treatment. Measurements of insulin, proinsulin and post-glucagon c-peptide levels were also measured after treatment was withdrawn, on two consecutive days, 48 hours before testing on the first day, and 72 hours before testing on the second day. After testing was completed, treatment was restarted. Fasting c-peptide levels were not significantly different
between the groups during the study, while post-glucagon c-peptide levels in the insulin group increased significantly from baseline at one year (p = 0.03) and from one to two years (p < 0.01), and remained unchanged in the glibenclamide group. A significant difference in post-glucagon c-peptide levels between the insulin and the glibenclamide group was seen at one year (p = 0.02). Fasting insulin levels increased in the insulin group as compared to the glibenclamide group at one year (p = 0.10), and at two years (p = 0.02). After one year of treatment, HbA1C levels in both groups decreased significantly from baseline levels (p < 0.01). At year two, HbA1C levels of the insulin group remained significantly different from baseline (p < 0.005). Although the HbA1C level for the glibenclamide group increased at year two, it was significantly different from year one (p < 0.01).21

Alvarsson 2008 follows the 34 Swedish patients remaining in the Alvarsson 2003 study for two more years.22 Fasting c-peptide levels increased in the glibenclamide group and were significantly higher at 30 months than the insulin group levels, which decreased during the study (p = 0.003). Fasting insulin levels were unchanged in the glibenclamide group and increased in the insulin group, however, there was no significant difference between groups. Fasting proinsulin-to-insulin ratios decreased from baseline in both groups during treatment, but remained significantly higher in the glibenclamide group than the insulin group for the duration of the study (p = 0.04). Hemoglobin A1C levels for the insulin group decreased at one year and remained below 6.5% for the duration of the study, while the HbA1C levels for the glibenclamide group increased each year, and were significantly different from the insulin group at four years (p = 0.04).22
When treatment was withdrawn for testing, fasting insulin levels for all four years, proinsulin levels at four years and proinsulin-to-insulin ratios at four years, were all higher in the insulin group than the glibenclamide group (p = 0.006, p = 0.004 and p = 0.066, respectively). Post-glucagon c-peptide levels were significantly higher in the insulin group than the glibenclamide group at one year (p = 0.004), and at two years (p = 0.02). For a total of all four years, the effect was significant (p = 0.018), however, there was no difference between groups after three years. A total of 51 subjects began the study and 34 completed all four years. Patients lost to follow-up included 1 subject who died in surgery, 1 died of cancer, 9 left for personal reasons, 4 glibenclamide subjects required insulin treatment, and 2 subjects developed insulin antibodies and were excluded from the study. A summary of study results is listed in Table 2.

**Discussion**

The primary goal of this study was to identify evidence from current medical literature on the effect of insulin treatment on β-cell function in newly diagnosed T2DM patients, as compared to metformin and/or sulfonylurea treatment. Considerable differences existed between study groups. Criteria used for diagnosing T2DM in all of the studies were consistent with ADA standards, however Chandra used three separate screenings prior to diagnosing T2DM, while all other groups screened subjects once. Relevant studies were conducted in India, China and Sweden, all of which have wide variations in diet. Treatment consisted of intensive glycemic control in Weng, and conventional treatment in Chandra, Alvarsson 2003 and Alvarsson 2008. Chandra included comprehensive diabetes education reinforced
at each visit, while Weng began the study with a 3-7 day period of dietary changes, and encouraged subjects to maintain glycemic control with diet and exercise. Alvarsson 2003 and Alvarsson 2008 evaluated subjects for T2DM during a one month period of dietary treatment, but make no mention of treatment including diet or exercise, both of which are important factors in weight loss and glycemic control.

Studies by Chandra and Weng evaluated remission and β-cell function, while the study by Alvarsson 2003 and Alvarsson 2008 evaluated β-cell function and metabolic control. Remission was defined as euglycemia and normoglycemia by Chandra and Weng, and target glycemic goals of FPG < 110 mg/dL were set, which still falls within the pre-diabetes range, based on ADA standards. Alvarsson 2003 and Alvarsson 2008 treated subjects to obtain a HbA1C level ≤ 1% above normal, which was likely 6.5%. Population size was very small in Chandra, Alvarsson 2003 and Alvarsson 2008, with 60, 51, and 34 subjects, respectively. With 382 subjects, the population in Weng was relatively large, and may be a more accurate representation of the T2DM population. Chandra reported findings at 6 months for 100% of study participants, and at 12 months for over 50% of participants. Weng reported findings from 1 year of study, Alvarsson 2003 from 2 years, and Alvarsson 2008 from 4 years. The effect of treatment was seen in all studies.

Chandra measured post-prandial c-peptide levels at baseline and six months, and testing was performed after subjects withheld treatment for 24 hours. C-peptide levels increased significantly in the insulin group, while little variance was seen in the gliclazide group. Elevated c-peptide levels indicate increased insulin secretion, but no other testing was done in this study to evaluate insulin action or resistance, which
is a limitation of this study. Hemoglobin A1C levels decreased from 10.4 to 6.2% in both groups, which meets the criteria for glycemic control established by the ADA. At 6 months, 80% of insulin subjects and 3.3% of gliclazide subjects were in remission, and at 12 months, 62.5% of the insulin subjects and 5% of the gliclazide subjects were in remission. These findings suggest that β-cell function improves with insulin treatment, indicated by increased insulin secretion, metabolic control and induced remission in most subjects. They also suggest that T2DM remission may be short-term, with fewer subjects remaining in remission at 12 months. This decrease in remission may relative, and due in part to the large number of patients lost after 6 months of treatment. Unchanged c-peptide levels in the gliclazide group suggest that, although metabolic control is maintained, insulin secretion and β-cell function are unaffected by this treatment.

The Chandra study was unique in that it included comprehensive diabetes education, which may be a contributing factor to the dramatically improved HbA1C levels in both groups and to the high remission rates in the insulin group. It does not, however, explain the lower remission rate seen in the gliclazide group, which received the same education. Because insulin works by a different mechanism of action than gliclazide, pharmacological differences may account for variance in remission rate. Another unique difference in this study is that the subjects chose their treatment, which may have contributed to increased compliance with the study requirements.

Weng thoroughly evaluated β-cell function by measuring HOMA B, HOMA IR, acute insulin response to glucose, and PI/IRI ratios, before and after 2-5 weeks of
intensive treatment with CSII, MDI or OHAs. HOMA B and acute insulin response increased in all groups, indicating increased insulin secretion, while HOMA IR and PI/IRI ratios decreased, indicating decreased insulin resistance and increased insulin secretory capacity. Acute insulin response levels remained elevated in the CSII and MDI groups after 1 year, and decreased significantly in the OHA group, which suggests that long-term improvement of β-cell function may be obtained with insulin treatment. HbA1C levels decreased in all groups from baseline, however, levels after 2-5 weeks of treatment ranged from 7.9-8.0%, which exceeded the ADA standard for glycemic control of ≤ 7%. At one year, 51.1% of the CSII group, 44.9% of the MDI group and 26.7% of the OHA group remained in remission, which is considerably lower than the remission rates for insulin treatment seen in Chandra. Duration of treatment in these two groups varied considerably. After meeting glycemic targets, subjects in the Weng study were treated for an average of 2-5 weeks, while in Chandra, insulin subjects were treated an average of 3 months. These findings suggest that intensive insulin treatment for greater than 5 weeks may increase remission rates and decrease HbA1C levels. One unique part of this study was the use of insulin pumps by the CSII group. An insulin pump closely mimics pancreatic function with a sustained infusion of basal insulin into the body 24 hours a day. Although the greatest improvement of β-cell function was seen in CSII group, the use of an insulin pump for short-term insulin therapy is neither cost-effective or practical. Alvarsson 2003 evaluated the effect of insulin or glibenclamide treatment on β-cell function and metabolic control by measuring fasting insulin, proinsulin, and
c-peptide levels, and post-glucagon c-peptide levels. Although this study included subjects who had received some pharmacological treatment, all subjects had FPG levels of 126-216 mg/dL while on dietary treatment alone. This pre-treatment of subjects in Alvarsson may account for the lower baseline HbA1C levels from 6.8-7.3%, as compared to Chandra, with HbA1C levels of 10.4%, and Weng, with HbA1C levels from 9.5-9.8%. At one year, HbA1C levels had decreased in both groups, and at two years, HbA1C levels increased in the glibenclamide group and remained decreased in the insulin group, suggesting better long-term metabolic control with insulin treatment. During the first two years of the study, post-glucagon c-peptide levels and fasting insulin levels increased in the insulin group, with significant differences from the glibenclamide group. These findings are consistent with Chandra and Weng, and suggest that increased insulin secretion improves with insulin treatment, which relates to improved β-cell function.

In Alvarsson 2008, fasting c-peptide levels and proinsulin-to-insulin ratios were consistently higher in the glibenclamide group than the insulin group, and fasting insulin levels began to decrease in the glibenclamide group suggesting a deterioration of β-cell function. During the short-term withdrawal of treatment, post-glucagon c-peptide levels decreased in both groups, with a greater decline seen in the glibenclamide group. At four years, proinsulin and proinsulin-to-insulin levels increased in the insulin group, HbA1C levels remained below 6.5% in the insulin group, and were approximately 7.0% in the glibenclamide group. As in Chandra, where remission rates were high early in the study and declined with time, Alvarsson
2008 further illustrates the gradual decline of function over time, with the greatest decline seen in OHA treated subjects, even while maintaining metabolic control.

The primary limitation to this study was the small number of studies pertaining to the subject matter. Because T2DM requires combination therapy as the disease progresses, it is difficult to find studies relying on monotherapy. Variability between studies was also a limitation, Chandra and Alvarsson evaluated insulin treatment vs. a sulfonylurea, and Weng evaluated two types of insulin treatment vs. metformin, a sulfonylurea, and metformin combined with a sulfonylurea. Doses between groups, glycemic targets, duration of treatment, inclusion criteria of study subjects and evaluation of β-cell function varied as well. Additional study is needed to fully evaluate the effect of insulin treatment on β-cell function in T2DM patients.

Recommendations

There is no cure for T2DM, and although the initial treatment for this progressive disease does not currently include insulin, a short course of treatment may provide the long-term benefits of improved β-cell function, and may induce remission in some patients. When the conventional step-wise approach to treatment is followed, it may be 10-15 years before insulin is used in a T2DM patient. Using insulin sooner will improve metabolic control and reduce the complications of nephropathy, neuropathy and retinopathy that occur with poor glycemic control. Insulin treatment is individualized, varied and based on the needs of the patient. Starting a patient on insulin involves time and training, which places a heavy burden on the provider and is often a barrier to beginning treatment. There is also the added risk of hypoglycemic events with insulin use, which rarely occur with OHAs.
Making the transition from insulin to OHAs is less difficult, as oral medication may be taken while tapering off insulin. Regardless of the treatment involved, T2DM is a disease which requires self-management by the patient. An integral part of treatment for all newly diagnosed patients should include comprehensive education regarding lifestyle change, diet, exercise and weight loss. Results from the Chandra study support this recommendation and suggest that education with reinforcement may correlate with better glycemic control.\textsuperscript{20}

**Conclusion**

Based on this literature review, it can be concluded that optimal improvement in $\beta$-cell function of T2DM patients is seen when early, intensive, short-term treatment with insulin is combined with comprehensive diabetes education regarding lifestyle changes, nutrition and blood-glucose monitoring. Increase in $\beta$-cell function will improve metabolic control, increase insulin secretion, increase acute insulin response and decrease PI/IRI ratios. Due to the progressive nature of T2DM however, this improvement in $\beta$-cell function will deteriorate gradually with time. Additional topics for future study may include the impact of diabetes education on maintaining glycemic control, and the treatment of existing T2DM subjects with intensive insulin therapy to evaluate $\beta$-cell function, or to evaluate whether insulin treatment will resensitize subjects to lower doses of OHAs.
<table>
<thead>
<tr>
<th>Author/Year Published</th>
<th>Study Type</th>
<th>Study Time</th>
<th>Pop Size</th>
<th>Patient Ages</th>
<th>Treatments Studied</th>
<th>Type 2 Diabetes Diagnosis Criteria</th>
<th>Target Glycemic Goal</th>
<th>Beta-Cell Function Criteria</th>
<th>Time of Measurements</th>
<th>Remission Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chandra 2008</td>
<td>Non-Randomized</td>
<td>1 yr</td>
<td>60</td>
<td>44 yrs (+10)</td>
<td>Insulin injections Gliclazide</td>
<td>Mean FPG &gt; 200 mg/dL 3 screenings</td>
<td>FPG &lt; 110 mg/dL</td>
<td>C-peptide</td>
<td>Baseline 6 mos</td>
<td>Euglycemia At 1 month post-treatment</td>
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<tr>
<td>Weng 2008</td>
<td>Randomized Multi-center</td>
<td>1 yr</td>
<td>382</td>
<td>25-70 yrs</td>
<td>Insulin pump Insulin injections Metformin Gliclazide</td>
<td>FPG 7.0 – 16.7 mmol/L (126-300 mg/dL) 1 screening</td>
<td>FPG &lt; 6.1 mmol/L (110 mg/dL)</td>
<td>HOMA B HOMA IR Insulin response PI/IRI ratio</td>
<td>Baseline Normoglycemia 1 year</td>
<td>Normoglycemia At 1 yr post-treatment</td>
</tr>
<tr>
<td>Alvarsson 2003</td>
<td>Randomized Multi-center</td>
<td>2 yrs</td>
<td>51</td>
<td>35-70 yrs</td>
<td>Insulin injections Glibenclamide</td>
<td>FPG 7.0 – 12.0 mmol/L (126-216 mg/dL) 1 screening</td>
<td>HbA1C &lt; 1% Over normal</td>
<td>C-peptide Proinsulin Insulin</td>
<td>Baseline 1 year 2 years</td>
<td>Not assessed</td>
</tr>
<tr>
<td>Alvarsson 2008</td>
<td>Randomized Multi-center</td>
<td>4 yrs</td>
<td>34</td>
<td>35-70 yrs</td>
<td>Insulin injections Glibenclamide</td>
<td>FPG 7.0 – 12.0 mmol/L (126-216 mg/dL) 1 screening</td>
<td>HbA1C &lt; 1% Over normal</td>
<td>C-peptide Proinsulin Insulin PI/IRI ratio</td>
<td>Baseline Yearly</td>
<td>Not assessed</td>
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Table 1. Summary of study criteria for reviewed articles. FPG = Fasting plasma glucose, Pop = population.
<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Counseling</th>
<th>Time to Normal FPG</th>
<th>Percent Remission 6 mos</th>
<th>Percent Remission 12 mos</th>
<th>HbA1C Baseline</th>
<th>HbA1C Post-Tx*</th>
<th>C-peptide Baseline</th>
<th>C-peptide*</th>
<th>PI/IRI Ratio Baseline</th>
<th>PI/IRI* Ratio Post-Tx</th>
<th>AIR Baseline</th>
<th>AIR Post-Tx</th>
<th>AIR 12 mos</th>
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<tbody>
<tr>
<td>Chandra 2008</td>
<td>Education Diet</td>
<td>Insulin 2-6 wks</td>
<td>80%</td>
<td>62.5%</td>
<td>10.4%</td>
<td>6.2%</td>
<td>3.2 ng/L</td>
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<td></td>
<td>Exercise</td>
<td>Gliclazide 2-6 wks</td>
<td>3.3%</td>
<td>5%</td>
<td>10.4%</td>
<td>6.2%</td>
<td>3.4 ng/L</td>
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<td>Weng 2008</td>
<td>Diet</td>
<td>CSII 4.0 days</td>
<td>51.1%</td>
<td>9.8%</td>
<td>8.0%</td>
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<td>23.8%</td>
<td>12.1%</td>
<td>-62 pmol/L/min</td>
<td>889 pmol/L/min</td>
<td>809 pmol/L/min</td>
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<td></td>
<td>Exercise</td>
<td>MDI 5.6 days</td>
<td>44.9%</td>
<td>9.7%</td>
<td>8.0%</td>
<td>26.5%</td>
<td>16.8%</td>
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<td>7 pmol/L/min</td>
<td>793 pmol/L/min</td>
<td>729 pmol/L/min</td>
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<td>OHA 9.3 days</td>
<td>26.7%</td>
<td>9.5%</td>
<td>7.9%</td>
<td>28.4%</td>
<td>21.2%</td>
<td>-95 pmol/L/min</td>
<td>736 pmol/L/min</td>
<td>335 pmol/L/min</td>
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<tr>
<td>Alvarsson 2003</td>
<td>N/A</td>
<td>Insulin N/A</td>
<td>7.3%</td>
<td>~ 6.0%</td>
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<td>Glibenclamide N/A</td>
<td>6.8%</td>
<td>~ 6.4%</td>
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</tbody>
</table>

**Table 2. Summary of study results for reviewed articles.** Numerical data was not provided by Alvarsson 2003 or Alvarsson 2008. *Measurements: Chandra-6 months, Weng-2 days post-normoglycemia, Alvarsson 2003-2 yrs, Alvarsson 2008-4 yrs. AIR = Acute insulin response, PI/IRI = proinsulin-to-insulin ratio, Tx = treatment.
References


24. Davidson MB. No need for the needle (at first) [editorial]. *Diabetes Care.* 2008;31:2070-2071.