



ADVERSE SKELETAL EFFECTS OF BIPHOSPHONATES: A REVIEW

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Since the release of alendronate in 1995, bisphosphonates have become the most common treatment for osteoporosis.¹ By 2006, an estimated 190 million prescriptions have been written in the United States for oral alendronate, risedronate, and ibandronate and more than 6 million patients have been treated with IV bisphosphonates for cancer worldwide.² All bisphosphonates reduce osteoclastic bone resorption.

Bisphosphonates are approved for the treatment and/or prevention of osteoporosis, Paget's disease, hypercalcemia, heterotopic ossification, osteolytic metastases and multiple myeloma (Table 1). Based on side chain properties, bisphosphonates are categorized as either nitrogen containing or non-nitrogen containing (Table 2). Nitrogen-containing bisphosphonates inhibit bone resorption 100 to 10,000 times more than the non-nitrogen containing etidronate.³ The older, non-nitrogen containing bisphosphonates create poisonous analogs of ATP causing osteoclastic death.⁴ The newer nitrogen-containing bisphosphonates are presently the most extensively used in practice and work to inhibit farnesyl pyrophosphate synthase (FPPS), reducing osteoclast activity and promoting apoptosis.

MECHANISM OF ADVERSE SKELETAL EFFECTS

Physiologic strains on bone continually generate

fatigue microdamage which activates bone remodeling, an essential component of bone mechanics.⁵ Critical to bone remodeling and repair are the osteoclasts, which serve to break down damaged bone. By inhibiting the activity of osteoclasts, the process of bone remodeling is disrupted and microcracks are not removed.

Several studies in dogs demonstrated bisphosphonates are associated with microcracks and inhibition of bone remodeling. In 2001, Mashiba et al evaluated the effects of reduced bone turnover on microdamage accumulation and toughness of the trabeculae of the vertebrae and iliac crest in beagles for 1 year.⁶ The dogs received alendronate or risedronate at 6 times the expected clinical dose. After 12 months, microdamage was significantly increased at all sites measured. Although the bisphosphonates significantly increased strength of the L-1 vertebra measured by a compression test, analysis of vertebral mechanical properties normalized for bone mass and shape showed tissue toughness was 21% lower in both the risedronate and alendronate-treated groups as compared with control. The reduction in vertebral toughness reached significance when risedronate and alendronate groups were pooled in a post-hoc fashion. In 2005, a study in beagles by Allen et al demonstrated risedronate and alendronate at clinical doses can sup-

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Table 1 | FDA-approved indications for selected bisphosphonates.

	Postmenopausal Osteoporosis		Glucocorticoid-induced Osteoporosis		Paget's Disease	Hypercalcemia	Heterotopic Ossification	Osteolytic Metastases	Multiple Myeloma
	P	T	P	T	T	T	T	T	T
Alendronate	✓	✓		✓	✓				
Etidronate					✓	✓	✓		
Ibandronate	✓	✓							
Pamidronate					✓	✓		✓	
Risedronate	✓	✓	✓	✓	✓				
Tiludronate					✓				
Zoledronate	✓	✓	✓	✓	✓	✓		✓	✓

P = prevention; T = treatment.

press remodeling and increase microdamage after 1 year of treatment.⁷ These studies suggest bisphosphonates inhibit bone remodeling and increase microdamage, reducing the toughness and intrinsic material properties of some types of bone.

OSTEONECROSIS OF THE JAW

The American Society for Bone and Mineral Research defines osteonecrosis of the jaw (ONJ) as the presence of exposed bone in the maxillofacial region that does not heal within 8 weeks after identification by a health care professional.⁸ In contrast, the American Association of Oral and Maxillofacial Surgeons defines ONJ as the persistence of exposed bone in the oral cavity, despite adequate treatment for 8 weeks, without local evidence of malignancy and without prior radiotherapy to the affected region.⁹ ONJ typically presents as exposed white or yellow hard bone, with or without pain, usually following invasive dental procedures such as tooth extraction or in persons with poorly fitting dentures.

The first report associating bisphosphonates with ONJ appeared in 2003 in a case series of 36 patients treated with IV pamidronate and zoledronate for skeletal complications of malignancy at 10 times the doses used to treat osteoporosis.¹⁰ However, the case

series was not adequate to prove a causal association.

From 2004 to 2006, several case reports emerged linking lower-dose bisphosphonates to ONJ.^{11,12} Still, most patients in these reports had cancer, introducing the likelihood for confounding bias by other ONJ associated treatments.

In light of the *possible* association between bisphosphonates and ONJ, in September of 2004, “Dear Doctor” letters were sent out describing labeling changes to two medications including cautionary statements about ONJ development.¹³ In 2005, the FDA released a warning about ONJ for all bisphosphonates, including oral products.¹⁴

In 2009, a retrospective review performed in Denmark reviewed 53 patients with malignancy (median age 69 years) treated with bisphosphonates during a 5 year period. Two cases of ONJ were registered. In the first case, the patient developed ONJ spontaneously, while the second patient acquired symptoms after a dental procedure.¹⁵

Based on case reports and reviews, ONJ may be more common in cancer patients. The incidence of ONJ in cancer patients receiving high doses of IV bisphosphonates on frequent dosing schedules is estimated to be as high as 1 to 10 per 100 patients.¹⁶ High doses, IV administration, presence of malignancy and use of concomitant medications such as steroids and chemo-

Table 2 | Structural classification of bisphosphonates available in the U.S. and year of 1st FDA approval.

NON-NITROGEN CONTAINING			NITROGEN CONTAINING		
Generic	Brand	Approved	Generic	Brand	Approved
<i>Etidronate</i>	Didronel [®]	1977	<i>Alendronate</i>	Fosamax [®]	1995
<i>Tiludronate</i>	Skelid [®]	1997	<i>Ibandronate</i>	Boniva [®]	2003
			<i>Pamidronate</i>	Aredia [®]	1991
			<i>Risedronate</i>	Actonel [®]	1998
			<i>Zoledronate</i>	Reclast [®] ; Zometa [®]	2002

Table 3 | Summary of ADA/AAOMS guidelines for patients undergoing oral or maxillofacial surgery.¹⁹

Bisphosphonate Related ONJ Risk	Recommendations
<i>On oral bisphosphonate < 3 years + no clinical risk factors</i>	<ul style="list-style-type: none">• No alteration or delay in the planned oral or maxillofacial surgery is necessary• Monitoring patients for ONJ• Considering alternate dosing of the bisphosphonate, drug holidays, or an alternative to bisphosphonate therapy
<i>On oral bisphosphonate < 3 years + concomitant steroids, or > 3 years ± concomitant steroids</i>	<ul style="list-style-type: none">• Consider discontinuation of the oral bisphosphonate for at least 3 months prior to oral surgery• Bisphosphonate should not be restarted until osseous healing has occurred

therapy may increase the incidence of bisphosphonate associated-ONJ. Also, poor dental health and hygiene can contribute to development of ONJ.

In contrast to cancer patients, the relative incidence of ONJ in the treatment of osteoporosis patients is quite low; Rough estimates suggest incidence of 1 in 10,000 to 1 in 100,000 patient years.¹² After more than 60,000 patient years of exposure to nitrogen-containing bisphosphonates in clinical trials for the treatment for osteoporosis, including trials with follow-ups as long as 10 years, ONJ was not observed.¹⁷ A retrospective review of the HORIZON (Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly) trial evaluated 7,736 women with osteoporosis using IV zoledronate for 3 years and revealed only 2 reports of ONJ, one in the zoledronate group and one in the control group.¹⁸

To date, no prospective, randomized placebo-controlled trials evaluating a definitive causal relationship between bisphosphonates and ONJ have been performed, however it is likely ONJ is associated with bisphosphonate use. Several mechanisms for bisphosphonate-induced ONJ have been suggested. First, bisphosphonates may accumulate in the jawbones as the jaws are a site of continuous remodeling due to constant use. In addition, bisphosphonates may hinder skeletal repair processes to remove necrotic areas associated with trauma or infection of the jaw bone. Also, imbalance between osteoblasts and osteoclasts may cause osteopetrosis (“marble bone”), antiangiogenesis and inhibition of T cell function, all which may contribute to ONJ.¹⁷ Lastly, bisphosphonates may create bony overgrowths blocking the sublingual artery, leading to decreased circulation near the jaw bone.²

Bisphosphonate treatment guidelines developed by the American Dental Association (ADA) and the American Association of Oral and Maxillofacial Surgeons (AAOMS) may be helpful to clinicians making clinical decisions about discontinuing a bisphosphonate based upon patient risk stratification.¹⁹ A summary of their recommendations for patients preparing

to undergo oral or maxillofacial surgery is described below (**Table 3**). Health care providers should be cautious of these guidelines as not all recommendations are evidenced based and rely heavily on clinical experience.

The comprehensive review published by the American Society for Bone and Mineral Research Task Force may also be helpful to practitioners.¹⁶ The review stresses the importance of good dental hygiene for bisphosphonate treated patients and discourages invasive dental procedures, especially in cancer patients treated with high-dose IV bisphosphonates. No evidence states discontinuing injectable bisphosphonates before dental procedure will reduce the risk of ONJ.²⁰ Unfortunately, data is lacking to help clinicians determine the appropriate length of time a patient should be off the bisphosphonate prior to invasive dental procedure.

ATYPICAL LOW-IMPACT FEMUR FRACTURE

Although bisphosphonates have been proven to reduce fractures due to osteoporosis, a link between bisphosphonates and atypical low-impact femoral fracture has been suggested in several case reports.

The first report to suggest a link between atypical low-impact femoral fracture and bisphosphonates was published in 2005. Odvina et al. described 8 postmenopausal women and 1 man with unusual nontraumatic nonvertebral fractures while on alendronate therapy for 3-8 years.²¹ Following the publication of this report, a plethora of case reports emerged relating bisphosphonates to mid-shaft femur fractures.²²⁻²⁷ A prodrome of symptoms typically occur before the fracture including bilateral femur pain, cortical hypertrophy, transverse fracture pattern and medial cortical spiking.²⁸

Retrospective analyses have suggested an association between bisphosphonates and atypical femoral fracture. In 2007, a retrospective study performed in Singapore reviewed 13 women who presented with

low-energy subtrochanteric fractures, 9 of whom were on long-term alendronate therapy.²⁹ The majority of fractures sustained by the alendronate group were at the femoral metaphyseal-diaphyseal junction and occurred after minimal trauma. Six of the alendronate patients experienced prodromal lateral femoral cortex thickening, 3 of which were bilateral. Five patients reported prodromal pain starting 2 to 6 months before the femoral fracture whereas none of the non-alendronate patients reported prodromal symptoms. This retrospective review is limited by the non-definitive nature of retrospective analyses and because patients treated with alendronate were younger (mean age of 66.9 years) and more active than those not treated with alendronate (mean age 80.3 years). The same group from Singapore elaborated on its findings with a retrospective review of 17 postmenopausal women (including the 13 described earlier) presenting with subtrochanteric insufficiency fractures and taking oral bisphosphonates.³⁰ Seventy-six percent of the patients experienced prodromal pain in the affected thigh from 1 week to 2 years before the low-impact fracture.

In 2008, investigators from the Hospital for Special Surgery in New York City reported 37% of patients presenting with low-energy subtrochanteric or diaphyseal fracture were on bisphosphonates. The authors described 15 postmenopausal women receiving alendronate for a mean of 5.4 years presenting with atypical low-impact fractures. Ten of these patients had simple transverse or oblique fractures with cortical beaking and thickening of the proximal femoral shaft.³¹ The group continued to investigate the link between bisphosphonates and femur fracture in a retrospective review of 70 patients (59 female, 11 male) with low-impact femoral shaft fractures.³² Thirty-six percent of the patients were treated with alendronate, most of them for osteoporosis. Seventy-six percent of the alendronate users experienced specific transverse, one-sided beaking of the cortex. Only 1% of the non-alendronate users experienced this same pattern of cortical beaking. The odds ratio for this pattern was 139.33 for patients taking alendronate compared to non-alendronate users.

A 2008 Danish register-based cohort analysis demonstrated alendronate was significantly associated with increased risk of atypical subtrochanteric fractures (2.9/1,000 patient years vs 1.9/1,000 patient years in the control).³³ These results may be misleading because hip fractures were also significantly more common in the alendronate group, suggesting the alendronate users had weaker bones than the control group at baseline.

Also, a recent retrospective analysis using the re-

sults of three large randomized bisphosphonate trials, the Fracture Intervention Trial (FIT), the FIT Long-term Extension (FLEX) trial, and the HORIZON Pivotal Fracture Trial (HORIZON-PFT), evaluated 12 subtrochanteric and diaphyseal femur fractures in 10 patients, occurring at a rate of 2.3 per 10,000 patient-years. In each of the three trials, risk of these fractures for bisphosphonate users was not significantly increased compared to placebo. Although these trials were randomized, there were not a sufficient number of events to make definitive conclusions and confidence intervals were wide. Although all of the three trials excluded concomitant use of corticosteroids, other antiresorptive medications were allowed in the HORIZON-PFT trial. The FIT and HORIZON-PFT placebo-controlled trials studied patients using bisphosphonates only 3-4.5 years and could not address whether the risk of femoral fracture increases as treatment duration is extended. The FLEX trial evaluated patients using bisphosphonates for 10 years, however the trial was not placebo-controlled.

One hypothesis suggests the bisphosphonate-associated atypical femur fractures are insufficiency fractures which occur in osteoporotic bone subjected to normal levels of stress.³² Although the subtrochanteric region of the femur is one of the strongest parts of the femur, such fractures may result from inhibited stress fracture repair by bisphosphonates. The relationship between bisphosphonates and femur fractures are thought to be due to long term suppression of bone remodeling leading to increased skeletal fragility. Minimal trauma is then required to produce a completed fracture. Case reports also suggest risk factors may be associated with these low-impact fractures such as concomitant corticosteroid use.^{25,35}

Overall, it appears the risk of subtrochanteric or diaphyseal femur associated with bisphosphonate use is extremely low, even in women with osteoporosis who received bisphosphonates for up to 10 years. However, according to the National Osteoporosis Foundation (NOF) Clinical Update of 2008, a 5-year drug holiday after alendronate use (5-10mg/day) for 5 years does not increase fracture risk and might be advantageous.³⁶ Moreover, they conclude women at high risk of vertebral fractures may reasonably continue alendronate for 10 years. The 2010 NOF Clinician's Guide to Prevention and Treatment of Osteoporosis does not discuss the recommended duration of treatment for bisphosphonates.³⁷ However, they do imply bisphosphonates should be withheld from postmenopausal women with osteopenia and should be saved for those with osteoporosis. The North American Menopause Society (NAMS) believes current evidence does not support recommendations regarding the op-

timal duration of bisphosphonate therapy.³⁸ Further randomized prospective studies must be conducted before recommendations can be made describing the optimal duration of bisphosphonates.

SUMMARY

By inhibiting bone remodeling, bisphosphonates may prevent the repair of microcracks in bone, leading to adverse skeletal effects such as ONJ, low-impact femoral fracture and bone pain. Although no definitive data exists to suggest bisphosphonates are directly causative of ONJ, a relationship does appear likely, especially in cancer patients treated with high-dose IV bisphosphonates. However, the risk for ONJ in patients treated with lower-dose oral bisphosphonates for osteoporosis appears to be relatively low. Patients are encouraged to maintain good oral hygiene but to avoid invasive dental procedures, especially in those at high risk for ONJ. No evidence exists to suggest discontinuation of injectable bisphosphonates before dental procedure will reduce risk of ONJ, however it may be considered. The risk of subtrochanteric or diaphyseal femur associated with bisphosphonate use is extremely low, even in women with osteoporosis who received bisphosphonates for up to 10 years. Current evidence is lacking on the recommended duration of bisphosphonate therapy to avoid atypical low-impact femoral fractures. After 5 years of continuous bisphosphonate use, a 5 year drug-holiday may be advantageous in patients at low risk for vertebral fractures. However, the benefits of continuing alendronate for 10 years may outweigh the risks for patients at high risk for vertebral fracture.

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CONTINUOUS SUBCUTANEOUS INSULIN INFUSION VS. MULTIPLE DAILY INJECTIONS: A REVIEW

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Type I Diabetes Mellitus (T1DM) is an autoimmune disorder in which more than 90% of insulin producing islet cells are destroyed.¹ T1DM affects over one million Americans, accounting for 5-15% of all patients diagnosed with diabetes. Approximately 30,000 new diagnosed cases of T1DM occur each year.²

Lack of natural insulin production requires external insulin administration. Conventionally, insulin is delivered parenterally. Because of the invasive nature of administration, patients and their providers have attempted to keep the number of daily injections to a minimum. However, the landmark Diabetes Control and Complications Trial (DCCT), published in 1993, established that intensive insulin therapy (IIT), by means of multiple daily injections (MDI; three or more insulin injections/day) or continuous subcutaneous insulin infusion (CSII; insulin pump therapy), significantly decreased complications arising from uncontrolled blood glucose (BG) levels. Such complications include nephropathy, neuropathy, and retinopathy (risk decreased by 50%, 60%, and 76%, respectively.)^{3,4} Additionally, in the EDIC study, a follow-up to the

DCCT trial published in 2005, it was found that IIT also reduced the risk for cardiovascular disease by 42%, and the composite incidence of nonfatal heart attack, stroke, or death from cardiovascular causes by 57%.⁵ For many participants, especially those whose BG remains uncontrolled with fewer insulin injections, IIT has become the standard of diabetic care. Though many participants utilize MDI, an increasing number of participants and their providers are taking interest in CSII. The purpose of this review is to evaluate the advantages and disadvantages of CSII, and compare its efficacy to that of MDI with regards to management of A1c in participants with T1DM.

CSII INSULIN PUMPS: ADVANTAGES/DISADVANTAGES

Insulin pumps were introduced as unsightly, bulky instruments in the late 1970s, and have since evolved into light, compact machines that have greatly decreased the burden of carrying insulin administration supplies. An insulin pump attempts to mimic normal pancreatic activity by providing a basal rate of short-acting insulin (e.g. lispro, aspart) by means of continual infusions via a cannula through an infusion site, usually located in the abdominal area.^{1,6} Pumps allow for variable basal rates during different hours of the day (ex: 0.5U/hr: 12am-9am, 1U/hr: 9am-3pm, etc). Pumps also allow for manually controlled bolus doses when necessary, such as after a meal or snack.

The use of pumps is increasing among older children (mean age: 14) and adolescents. In an observational, population-based study in children less than 20 years of age, approximately 47% of 2,743 participants utilized CSII.⁷ Insulin pumps were more common in older children (mean age: 14), non-Hispanic whites [26.3%; compared to three MDI regimens (glargine + rapid; glargine + rapid + other; no glargine) and 1-2 injections per day without glargine], those of families with higher incomes (30.7%; \$75,000+/yr), higher parental education (29.5%;

Bachelors degree or higher), and those with private insurance (25.2%). These differences significantly distinguished pump users from those who used injection therapy. CSII can provide many advantages over MDI (**Table 1**).

A wide variety of features allows a patient to select a pump that is suitable to their needs (**Table 2**). All currently available pumps have a maximum basal rate and bolus limit.

Pump complications exist despite the multiple advantages of CSII. These complications are especially prevalent in patients who are not thoroughly instructed on proper pump management, or for those who disregard proper infusion site replacement procedures. A double-blind crossover randomized control trial (RCT) in twenty participants found that when the infusion site was not changed after the recommended 48 hours of use, participants lost control over insulin administration during days 3-5.¹⁰ Average total daily insulin dose increased from 48.5 Units (U) on Day 1 to 55.3 U on Day 5 in order to correct for rising BG levels. Statistically significant increases were still observed in average daily BG (122.7 mg/dL on Day 2 to 163.9 mg/dL on Day 5, P<0.05), fasting BG (120.3 mg/dL, 154.5 mg/dL, P<0.05), 2-hour post-prandial BG (114.6 mg/dL, 172.1 mg/dL, P<0.05), and daily max BG (207.7 mg/dL, 242.8 mg/dL, P<0.05). In addition to disrupting BG control, infection may occur when an infusion site is not changed regularly. Two case reports of Toxic Shock Syndrome due to *Staphylococcus aureus* originating at the infusion site have been reported.¹¹

In addition to complications associated with infusion site management pump failure can occur. In March 2010, the FDA's General Hospital and Personal Use Devices Panel met to review reports concerning 16,849 pump-related events, including 310 deaths, reported between October 2006 and September 2009.¹² Commonly listed problems included: an "error" message on the pump screen (5%), failure of dose delivery (3%), and need for repair (3%). Reported ef-

Table 1 | Advantages and disadvantages of CSII compared with conventional insulin administration.

Advantages	Disadvantages
<ul style="list-style-type: none"> • No injections • Easier management of DM (improved QOL) • More accurate dose delivery • Predictability of short-acting insulin • Fewer BG level swings • Improved A1c (addressed further in article) 	<ul style="list-style-type: none"> • Cost • Attached to pump 24hrs/day (bothersome) • Time commitment for initial training of pump use (full day in outpatient setting) • DKA if catheter mistakenly detached for hours • Possible weight gain • Possible pump failure/complications (i.e., cannula kinks, site infections, irritation and discomfort)^{9,10}

BG = blood glucose; DKA = diabetic ketoacidosis; DM = diabetes mellitus; QOL = quality of life.

Table 2 | Comparison of commercially-available insulin pump systems.

Pump Model (Manufacturer)	Weight (oz.) ^a	Basal Increment ^b	Total Basal Rates/Profile ^c	Bolus Increments/Max ^d	1U Bolus Duration ^e	Water Properties ^f
Medtronic Paradigm® 522/722 (Minimed)	3.5-3.8	0.05U	3 patterns, up to 48 rates each	0.1U/ 25U	40 s	3 ft for 30 m
OneTouch Ping® (Animas)	3.13	0.025U	12 each day for each of 4 basal programs	0.05U/ 25U	User selected	12 ft for 24 h
Accu-Chek Spirit® (Disetronic)	4.0	0.1U	5 profiles up to 24 rates each	0.1 to 2.0U/ 25U	5 s	8 ft for 60 m
Omnipod® (Insulet)	4.0	0.05U	7 programs up to 24 segments each (30 m increments)	0.05 to 0.5U/ 30U	40 s	8 ft for 30 m
Amigo® (Nipro)	3.4	0.005U	4 profiles up to 48 rates each	0.05U/ 30U	5 s	1 meter for 35 m
DANA Diabecare II/IIS/ IISG/R® (Sooil)	1.8-1.9	0.1U	1 profile up to 24 basal rates	0.1U/ 80U	12 s	watertight

Adapted from: http://www.diabeteshealth.com/media/pdfs/PRG2010/4-Insulin_Pumps_Chart-Diabetes_Health_2010.pdf

ft = feet; h = hours; m = minutes; sec = seconds, U = units.

^a weight based on full battery and cartridge.

^b increment at which basal doses may be adjusted.

^c number of profiles allowed on each unit, with number of insulin administration schedules programmable per profile.

^d increment at which bolus doses may be adjusted.

^e time required to deliver 1U of bolus insulin.

^f depth and time pump may be submerged in water and remain fully functional.

fects of such problems included hospitalization (21%), DKA (8%), and hyper- or hypoglycemia (8% and 5%, respectively.) However, most reports were neither complete nor thoroughly investigated, and 20% were filed as “problem unknown.”

The cost of the pump and its supplies is an important issue when considering CSII (Table 3). A pump and its accessories (dressings, tubing, syringes, and cartridges) costs approximately \$5,000- \$6,000 USD.¹³ Monthly supplies may cost \$500, depending on frequency of site change and brand name.¹⁴ Even with insurance coverage, out-of-pocket expense may be cost-prohibitive.

CLINICAL TRIALS: CSII vs MDI

Multiple clinical trials and meta-analyses have compared the two forms of IIT in participants with T1DM (Table 4). According to the 2010 Standards of Medical Care in Diabetes Guidelines, the American Diabetes Association (ADA) recommends a general goal A1c of <7% in non-pregnant adults.¹⁵ Because A1c reflects the estimated average glucose over the past three months, only those trials with a follow-up time of at least 12 wks were included (unless observational or select meta-analyses).

Youth-Centered Studies

T1DM is typically diagnosed during early adolescence into young adulthood, and many trials compar-

ing CSII and MDI efficacy have been conducted exclusively within this patient population.

DiMeglio, et al. conducted a randomized control trial of forty-two participants under the age of five, who had been diagnosed with T1DM for at least one year, and regularly took insulin injections.¹⁶ Participants were studied for six months with the primary endpoint of A1c (measured at baseline, 3 and 6 months), and multiple secondary endpoints, including severe hypoglycemic episodes, BG variability, BMI, meter-detected hypoglycemia, and patient satisfaction. Participants were randomly assigned to receive insulin by means of CSII (lispro via MiniMed 508®) or MDI (various insulin brands). Thirty-seven participants completed the study. After three months, CSII was significant when compared with MDI groups (8.4% vs. 8.8%, P<0.05). However, after six months, the two groups were comparable (CSII 8.5%, MDI 8.7%) and no statistically significant difference was found. Patient satisfaction with pump therapy resulted in 95% of families deciding to continue CSII after the study. The authors found no statistically significant differences among the secondary endpoints.

A randomized, prospective study by Nabhan, et al. found that though there was an initial significantly significant decrease in A1c between CSII and MDI, A1c was comparable by the study's end.¹⁸ Thirty-five T1DM participants less than five years of age were randomized to either CSII or MDI treatment for six months, followed by crossover to the other arm for six

Table 3 | Insulin pump and supply costs.

Pump Model (Manufacturer)	Cost of Pump ^a	Cost of 1 month supply infusion sets (10 sets) ^a	Cost to Upgrade from Older Model ^b	
Medtronic Paradigm® 522/722 (Minimed)	\$5,260	\$110-115	<u>Model</u>	<u>Cost</u>
			715/515	\$899
OneTouch Ping® (Animas)	\$4,200	\$110-134	722/522	\$799
			<u>Model</u>	<u>Cost</u>
			1220	\$599
			1250	\$399
Accu-Chek Spirit® (Disetronic)	\$4,600	\$94	2020	\$299
			<u>Time Current Pump</u>	<u>Cost</u>
			<u>Owned</u>	
			<7mos	Free
			7-12mos	\$299
Omnipod® (Insulet)	\$666	\$396	13-24mos	\$399
			25-36mos	\$599
			\$299.99 to switch from other pump to Omnipod	
Amigo® (Nipro)			Data Unavailable	
DANA Diabecare II/IIS/IISG/R® (Sooil)			Data Unavailable	

All costs in USD.

^a actual cost to patient can be less; prices based on <http://www.americandiabeteswholesale.com/StoreFront.bok>.

^b upgrade costs attained from manufacturer sites on May 18, 2010.

months. However, due to patient family anxiety in the initial CSII group of returning to MDI administration, they were allowed to continue CSII for the following six months. After six months of CSII therapy, regardless of time of initiation, a significant decrease in A1c was noted (P=0.002). However, overall, there was no significance between A1c when comparing MDI to CSII (P=0.518) or when comparing time and group (P=0.454).

Conversely, trials in older youth reflected a statistically significant difference in A1c levels when compared to baseline.¹⁷ Doyle, et al. conducted a randomized, prospective trial on thirty-two CSII-naïve T1DM participants, aged eight to twenty-one. The primary endpoint was A1c reduction and the secondary endpoint was total daily dose (TDD) of insulin. Participants were randomly assigned to receive insulin by means of CSII (aspart via MiniMed 508®/Paradigm 511®) or MDI (glargine + aspart) for sixteen weeks. While participants in the MDI group did not have a significant difference from baseline A1c (8.2% vs. 8.1%, P=0.89), those in the CSII group saw a decrease in their A1c from 8.1% to 7.2% (P<0.02). TDD was also significantly less with CSII than MDI (0.9U/kg vs. 1.2 U/kg, P=0.03).

In the SEARCH study, over 2700 participants under the age of twenty were studied.⁷ After adjustment for sociodemographic and clinical factors, CSII participants also had a significantly lower A1c. The mean A1c

of CSII participants was 8.0%, whereas participants using MDI achieved 8.5% (glargine/rapid insulin), 8.9% (glargine/rapid + other), 8.6% (MDI: no glargine) and 8.6% (two or less injections + no glargine) (P<0.0001). Additionally, CSII participants had a significantly fewer of ER visits (P<0.0001) and hospitalizations (P<0.0001).

Adult-Centered Studies

As with the youth-centered trials, conflicting evidence exists as to the efficacy of A1c control when comparing CSII to MDI in adults with T1DM.

Noninferiority of MDI vs. CSII was demonstrated in a randomized parallel multi-center study by Bolli, et al.¹⁹ Forty-three participants aged eighteen to seventy were randomized to CSII (lispro via MiniMed 508®) or MDI (glargine + lispro), and followed for twenty-four weeks. All participants were CSII-naïve and previously used an NPH-based MDI regimen. The primary outcome was A1c, and secondary outcomes included BG levels (pre- and postprandial, bedtime and 3am levels, and within day variability), frequency of hypoglycemic episodes, adverse events, costs, and patient satisfaction. A1c results were similar between CSII and MDI (-0.7% vs. -0.6%) and all secondary endpoints were comparable, with the exception of cost. Including the cost of the pump and site-change kits, lispro-based CSII was 3.9 times more costly than MDI (\$3722 vs. \$959; at a conversion of 1 Euro= 1.23 USD).

Table 4 | Summary of Clinical Trial Comparing Efficacy of CSII and MDI.

Study (year)	Design	Participant ages (n)	F/U	Results
<i>Youth-Centered Studies</i>				
DiMeglio, et al. ¹⁵ (2004)	RCT	<5 years (n=37)	6 mos	<ul style="list-style-type: none"> • CSII and MDI comparable • High patient satisfaction with CSII (95%)
Doyle, et al. ¹⁷ (2004)	RCT	8-21 years (n=32)	16 wks	<ul style="list-style-type: none"> • CSII decreased A1c more than MDI (P<0.02) • CSII requires less TDD than MDI (P=0.03)
Nabhan, et al. ¹⁸ (2009)	RCT	<5 years (n=25)	12 mos	<ul style="list-style-type: none"> • CSII and MDI comparable
Paris, et al. ⁷ (2009)	Multicenter observational population-based	<20 years (n=2743)	--	<ul style="list-style-type: none"> • CSII participants had a lower mean A1c than various MDI regimens or those receiving \leq 2 shots/day (P<0.0001) • CSII participants had less ER visits and hospitalizations (both P<0.0001)
<i>Adult-Centered Studies</i>				
Bolli, et al. ¹⁹ (2009)	Randomized Parallel Multicenter	18-70 years (n=43)	24 wks	<ul style="list-style-type: none"> • similar A1c reduction in CSII and MDI participants • costs ~4 times more with CSII therapy
Hanairr-Broutin, et al. ²⁰ (2000)	Open-Label Randomized crossover	21-65 years (n=40)	32 wks	<ul style="list-style-type: none"> • significantly lower A1c, mean BG, TDD of insulin, basal and bolus dose with CSII • 72.5% preference for CSII continuation post-study
<i>Non-Specified Meta-Analyses</i>				
Fatourechi, et al. ²¹ (2009)	Meta-Analysis (13 trials)	1+ years (n=669)	5-52 wks	<ul style="list-style-type: none"> • lower A1c, rates of severe/nocturnal hypoglycemia (unknown significance) in CSII-treated participants
Monami, et al. ²² (2009)	Meta-Analysis (11 trials)	Various (n=833)	12+ wks	<ul style="list-style-type: none"> • CSII (both aspart and lispro) significantly reduces A1c more than MDI in participants >10yoa
Pickup, et al. ¹ (2002)	Meta-Analysis (12 trials)	Various (n=600)-	2.5 – 24mos	<ul style="list-style-type: none"> • minimal beneficial reduction in A1c, TDD, mean BG concentration

BG = blood glucose; CSII = continuous subcutaneous insulin infusion; F/U= follow up; MDI = multiple daily injections; mos = months; RCT = randomized controlled trial; TDD = total daily dose; wks = weeks.

On the other hand, some studies demonstrate that CSII is superior to MDI. In an open-labeled, randomized crossover trial conducted by Hanairr-Broutin, et al., forty IIT-naïve T1DM participants were randomized to CSII (lispro via MiniMed 506/507® or HTron D/V®) or MDI (NPH + lispro).²⁰ Participants used one method of administration for four months, and then switched to the other for four months. A significant difference was found in the primary outcome and all but one secondary outcome (number of people with BG <60 mg/dL). At study end, A1c with CSII was less than MDI (7.89% vs. 8.24%, P<0.001). Statistically significant differences between CSII and MDI were found with BG (165 mg/dL vs. 175 mg/dL, P<0.05; respec-

tively), TDD (38.5% vs. 47.3%, P<0.0001), basal insulin dose (20.8 U/day vs. 27.5 U/day, P<0.03), and bolus insulin dose (17.7 U/day vs. 19.8 U/day, P<0.04). At the end of the study, twenty-nine participants preferred CSII (21 on CSII last 4 mos; 9 on MDI last 4 mos), while only eleven preferred MDI (1 on MDI last 4 mos; 10 on CSII last 4 mos).

Meta-Analyses

In 2002, a meta-analysis of twelve trials by Pickup, et al. was published comparing pump therapy to MDI.¹ The study analyzed twelve RCTs from 1975-2000, with each study lasting 2.5-24 months, and a combined six hundred T1DM participants were ac-

counted for. Primary outcomes were BG concentrations and A1c, with TDD as a secondary outcome. The standardized mean difference in BG levels between CSII and MDI was 0.56 (95% CI: 0.35-0.77; mean of 1mmol/L), A1c values differed by 0.44 (95% CI: 0.2-0.63) (mean 0.5% less with CSII), and between insulin TDD was 0.58 (95% CI: 0.34-0.83) (average 15% TDD reduction with pump therapy). Overall, pump therapy was minimally more beneficial than MDI therapy.

In the more recent 2009 meta-analysis by Fatourech, et al., similar outcomes were seen.²¹ This study focused on those eligible RCTs comparing CSII and MDI published after the Pickup, et al. meta-analysis (2002) until March 2008. Thirteen studies (total n=669) of T1DM participants were analyzed, each study lasting five to fifty-two weeks. Participants using CSII vs. MDI had a greater reduction in A1c by 0.2% (95% CI: 0.1-0.3), a finding of unknown clinical significance. A statistically nonsignificant advantage was found with CSII with respect to severe hypoglycemic episodes (OR 0.48, 95% CI: 0.23-1.0) and nocturnal hypoglycemia (OR 0.82, 95%CI: 0.33-2.03) in adolescents and adults. However, an increased risk of minor hypoglycemia in CSII-treated children enrolled in parallel studies was present.

In another 2009 meta-analysis, Monami, et al. analyzed eleven randomized control trials (crossover or parallel series design) (total n=800+) of T1DM participants comparing CSII and MDI efficacy.²² All trials were published before July 2008 and were at least 12 weeks in length. A1c was significantly lower in those participants with CSII than MDI. CSII reduced A1c by an average of 0.2% (with lispro, P=0.001) and 0.6% (with aspart, P=0.002) when compared with MDI. Consistent with the results of the youth-centered trials, there was a significant reduction in A1c(-0.3%, P<0.001) in those trials where the average age was greater than ten, but not in trials of younger children (-0.1%, P=0.48). Episodes of severe hypoglycemia were comparable across all age groups.

SUMMARY

Type I Diabetes Mellitus affects many people in America and the appropriate management of their disease is vital. Studies have shown that IIT provides better control of A1c than less intensive therapy. Compared with standard injection therapy, CSII has advantages and disadvantages which should be considered on a patient-by-patient basis. Several trials suggest that CSII does not provide significant long-term benefit in young children. However, several studies show benefit when compared to MDI and support its use in select adolescents and adults.

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