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Durability of Glycemic Control using U-500 Insulin

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Abstract

Previous short-term studies evaluating U-500 insulin have reported improvements in glycemic control but with significant weight gain. This study was performed to examine the glycemic durability of U-500 insulin in highly insulin resistant subjects, and to determine if weight gain was continuous with use. Patients using U-500 insulin provided consent for chart reviews for up to 3 years prior to and 3 years after use of U-500 insulin. Charts were reviewed for physical and metabolic data from 53 subjects using U-500 insulin of which 20 used U-500 insulin for 3 years. Use of U-500 insulin led to an approximate 1% decrease in HbA1c within 3–6 months of use which was sustained for up to 3 years. Patients required increased insulin doses (by ~80%) over the first 6–12 months with a corresponding weight gain (~10 lbs) and a spike in hypoglycemia symptoms, but then insulin doses and body weight, as well as glycemic control and hypoglycemic symptoms, stabilized over subsequent follow up. Use of U-500 insulin in a clinical diabetes practice leads to sustained improvements in glycemic control following a period of insulin titration and weight gain. Despite the weight gain, glycemic control was sustained for up to 3 years.

Keywords

insulin resistance; HbA1c; weight gain; hypoglycemia

Introduction

U-500 insulin is a 5-fold concentrated form of regular (U-100) insulin that is often used in individuals with extreme insulin resistance, commonly defined as insulin requirements > 200 units/day. Due to its concentration, 100 units of insulin can be administered in an injection volume of 0.2ml, as compared to 1.0 ml of U-100 insulin, thereby facilitating the administration of large amounts of insulin in smaller and/or fewer shots. In parallel with the obesity epidemic, there have been an increasing number of publications on U-500 insulin use in recent years (for review see [1]). Most studies are short term studies demonstrating efficacy of U-500 insulin in attaining glycemic control; however, several studies have reported weight gain [2–5]. We previously published a report on the outcomes in body

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Conflict of Interest

The authors declare that they have no conflict of interest.

weight, glycemic control, insulin doses, hypoglycemia, and patient satisfaction in 40 subjects using U-500 insulin for 3 months, 36 using it for 6 months and 24 using it for one year. Within 6 months of transitioning to U-500 insulin subjects had an average 1.4% decrease in HbA1c, but at the expense of increased insulin doses and a 10–12 pound weight gain [3]. This weight gain has the potential to exacerbate insulin resistance, and could set up a vicious cycle of increased weight leading to increased insulin resistance, leading to increased insulin requirements, leading to further increases in weight. The purpose of this study is to report outcomes after 2–3 years of U-500 insulin use.

Materials and Methods

The subjects and methods have been previously described [3]. Subjects attending diabetes clinics at the University of Kentucky or the Lexington, Kentucky Veterans Affairs Medical Center who had been using U-500 insulin for at least 3 months (initiated by their diabetes care provider) were invited to participate. All subjects provided informed consent as approved by the Institutional Review Board and Research and Development Committee of the University of Kentucky and the Lexington, Kentucky Veterans Affairs Medical Center. Participation involved collection of physical and metabolic data from the medical records of participating individuals for up to 3 years prior to U-500 insulin therapy initiation, and up to 3 years after starting U-500 insulin. There were no exclusion criteria, and no interventions. Data collected included age, body weight and height, blood pressure, total daily insulin dosage, fasting lipid panel, HbA1c, urine microalbumin levels, and review of medication lists. Hypoglycemic events were self reported at routine clinical follow up visits. The baseline visit, or time zero, was defined as the visit at which U-500 insulin was initiated.

Statistical analyses

Data are presented as mean $\pm$ SEM and were analyzed by one-way repeated measures ANOVA. P values < 0.05 were considered statistically significant.

Results

A total of 53 subjects provided consent to participate in this observational study. Of these 53, six died during the 3 year follow-up (all from pre-existing medical conditions), 7 discontinued use of U-500 insulin (1 due to prolonged illnesses requiring prolonged inpatient admission; 2 due to decreased insulin needs following development of end stage renal disease and initiation of hemodialysis; 1 following liver transplantation; 1 following significant weight loss after lap band surgery; 1 due to noncompliance with insulin use and physician follow-up visits and 1 due to patient preference) and 4 patients were lost to follow up. The data from each of these subjects is included until the point at which they died, discontinued insulin, or were lost to follow-up. Thus, the present report summarizes 53 patients using U-500 insulin for 6 months, 48 patients using U-500 insulin for 1 year, 35 patients using U-500 insulin for 2 years, and 20 patients using U-500 insulin for 3 years.

Table 1 summarizes the patient characteristics. The mean age at time of U-500 initiation was 57 years (range 35–72 years). The gender demographics reflect that 41 of the 53 patients were recruited from the Lexington KY Veterans Affairs diabetes clinic (40 male, 1 female); the other 12 patients were recruited from the University of Kentucky diabetes clinic (4 males, 8 females). Most subjects were at or near American Diabetes Association recommended targets for blood pressure and lipid levels, with an average of 2.3 blood pressure medications and 1.5 lipid lowering medications used per patient. There was no effect of U-500 insulin use on blood pressure, LDL-cholesterol, HDL-cholesterol or number of lipid lowering or blood pressure medications used during the 3 years of follow-up, although there was a trend for decreased triglyceride levels with U-500 insulin use. During

the observation period there was a trend for increased urine albumin excretion over time: 2 subjects developed end stage renal disease and initiated hemodialysis and 5 subjects progressed to macroalbuminuria (> 300 mg/g creatinine).

Thirty-six of the 53 subjects had documentation of cardiovascular disease at the time of initiation of U-500 insulin. Most of the subjects used metformin concurrently with U-500 insulin; however, this use was variable over time as metformin was discontinued if creatinine rose over time, and was held for various durations during inpatient admissions or radiological procedures.

We previously reported that within 3 months of transition to U-500 insulin, subjects had an average 1.4% drop in HbA1c with 30–40% achieving HbA1c $< 7.5\%$ [3]. We now report that this drop in HbA1c is sustained up to 3 years ($P<0.001$; Fig. 1A), with 53% (25 of 47 patients) achieving HbA1c $\leq 7.5\%$ at 1 year, and 37% (7 of 19) with HbA1c $\leq 7.5\%$ at 3 years. As we previously reported [3], this improvement in glycemic control was obtained by significant increases in total daily insulin dose ($P<0.001$); however, beyond the first year, the total daily insulin doses stabilized (Fig. 1B). At the time of initiation of U-500 insulin the average insulin dose was 1.9 ± 0.08 units/kg/day; at 6 months following transition to U-500 insulin this dose had increased to 2.6 ± 0.17 units/kg/day; by 1, 2 and 3 years after U-500 initiation this dose was stable at 2.9, 2.8 and 3.1 units/kg/day respectively. This increase in total daily insulin doses raises the concern of ongoing weight gain; however, weight gain and body mass index stabilized after 1 year of U-500 insulin use (both $P<0.001$, Figs. 1C, D).

Shortly after transition to U-500 insulin there was an increase in self-reported episodes of symptomatic hypoglycemia, as may be expected given the increase in insulin doses administered. However, despite maintenance of improved glycemic control (Fig. 1A), the frequency of self-reported hypoglycemia dropped to an average of 0.5 episodes/person/week (Fig. 2). Glucose values during symptomatic hypoglycemia were not always measured, thus this data reflects patient report of symptoms only. Patient satisfaction with U-500 insulin was previously reported and shown to be significantly improved after U-500 insulin initiation [3]; only one individual requested discontinuation of U-500 insulin (after 1 year of use), and this was not due to hypoglycemia. U-500 insulin was discontinued in 6 other individuals due to decreased insulin requirements related to significant weight loss ($n=1$) and major medical illnesses ($n=5$).

Discussion

We and others have previously reported that the use of U-500 insulin can lead to improvements in glycemic control but at the expense of increased weight gain [2–5]. This raises the concern that the use of U-500 insulin may initiate a vicious cycle whereby weight gain leads to increased insulin resistance requiring more insulin that contributes to more weight gain, or impairing glycemic control. To address this, we studied the physical and metabolic changes in a group of subjects using U-500 insulin for up to 3 years. With up to 3 years of follow-up the use of U-500 insulin lead to a sustained, approximate 1% reduction in HbA1c within 3–6 months of initiation that was maintained for up to 3 years. Although patients required significant increases in total daily insulin dose to achieve the improved glycemic control, this stabilized after 1 year of use. Furthermore, weight gain was limited to the time of insulin titration, and stabilized after the first year of use. Although there were relatively few women in the study, there was no evidence of gender differences in weight gain with use of U-500 insulin. This pattern of weight gain supports the concept that the population was insufficiently treated with insulin prior to initiation of U-500 insulin, and that the weight gain occurred as the subjects achieved adequate insulin doses, as shown by

improvement in HbA1c. Body weight then stabilized once a therapeutic insulin dose was achieved.

The frequency of hypoglycemia by patient report peaked early after initiation of U-500 insulin (3 months) then decreased despite ongoing insulin titration. Hypoglycemia was by patient report, without confirmed glucose levels. As many of these subjects had very poor glycemic control prior to initiation of U-500 insulin, it is likely that symptoms of hypoglycemia may have been reported even with blood sugars in the normal or elevated range. In support of this was the observation that patient report of hypoglycemia frequency dropped after 3 months despite ongoing insulin titration. However, it is important to note that the reported frequency of hypoglycemia symptoms was greater after U-500 initiation than it was prior to U-500 initiation. This is not unexpected given the improvement in glycemic control observed.

Several previous case series have reported on the clinical efficacy of U-500 insulin use in insulin resistant subjects. There is consistency amongst these reports in terms of the glycemic control efficacy with most studies reporting a decrease in HbA1c of at least 1% [2–12]. However, most of these papers report on fairly short term use of U-500, and as many of them also report weight gain over time [2–5, 8, 10], there is concern that the glycemic control may not be durable, or come at the cost of continued weight gain. We now report serial observations in a cohort of 48 individuals using U-500 insulin for 1 year, 35 using for 2 years, and 20 using for 3 years, and report that the weight gain is limited to the first 6–12 months, whereas glycemic control is maintained through 3 years of follow up. Importantly, these observations were made in a cohort of “real world” patients, attending routine diabetes clinics. As this was not a clinical trial, there was no additional effort beyond routine care in terms of patient education, compliance, or insulin titration. The majority of our subjects were from our Veterans Affairs medical center. A recent publication from the North Texas VA Health Care System similarly reports clinical efficacy using U-500 insulin. However, in this report the improvement in glycemic control occurred over a longer time period than in our study, which could account for their findings of no significant increases in total daily insulin dose or body weight [12]. The consistent findings of glycemic efficacy in these reports support the routine use of U-500 insulin in highly insulin resistant diabetic subjects.

A total of 6 of 53 subjects died during the 3 year follow-up period. All deaths were attributable to pre-existing medical conditions and no deaths were related to hypoglycemia. However, this mortality rate (11% over 3 years) highlights the significant co-morbidities of this group of highly insulin resistant subjects; 36 of the 53 subjects had known cardiovascular disease at the time of U-500 initiation. At the time of U-500 initiation the mean blood pressure was 135 ± 2 systolic / 73 ± 1 diastolic mmHg with an average of 2.2 ± 0.1 blood pressure medications, and the mean LDL and HDL cholesterol levels were 69 ± 5 and 32 ± 1 mg/dl respectively, with patients prescribed an average of 1.5 ± 0.1 lipid lowering medications. Thus, even though overall this cohort was at goals for blood pressure and lipids, they needed medications to achieve these goals, and still displayed a high mortality. Although there has been an impressive decline in both all cause and cardiovascular mortality in subjects with type 2 diabetes in recent decades [13], the mortality is still higher in subjects with type 2 diabetes than those without, despite best current clinical management. The total mortality reported in the recent glycemic control studies ACCORD and ADVANCE were 4–5% and 9% respectively [14, 15]. Although critical analyses of these glycemic intervention studies suggest that intensive glycemic control is less effective in decreasing mortality in subjects with longer durations of diabetes and pre-existing macrovascular disease compared to subjects with more recently diagnosed diabetes and/or absence of known macrovascular disease [16], further analyses clearly indicate associations with high HbA1c levels and cardiovascular complications [17]. Furthermore, the relationship between improved

glycemic control and reduced microvascular complications is robust. Thus, aiming for improved glycemic control even in high risk diabetic subjects is important.

In a total of 53 individuals only one subject discontinued U-500 for personal reasons. In a second subject U-500 insulin was discontinued because of patient noncompliance with medical follow-up. An additional 4 subjects discontinued U-500 insulin use, primarily due to decreased insulin requirements following development of major medical illnesses (1 underwent liver transplantation, 2 subjects initiated hemodialysis, and one subject had a > 6 month hospital admission for surgical complications following a digital amputation). Each of these individuals lost significant amounts of weight and was changed to U-100 insulin by their diabetes care provider. An additional subject discontinued U-500 insulin after surgically induced weight loss; as of 6 months post-laparoscopic band surgery this subject has completely discontinued insulin and maintains an HbA1c of <6%. The reduction in insulin requirements with weight loss in these subjects implies that excessive caloric intake and obesity is a major contributor to the extreme insulin resistance displayed by this group. Indeed, when a patient using U-500 insulin is admitted to our acute care facility (where caloric intake is often significantly less than outpatient ad lib intake) our routine is to decrease total daily dose by 50–75% and convert to U-100 insulin by basal plus bolus therapy. Many of our patients maintain good inpatient glycemic control on these vastly reduced insulin doses; however, following discharge home they often revert back to U-500 insulin. Sustainable strategies to limit caloric intake and achieve weight loss are likely necessary to reduce U-500 insulin usage.

In conclusion, these data demonstrate that use of U-500 insulin in highly insulin resistant subjects is effective. Although most subjects need insulin titration even after initiation of U-500 insulin, reductions in HbA1c can be attained, and weight gain is primarily limited to the insulin titration timeframe. As the insulin is titrated and glycemic control improves there is an increase in self-reported hypoglycemia symptoms; however, over the long term the frequency of hypoglycemic symptoms declines although improved glycemic control persists. The extreme insulin resistance observed in these patients is likely due to their obesity and excessive caloric intake; if lifestyle modification and/or medications such as metformin or GLP-1 analogs are not sufficient to reduce their insulin resistance, use of U-500 insulin can help with attainment of glycemic goals.

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Fig. 1.
Effects of U-500 insulin on HbA1c (panel A), total daily insulin dose (panel B), body weight (panel C) and body mass index (BMI, panel D). Time 0 is the visit at which U-500 insulin was initiated.

Hypoglycemic events (number/week)

Fig. 2.
Effects of U-500 insulin on hypoglycemia based on patient report of number of symptomatic episodes per week. Time 0 is the visit at which U-500 insulin was initiated.

Table

BP: blood pressure. Data shown is mean $\pm$ SEM. Baseline is the visit at which U-500 insulin was initiated.

Parameter	Baseline	6 months	1 year	2 years	3 years
N	53	53	48	35	20
Age (years)	57.2 $\pm$ 1.2				
Male/female	44/9	44/9	41/7	30/5	17/3
Systolic BP (mmHg)	135 $\pm$ 2.3	130 $\pm$ 2.2	130 $\pm$ 2.6	133 $\pm$ 2.3	138 $\pm$ 3.9
Diastolic BP (mmHg)	73 $\pm$ 1.2	72 $\pm$ 1.3	71 $\pm$ 1.8	73 $\pm$ 1.4	76 $\pm$ 2.5
Number of BP medications	2.2 $\pm$ 0.14	2.3 $\pm$ 0.15	2.0 $\pm$ 0.13	2.15 $\pm$ 0.16	2.3 $\pm$ 0.28
Total cholesterol (mg/dl)	175 $\pm$ 16	178 $\pm$ 10	163 $\pm$ 8	179 $\pm$ 13	168 $\pm$ 9
LDL-c (mg/dl)	69 $\pm$ 5	78 $\pm$ 6	77 $\pm$ 4	83 $\pm$ 5	78 $\pm$ 7
HDL-c (mg/dl)	32 $\pm$ 1	35 $\pm$ 2	35 $\pm$ 1	35 $\pm$ 1	35 $\pm$ 2
Triglycerides (mg/dl)	642 $\pm$ 232	474 $\pm$ 176	330 $\pm$ 119	462 $\pm$ 233	329 $\pm$ 79
Number of lipid lowering medications	1.5 $\pm$ 0.15	1.4 $\pm$ 0.15	1.5 $\pm$ 0.14	1.5 $\pm$ 0.17	1.5 $\pm$ 0.25
Urine albumin excretion (mg/g creatinine)	32 $\pm$ 8	128 $\pm$ 74	145 $\pm$ 51	172 $\pm$ 75	38 $\pm$ 21