

Injection Technique (I.T.), Glycemic Variability, and Lipohypertrophy

Why I.T. All Matters

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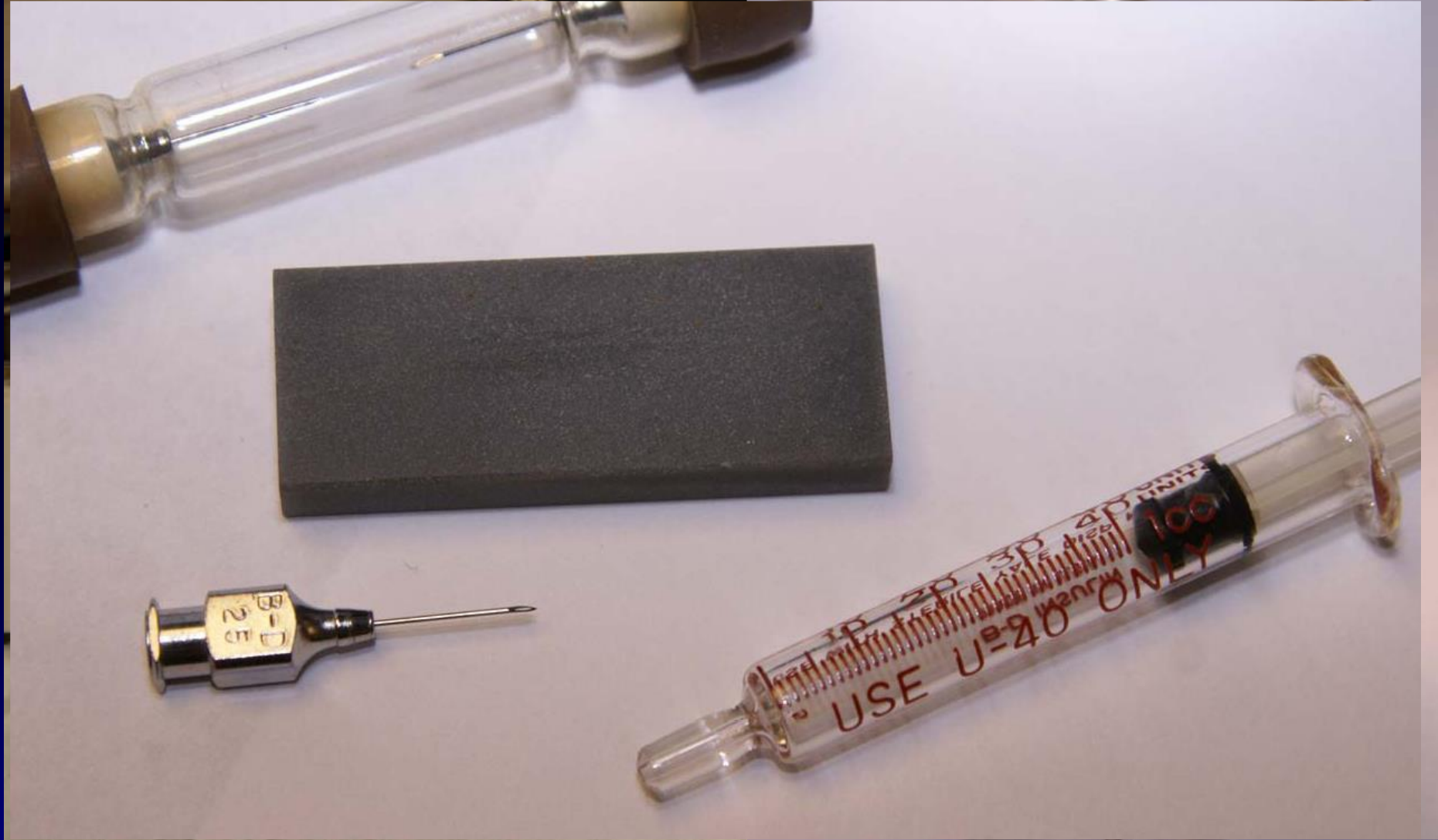
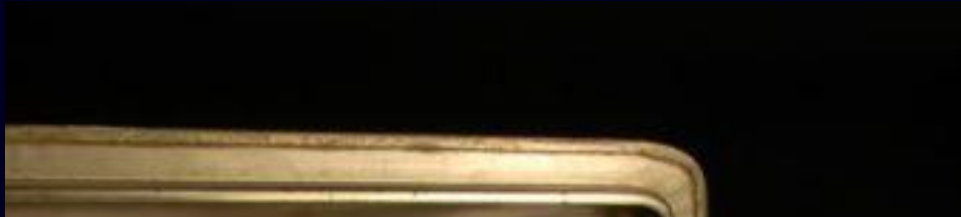
29 September 2017

Disclosures / Disclaimer

- Previously worked at Merck (MSD), 1988-2006
- Employed by BD since 2006
 - Own stock / stock options in each company
- Long interest in proper insulin injection therapy...
- ...Have lived with type 1 diabetes and taken insulin injections for nearly 60 years
- Co-Founder of the 2015 FITTER* conference

Outline

- A brief history of insulin injection therapy
- The type of insulin is important, and so is HOW you give it (Injection Technique)!
 - Many factors affect insulin uptake and action
 - Rationale for “smaller” needles
- Lipohypertrophy (enlargement of fat cells)
 - – Common complication of insulin therapy -
Has major effects on insulin uptake and efficacy
- Worldwide Injection Technique Survey & Recs
 - Injection practices in Korea, Vs WW



**Wollongong
2011**



Australia

**Queensland
2012**



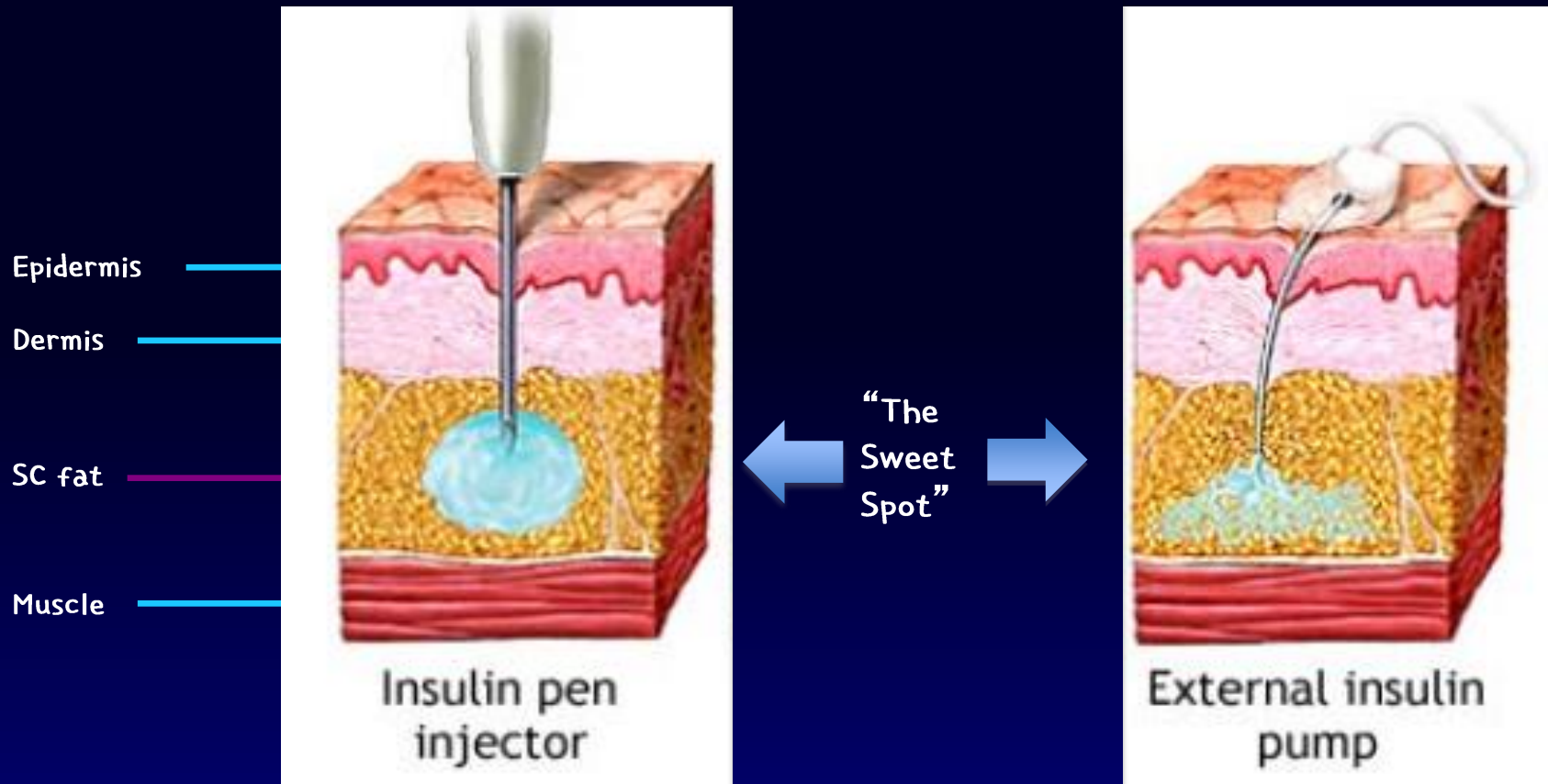


WHERE WE ARE TODAY

Insulin Uptake

- Many factors affect the uptake of insulin:
 - The type of insulin
 - Insulin dose volume, concentration
 - Body site – some insulins are absorbed faster depending where they are injected
 - If the injection site is warm or is exercised
 - Lipohypertrophy
 - Whether insulin is injected into skin, or the fat layer under skin, or muscle below the fat
- In short, WHAT is injected is important
- But, so is HOW the insulin is injected

Insulin Injection: Target Sites

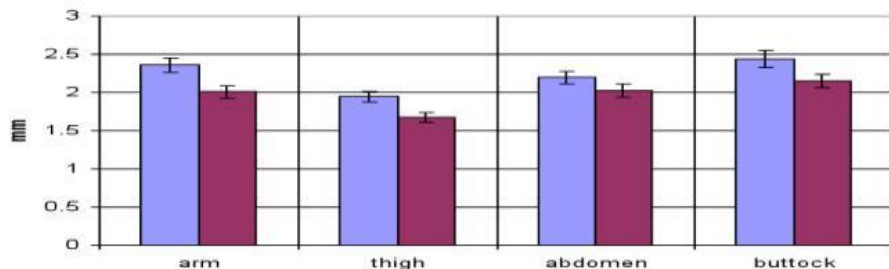


We want to deposit insulin into the SC fat tissue

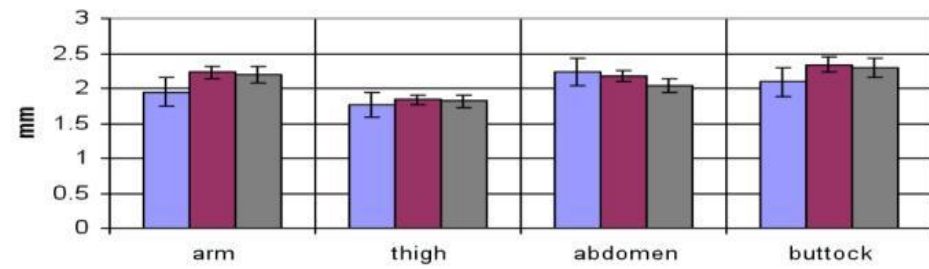
Skin Thickness in Adults

- Average ~ 2-2.5 mm (range ~ 1.25-3.25 mm), regardless of gender, age, ethnicity or BMI

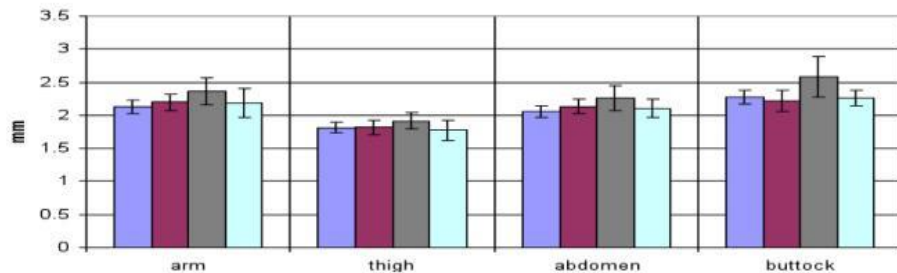
Gender



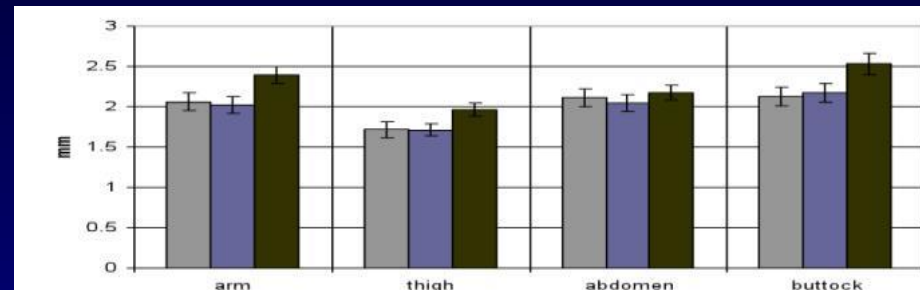
Age



Ethnicity



BMI



Recent Skin Thickness Studies

- Sim KH et al. *Diabetes Metab J* 2014;38:120-13
 - 156 **Korean** adults with diabetes, BMI $24.1 \pm 3.4 \text{ kg/m}^2$; Measured abdomen 10 sites, arm 8 sites
 - Abdomen: ST $2.3 \pm 0.4\text{mm}$; Upper arm: ST $2.0 \pm 0.3\text{mm}$
- Catambring I et al. *JAFES* 2014;29:24-32
 - 293 diabetic **Filipino** adults, BMI $25.8 \pm 4.3 \text{ kg/m}^2$
 - Abdomen $2.3 \pm 0.5\text{mm}$; Upper arm: $2.1 \pm 0.5\text{mm}$
- Wang W et al. *Diab & Metab* 2016;42(5):374-7
 - 509 diabetic **Chinese** adults, Peking. BMI $24.7 \pm 3.2 \text{ kg/m}^2$
 - Abdomen $2.5 \pm 0.4\text{mm}$; Upper arm: $1.9 \pm 0.4\text{mm}$

Implications of ST-SCT Studies

- Multiple studies confirm: “*Skin is Skin*”
- ST does *not* differ by clinically important amounts by age, gender, BMI, or ethnicity
- Needles as short as 4mm get through the skin, into the fat, and have lowest IM risk
- SCT (fat layer) is much more variable
- The data support the “*Shift to Short*” in needle length

- **Do “small” pen needles really work in all patients?**
- **What about obese patients?**
- **Don’t small needles leak more?**

Summary of Studies of Different Size Pen Needles

- ~ **8** studies – most prospective, RCTs with crossover design, including several in obese patients – that compare different length PNs, show smaller needles provide:
 - Equivalent BG control
 - No increase in leakage
 - Less pain and greater patient preference

FITTER* Meeting

- Convened in Rome Oct. 22-24, 2015
- ~ 180 invited KOLs (worldwide) attended
- ~ *15,000* virtual attendees registered online and viewed live stream webcasts
 - Review of ITQ Survey findings: ~ *13,300 respondents from 42 countries (180 in Korea)*
 - Intense debate and critique of draft New Recommendations (Injection, Infusion, Safety)
- Plans for rapid publication; dissemination of FITTER ITQ outcomes, Recs.

2014-2015 ITQ Patient Profile*

	WORLDWIDE		S. Korea N=180
	Responses	Mean	Mean
Age, years	13,225	51.9	50.8
Adult	9,531	90.5%	88.1%
BMI (kg/m ²)	12,806	26.6	23.8
Male	13,289	48.7%	49.4%
T2DM	8,254	65.2%	72.8%
Years on Insulin	8242	8.7	6.7
TDD Insulin, Units	7756	48.5	41.9
Use Pen / Syringe	12,829	85.6 / 9.6%	93.3 / 5.0%
HbA1c	7663	8.5 (2.1)%	9.1 (2.1)%

*Frid A et al. *Mayo Clin Proc.* 2016;91(9):1212-1223

Needle Length WW: How does S. Korea compare?*

Syringes:
5% Korea
10% WW.

Pens:
93% Korea
86% WW.

NEEDLE LENGTH	% 2014-15	% 2014-15 S. Korea†
12.7 mm	1.0	-
8 mm	16.0	31.1
6 mm	15.1	20.0
5 mm	28.6	14.4
4mm	20.9	16.7
Don't know	13.2	15.0

Message: Opportunity to increase use of shorter needles in Korea

FITTER ITQ, 2014-15

*Frid A et al. *Mayo Clin Proc.* 2016;91(9):1212-1223

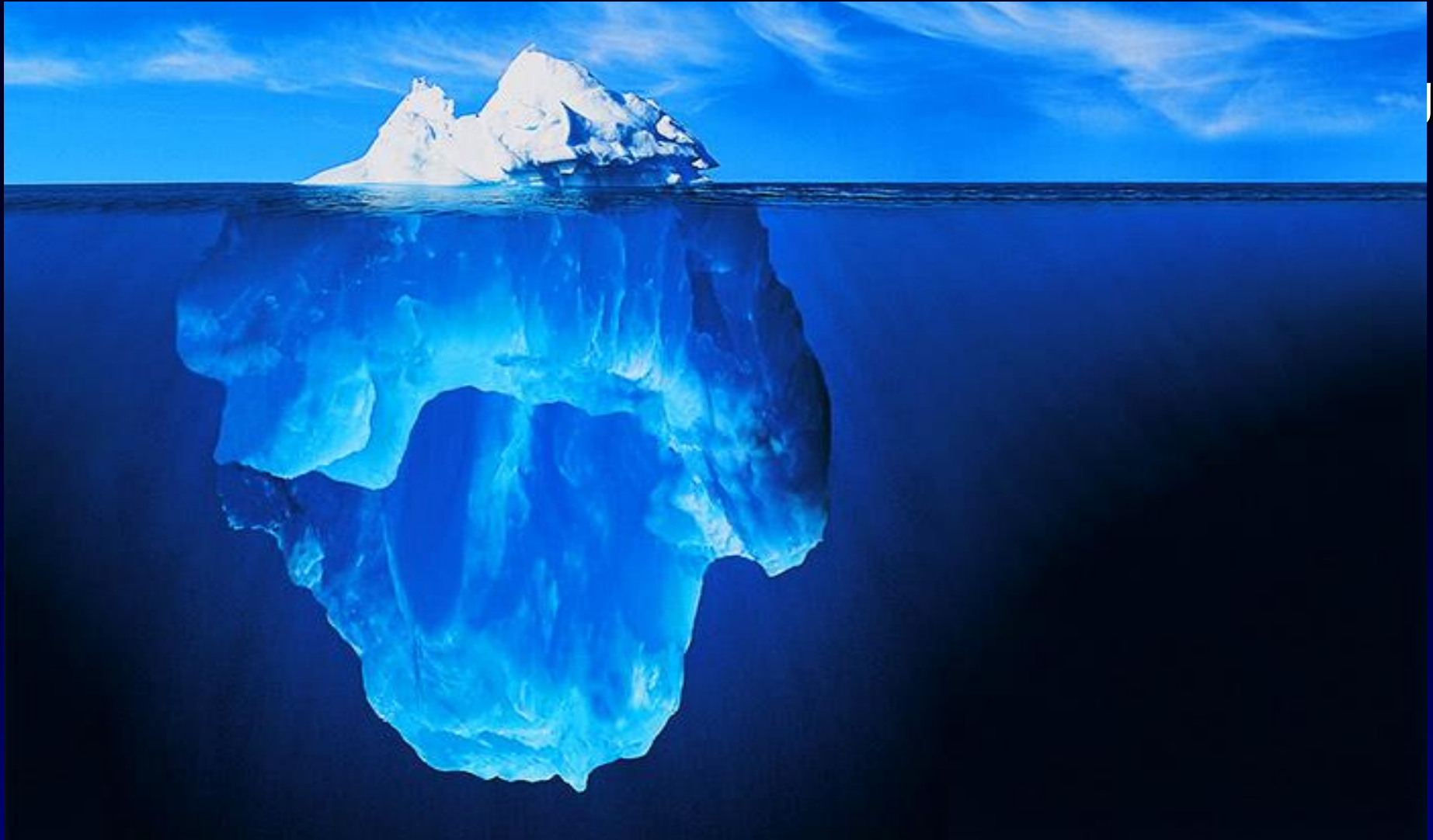
Lipohypertrophy



An overlooked bump in the road to
consistent insulin therapy

The different 'pinch' characteristics of normal versus
lipohypertrophic tissue.

Lipohypertrophy Is Common!



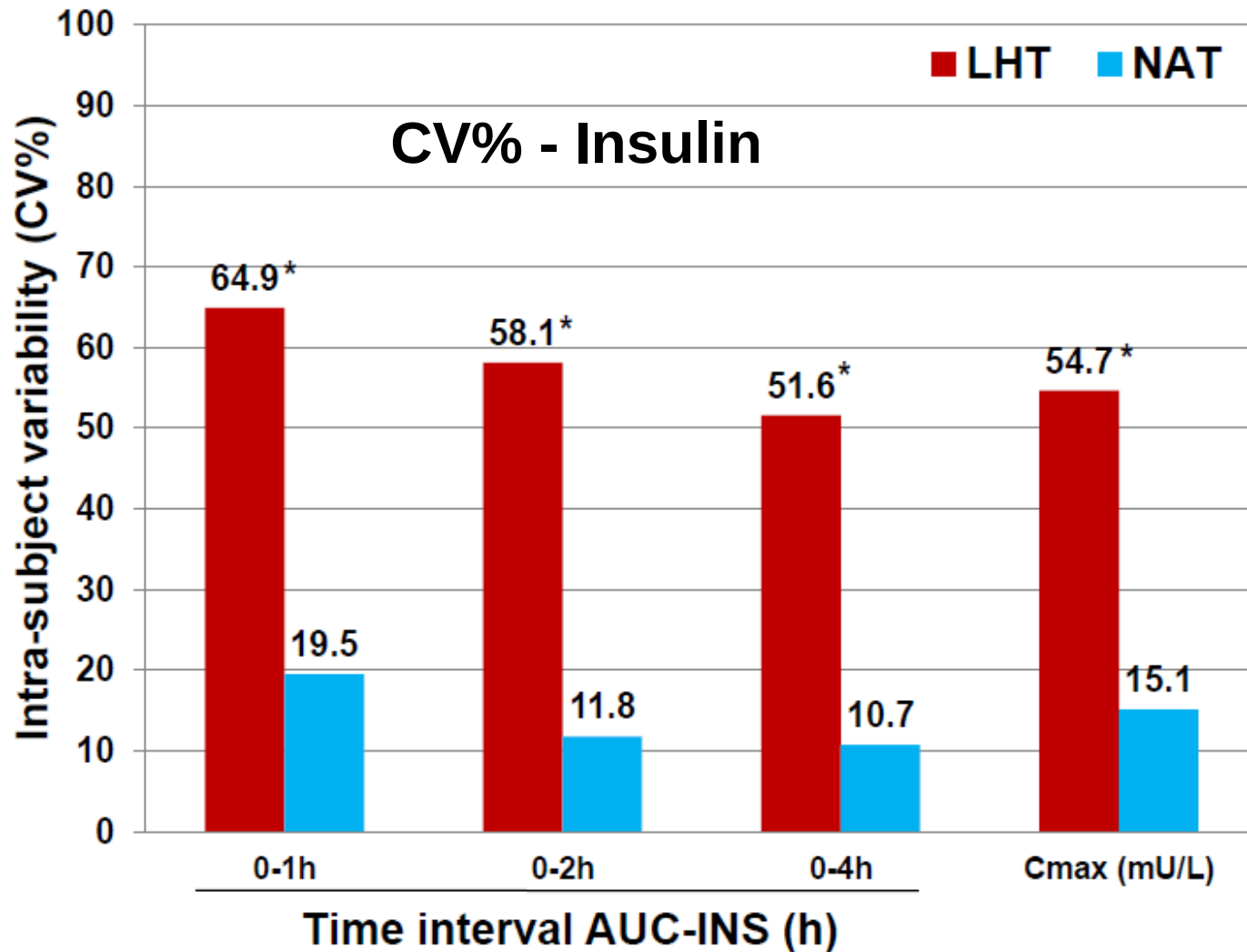
*Frid A et al. *Mayo Clin Proc.* 2016;91(9):1224-1230

How Lipos Affect Insulin Uptake & Action*

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September 2016



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Question

- What are the main risk factors associated with development of lipohypertrophy?
 1. Incorrect site rotation – by far the strongest
 2. Frequency (# of times) of needle reuse
 3. Duration of taking insulin
 4. Number of injections per day
 5. We can modify #s 1 and 2, but not 3 and 4

**Needle length, BMI, type of insulin
are *NOT* risk factors for LH**

ITQ Findings for Site Rotation: WW vs Korea

- 90% (WW) and 94% (Korea) of patients say they rotate their injection sites
- *How many do it correctly?*
 - (Moving injections at least 1 cm from previous injection in a pattern to avoid the same spot for > 2 weeks)
- Korea ~ 29%
- WW ~ 30%
- Message: Further I.T. education is needed

Pen Needle Reuse – WW & Korea

**In Korea,
40% reuse**

Reuse Needle?	WW%	Frequency	WW%	Korea %
		2 times	30.7	37.5
		3 to 5 times	39.7	40.3
Yes	55.8	6 to 10 times	16.0	9.7
		More than 10 times	13.6	12.5

WHY?

Reasons	WW%	Korea %
Because I did not have another pen needle available	9.2	2.8
To save money	23.3	27.8
To prevent excess waste (environmental concern)	6.8	---
For convenience	41.2	47.2

How often do patients say the nurse or doctor examine injection sites?

Frequency	WW	Korea
Routinely every visit.	28.3%	7.9%
Once a year	12.6%	5.6%
Only if I complain of a problem at a site	20.2%	9.6%
I can't remember my sites ever being checked	38.9%	77.0%

FITTER ITQ Survey

Message: HCPs may benefit from I.T. training

Important Relationships in FITTER ITQ

- Patients with LH, who inject into LHs...
- Patients using incorrect site rotation...
- Patients' injection sites not inspected...
- Lack of I.T. training by a nurse educator...
 - *All* have associations with:
 - Higher HbA1c (~ 0.5-0.6%)
 - Higher TDD insulin (~ 5 units)
 - More glycemic variability
 - More unexplained hypos; more hyperglycemia
- These suggest that proper I.T. is clinically important

China Observational LH Study*

- N = 401 adults in 4 cities; ~ 94% T2DM
- Main Results:
 - LH prevalence 53% by physical exam
 - Main risk factors: poor site rotation; needle reuse frequency (~13X in LH+ Vs 7.5X in LH-)
 - Daily insulin dose ~32% higher (~38 vs 27 units)
 - HbA1c increased significantly (~0.5%)
 - Conservative estimate of yearly *incremental* insulin costs associated w/ lipohypertrophy: ~ RMB 2 billion, or \$297 million

Can I.T. Training Change Clinical Measures in Patients with LH?

Torino, Italy Study*

- **346 patients, 18 clinics, northern Italy injecting insulin >4 yrs (median ~13 yrs)**
- **I.T. assessed; LH evaluated, then I.T. training provided**
 - **All patients taught to rotate injection sites, switched to 4mm PN to reduce IM risks, and asked to not reuse.**
- **Nearly 50% had LH. After 3 mos, both HbA1c (-0.58%) and TDD insulin (-2 IU) significantly lower; patients using better I.T.**
- **LH prevalence / lesion size not changed**

***Grassi G, et al. *J Clin Transl Endoc* 2014;1:145-150**

ESLA – UK Trial*

- 75 injecting patients randomly selected at 18 UK clinical centers; most had LH in abdomen, also thigh
- I.T. assessed; then I.T. training provided. In 3-6 mos:
- LH prevalence, lipo lesion size, HbA1c (-0.4%), and TDD insulin (-5.6 IU) *all* reduced, significantly
- Percent rotating injection sites properly ↑5X; percent using 4mm PN ↑ from 38 to 96%
- Percent injecting into lipos ↓ from ~90% to 20%; unexplained hypos and BG variability also reduced

I.T. Training Studies: Limitations

- **Both were uncontrolled, “pre-post” studies**
- **In Grassi study, 25% of patients lost to F/U**
- **Prof. Chen at Tianjin Metabolism Hospital has started a prospective RCT of I.T. training & use of BD 4mm pen needle, in patients with LH – sponsored by BD DC**

Lipohypertrophy Intervention Study in France (LHYRE)*

- **Randomized, prospective, controlled study:**
 - In patients with LH who inject into it, what is the impact (TDD insulin, HbA1c) when taught to inject into normal tissue, to rotate sites, and to use BD 4mm pen needle (and avoid reuse), for 6 mos?
- **Control patients:** informed they had lipos, the impact on insulin uptake, how to rotate sites properly, and to reduce dose when using normal injection sites
- **Intervention group:** more education, use of injection grids, videos, phone reminders, free BD 4mm PNs
- **Sample size ~190 to detect TDD 2.5 unit reduction, relative to control group, with 90% power**

Lipohypertrophy Intervention Study in France (LHYRE): Intervention Results

- Recruited 123, analyzed 109
- Significant ↓ in TDD insulin (8.5%, 5 units/day)
- Significant ↓ in HbA1c (~0.5%)
- Decreased unexplained hypoglycemia
- Decreased glucose variability
- Significant increase in proper site rotation
- BUT: similar, lesser changes in *control* group – so between-group differences NS

Lipohypertrophy Intervention Study in France (LHYRE): Interpretation

- **Study was underpowered: only 2/3 of planned N**
 - **Likely type 2 statistical error**
- **“Control” patients received meaningful education – required by Ethical Review Committee**
- **Insulin-injecting patients in France are fairly well-educated as part of their regular care**
- **Study centers also well-trained in I.T.**
- **Lipo intervention trials are difficult!**

Key FITTER Recommendations

- Short needles (4mm pen; 6mm syringe) are strongly recommended in all patients
- Needles that are more comfortable (5-bevel tip) and easier-to-dose (extra thin walls) are preferred
- Proper site rotation (moving injections > 1 cm from prior injection, and using multiple body sites) appears to prevent / reduce lipohypertrophy. This improves insulin absorption, AND reduces TDD of insulin used
- HCPs giving injections should NEVER recap the needle after use, should immediately place in a sharps container. They should use safety needles, including those that shield *both* ends



New Insulin Delivery Recommendations



Anders H. Frid, MD; Gillian Kreugel, DSN; Giorgio Grassi, MD; Serge Halimi, MD; Debbie Hicks, DSN; Laurence J. Hirsch, MD; Mike J. Smith, DSN; Regine Wellhoener, MD; Bruce W. Bode, MD; Irl B. Hirsch, MD; Sanjay Kalra, MD; Linong Ji, MD; and Kenneth W. Strauss, MD

Abstract

Many primary care professionals manage injection or infusion therapies in patients with diabetes. Few published guidelines have been available to help such professionals and their patients manage these therapies. Herein, we present new, practical, and comprehensive recommendations for diabetes injections and infusions. These recommendations were informed by a large international survey of current practice and were written and vetted by 183 diabetes experts from 54 countries at the Forum for Injection Technique and Therapy: Expert Recommendations (FITTER) workshop held in Rome, Italy, in 2015. Recommendations are organized around the themes of anatomy, physiology, pathology, psychology, and technology. Key among the recommendations are that the shortest needles (currently the 4-mm pen and 6-mm syringe needles) are safe, effective, and less painful and should be the first-line choice in all patient categories; intramuscular injections should be avoided, especially with long-acting insulins, because severe hypoglycemia may result; lipohypertrophy is a frequent complication of therapy that distorts insulin absorption, and, therefore, injections and infusions should not be given into these lesions and correct site rotation will help prevent them; effective long-term therapy with insulin is critically dependent on addressing psychological hurdles upstream, even before insulin has been started; inappropriate disposal of used sharps poses a risk of infection with blood-borne pathogens; and mitigation is possible with proper training, effective disposal strategies, and the use of safety devices. Adherence to these new recommendations should lead to more effective therapies, improved outcomes, and lower costs for patients with diabetes.

Questions?

