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REVIEW

The Role of Comfort and Discomfort in Insulin Therapy

Ronnie Aronson, M.D., FRCPC, FACE

Abstract

Despite the recognized importance of optimal insulin therapy, patient adherence to insulin therapy is an ongoing clinical care challenge. Insulin omission continues to be frequent and underestimated and has been correlated with poorer glycemic control and increased rates of diabetes-related complications. Insulin users consistently indentify multiple factors that contribute to insulin injection-related anxiety and to non-adherence. Injection-related discomfort continues to bear a significant contribution. Over the last decade, with advances in needle manufacturing technology, shorter and narrower needles have been associated with progressively improving patient self-rating of injection discomfort. Consequently, patient surveys of insulin users show discomfort to rank in the bottom third of significant contributors by prevalence. However, healthcare providers (HCP) and family member care providers continue to demonstrate a high level of anticipated and perceived pain for the patient. HCP anxiety and pain anticipation are each associated with patient anxiety and may therefore play a significant contributing role in patient non-adherence.

Introduction

Since the 1922 introduction of insulin, patient self-care challenges have played a prominent role, leading, for example, to the early switch from intramuscular to subcutaneous injection. Awareness of intensive glycemic control grew significantly following the mid-1990s publication of the Diabetes Control and Complication Trial[1] and the United Kingdom Prospective Diabetes Study.[2] Their impact on clinical care standards was nearly immediate, effectively eliminating the then-common practice of dosing in response to hyperglycemia symptoms. The subsequent growth of evidence-based practice guidelines, which found a natural home in the complex and dynamic world of diabetes, further advanced the new imperative of adherence to intensive glycemic control.

Despite this recognized priority, adherence to insulin therapy has remained a clinical care challenge and is closely linked to poor patient outcomes. The DARTS Medicines Monitoring Unit[3] found that glycosylated hemoglobin, diabetes complications, and diabetic ketoacidosis were related to omission of insulin. Twenty-five percent of this Tayside, Scotland, UK cohort were receiving less than two-thirds of their prescribed insulin. The Joslin Behavioural Research group found that 30.5% of their type 1 diabetes patients self-restricted their insulin and that after a decade of follow-up, these patients had threefold higher mortality and a doubling in prevalence of nephropathy and foot problems.[4] Fifty-seven percent of American insulin users reported omitting insulin that "they knew they should take."[5] Similarly, the DAWN survey[6] found that 20% of the respondents "often or sometimes" skipped their injections and 10% restricted their number of daily injections. Insulin omission is also common internationally, varying from 19.9% in France to 42% in the United States and 44% in Japan.[7] In a large managed care analysis of 27,000 type 2 diabetes patients newly started on insulin, prescription records identified that 4.5% did not fill their initial prescription, and 25.5% never refilled their first prescription.[8]

Anxiety plays a significant role in insulin therapy non-adherence. Although the DSM IV diagnosis of "blood-injection-injury phobia" is as rare in diabetes populations (5%) as in the general population (3%),[9,10] up to 94% of insulin-users did have *symptoms* of anxiety, distress, or phobias.[10] The DAWN survey,[6] for example, also found that 33% "dreaded" their injections and 22% had to mentally prepare themselves for injections. Most important is that, in insulin-users, the presence of these anxiety symptoms was strongly associated with less self-monitoring, fewer daily insulin injections,[11] poorer glycemic control,[9,12] and a significant increased risk of cardiac and peripheral vascular disease.[9]

In insulin-refusers, anxiety, or unbased fear, may be even more common, reported by 61% of poorly controlled patients in an Israeli managed care setting,[13] 29.5% of American patients "unwilling" to initiate insulin,[14] and 48% of the TRIAD cohort of insulin-refusers.[15] In newly diagnosed pediatric

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patients,[16] although 40% overall reported moderate-severe levels of fear, prevalence of fear reached 75% in children <9 years of age.

Anxiety similarly impacts compliance in other injection-using populations, such as blood donors,[17] pediatric venipuncture patients,[18] and young adult travelers requiring vaccination.[19] In multiple sclerosis patients, injection anxiety has also been found to be strongly associated with both nonadherence to disease-modifying therapies and with poorer outcomes.[20]

In surveys, patients have identified several contributors to injection anxiety, including poor healthcare provider (HCP) counseling[21] and their own limited health literacy,[15] lack of self-confidence in ability to manage the injection logistics,[8,22,23] and implication of disease severity.[14,22]

Injection discomfort is also consistently identified as a contributor to anxiety but with lower prevalence (from 8%[24] to 30%[15]). Improvement in injection comfort represents a particular area of recent technological advance. However, even as comfort in insulin therapy has progressively improved for patients, it continues to be a contributor to injection anxiety, possibly to a greater extent among HCPs than among patients themselves.

We undertook a structured review of injection anxiety and the contributing role of pain or discomfort. Primary sources investigating injection pain and anxiety, published between 2000 and 2011, were collected from the Medline, Embase, Proquest, CINAHL, and Cochrane databases. "Injection," "pain," "needle," "comfort," "anxiety," "insulin," and "phobia" were used as key words. The searches were limited to the English language and human subjects, with publication types and age groups unselected to include a range of results. The reference lists of relevant articles were further reviewed to identify other publications where the key words appeared in the title. Articles were gathered by manual searches in Ovid Medline. To mitigate potential publication bias and maximize the search, doctoral theses and references listed in reviews and/or primary sources were also reviewed.

The database and manual searches yielded 94 publications. A personal collection of 40 additional sources included additional primary sources, posters, presentations, and a graduate thesis. Articles meeting the following selection criteria were included: (1) the study included approaches to control for confounding and other types of potential bias; (2) the full text of the article included a full description of the study design and methods used to measure and assess patient-reported outcomes; (3) the publication was written in English or translated into English; and (4) study subjects were children, adolescents, and/or adults exposed to injection as a medical procedure.

Injection Pain

Patient awareness of injection discomfort has been studied extensively and is related to three key factors: needle length (and tissue level penetrated); needle diameter; and injection context. Injection context is defined by noise, view of the needle, and the apprehension of HCPs, both professional and family. Needles are typically manufactured by rolling a flat sheet of stainless steel or polymer into a tube, welding the seam, and then lengthening the resulting hollow tube over a mandrel core through an engineered dye. After cutting, the appropriate bevels, in the required angle, are then ground on one end, and a lubricating coating is applied to the chassis. Even as needle length and diameter are continually improved through advancing technology, a reproducible awareness of injection pain persists based on two environmental contributors: (1) the visual stimulus of the needle itself and (2) the level of pain anticipation among patients' HCPs.

Needle length

Modern insulin therapies are intended for introduction into the subcutaneous space. A needle needs to be long enough to successfully penetrate the dermis and short enough to avoid penetration of underlying sensitive muscle fascia, to avoid trauma and discomfort. Insulin absorption may also differ significantly between various sites.[25] The highly innervated muscle fascia layer may account for many of the infrequent injection-related pain sensations (4.2–6.6%), which are often described by patients as "I hit a nerve."[21]

Traditional 12.7 mm needles in children, despite appropriate skin-lift technique, have been found by sonography to result in an intramuscular location in 86% of injections.[26] More recently, a computed tomography and magnetic resonance series[27] examined pediatric skin–bone thicknesses in mid-Western American children to reduce overpenetration to bone of intramuscular vaccination needles. It is ironic that the 12.7 mm needle, long-used for subcutaneous injections, would not only overpenetrate skin but would also overpenetrate muscle and therefore injure the periosteum in 1.8% of deltoid injections. The comparable risk of overpenetration to bone may be even higher in children of developing countries.

Birkebaek et al.[28] have since showed that in prepubertal children, up to 84% of girls and up to 95% of boys had abdominal skin thickness of <8 mm. Measurements at the thigh were far more variable depending on the site assessed, and measurements at the buttocks showed a generally higher skin thickness. It is important that skin compression during injection reduced skin thickness by up to a further 35%. Needle lengths for subcutaneous injections should therefore not be longer than 8 mm and, arguably, not longer than 6 mm.

Shorter needle lengths have also been consistently shown to not negatively affect glycemic control. Ross et al.[29] first proved this point comparing 12.7 mm needles with 8 mm needles in 1999. Several subsequent investigations confirmed that with further decreasing needle lengths of 6 mm,[30,31] 5 mm,[32–35] and 4 mm,[36,37] glycemic control remains unaffected. Mean scores from pain rating scales have generally also found a significant reduction in anticipation of pain[38] and in injection pain with shorter needles,[32,33] especially when assessed at home in relation to the injection itself. However, when blinded to needle length, patients find no overall difference in pain.[31] Regardless, even if blinded users have not shown a difference in overall pain scoring, it remains possible that the discomfort of the occasional inadvertent intramuscular injection (the "I hit a nerve" sensation) may still be further reduced by shorter needles.

Needle diameter

In 1999, investigators at the Centre for Sensory-Motor Interaction in Denmark published a comprehensive controlled evaluation of the mechanics of invasive injury to human skin, using a needle insertion device that could be controlled for both speed and force of injection.[39] By varying needle diameters and including a measure of skin distensibility, they were able to determine workforce of an injection and then correlate each of these measures to healthy subjects' injection pain. They identified that higher-gauge (narrower-diameter) needles are associated with less penetration force and lower injection workload, resulting in fewer reports of injection pain. They were also able to confirm the long-held suspicion that bleeding is more likely to be associated with injection pain and, in an important finding, that finer-gauge needles cause less bleeding and therefore less pain related to bleeding.

Injection pain was correlated with injection workload and was proven higher for injections at 45° (vs. 90°) and was consistently higher for men. It is interesting that speed of insertion (2 mm/s vs. 19 mm/s) did not affect pain frequency but did affect pain quality: slower injections were more likely to cause dull pain, whereas faster injection speeds were more associated with sharp pain.

Patients experience varying degrees of injection pain in different anatomical injection areas, although the cause of this variability had not been well understood. Using the same device to administer controlled injections, along with sonographic measures of tissue density, the same investigators subsequently showed no difference in pain frequency between anatomical regions.[40] Penetration force declined from thigh to deltoid to abdomen, but because the thigh has lower skin distensibility, the overall workload for injection was found to be lower in the thigh than both the abdomen and deltoid area.

The most common type of pain described overall was sharp (67–76%) versus dull. Dull pain is due mainly to C-fiber nociceptor activity, whereas sharp pain is mainly due to A-delta fiber activity.[41] Because C-fibers are thought to respond to temporal summation of stimuli, slower injections, lasting nearly 10 times longer, would be more likely to activate C-fibers and initiate a dull pain sensation than a fast injection. Separately, pain associated with bleeding complications may be related to inflammatory mediators or may be directly related to stimulation of vascular nociceptors.

Injection pain is generally documented to diminish with the patient's injection experience, leveling off after 5 years of self-injection. It is interesting that, under these controlled injection conditions, investigators could not find any sensitization or habituation.

Nearly all subsequent studies, blinded and unblinded, have found similar reductions in injection pain with increasing needle gauge. A subsequent study again using the same Danish controlled injection device went on to compare five different needle gauges, from 27-gauge to 32-gauge, in blinded healthy volunteers[42] and confirmed the same pattern. Furthermore, for four of the needles, bleeding complications were also correlated with needle diameter, and bleeding events were associated with higher pain scores. More recently, a similar study examining response in 30-gauge versus 29-gauge versus 27-gauge syringe needles also showed that penetration force correlated with needle diameter.[43] Both patients and HCPs have reported less pain and greater preference for thinner needles in comparisons of 33-gauge tips versus 31-gauge needles (unblinded),[44] 29-gauge versus 27-gauge in blinded multiple sclerosis patients using prefilled syringes,[45] 29-gauge versus 27-gauge in blinded multiple sclerosis patients,[46] 32-gauge versus 30-gauge pen needles (unblinded),[47] 32-gauge versus 31-gauge pen needles,[38] and in comparison of 31-gauge needles, normal to thin wall.[48] Finally, Japanese patients found less pain and bruising using a 33-gauge needle in a crossover study with a 31-gauge comparator needle.[49]

One small study of 12 patients in Germany[50] was unable to document a difference between 27- and 28-gauge needles, although the study was underpowered.

In contrast, two well-designed studies were not able to confirm a relationship between comfort and needle gauge. In two sufficiently powered studies of 15-year-olds with a mean diabetes duration of 6 years, Hanas et al.[51] found that patients could not differentiate among three different gauges of needles (28-, 29-, and 30-gauge). Similarly, Schwartz et al.[31] found no difference in Visual Analogue Scale scores among 15-year diabetes veterans comparing 31-gauge and 29-gauge needles. However, both populations studied were very experienced injectors and received their blinded injections by a designated nurse or were asked to recall their prior home experience at the study visit, rather than more optimally recording the home experience in a real-time diary. Injections provided by a third party are often associated with lower overall pain ratings[52] and perhaps reduced the subjects' ability to differentiate between needle gauges. More important is that both studies reported on pain severity rather than the more commonly reported outcome of pain frequency.

Needle tips have also been compared in studies of comfort. Asakura et al.[44] compared two different tip gauges and found less pain with a 29-gauge microtapered needle that slimmed to a 33-gauge tip. In two French trials, covering 241 patients, less pain was found with a five-bevel tip[45] that happened to be on a narrower 29-gauge needle. The comparison by Mayer et al.[43] of piercing forces of three needle gauges also included comparisons of five-bevel and three-bevel tips, but found that gauge was the primary determinant of cutting and piercing force. In a trial to assess benefit to penetration force, individuals on a panel of blinded nurses administering injections were each able to differentiate between a three-bevel and five-bevel tip and rated the five-bevel as requiring 25% less penetration force.[53] Patients also found the five-bevel less painful, but the difference did not reach statistical significance. Very recently, Hirsch et al.[54] studied needles from several manufacturers in several gauges, ranging from 30-gauge to 32-gauge, to compare a new five-bevel needle tip to the standard three-bevel design. Penetration force during computer-controlled insertions using a human skin substitute was 23.7% less using a five-bevel tip versus matched needles with a three-bevel tip. In a series of paired, blinded injection comparisons, five-bevel tips were found to be non-inferior by insulin-taking patients. In continued home usage thereafter, when asked to evaluate needles with a new design, the patients significantly preferred the five-bevel tip on parameters such as ease of insertion, comfort, and preference. Finally, in a third round of comparison testing, during which subjects were then unblinded and oriented to the reduced penetration force benefits of the five-bevel needle, patients continued to significantly favor the five-bevel design in each of the same rating parameters.

Injection context

In fetal development, afferent sensory fibers emerge and eventually conduct sensory excitation (nociception) back to the dorsal root ganglia, contributing to a local reflex arc. With further development, sensory fibers ascend to the brain, and the same sensory excitation can be perceived as pain. For a given degree of nociception, the perception of pain is quite variable and determined by temperament,[55] perceptual sensitivity, and prior negative painful experiences.[56]

Perception of pain and the distress related to pain are each separate but related factors in consideration of comfort in painful procedures. In children undergoing dental injection, those with higher baseline anxiety experienced nearly double the intensity of pain.[57] It is significant that, although pain itself may diminish with exposure in pediatric populations, the associated emotional distress does not itself typically diminish with exposure.[58] Pain and distress can each be independently modified by various psychological maneuvers, including placebo anesthesia, distraction, and procedural counseling.[59] A Cochrane collaboration review[60] of psychological interventions for needle-related pain and distress found, for example, that distraction, hypnosis, and cognitive behavioral therapy were successful in reducing pain, distress, or both. However, the reviewers highlight the commonly seen discrepancy in level of distress perceived by independent observer versus by self-report (in children). Similarly, a pediatric venipuncture series comparing combinations of these interventions[61] found partial benefits of both placebo cream and topical anesthetic (EMLA; Astra Zeneca, London, UK) cream in self-report of pain, but limited (EMLA) or no (placebo) impact on the associated distress. Goodenough et al.[18] found that placebo with the suggestion of benefit led to lower independently observed distress behavior in children, even when the patients did not perceive a benefit to their level of pain.

In seeking to understand injection pain or distress, the dissociation between HCP observation versus patient self-report becomes very important. Advances in injection technology, such as pens, needles, and needle tip design, have led to reduced patient awareness of pain, even to the point of making it increasingly challenging to further differentiate new technologies. Patient ranking of discomfort as a barrier is no longer in the "top 5" in lists of objections.[13,15] In a large observational study of German teenagers, only 10.5% ranked pain as the most annoying aspect of their injections.[22] In a large United Kingdom survey of insulin-using adults, only 6.6% reported "sometimes" having pain with injection.[21]

Yet among HCPs—either professional or family members—the persistent perception of patient discomfort may actually present the greater barrier to effective injection therapy. Surveys of pediatricians and pediatric trainees in vaccination settings[62] and of pharmacists involved in diabetes self-care[63] show a very high perception of patient pain/distress, discordant with typical patient self-reports. Vaccination anxiety in the eyes of pediatricians ranged in score from 7.7 to 8.3 out of 10 and was lower in female HCPs and those with greater injection experience; pediatric self-reports of vaccination anxiety, by comparison, are typically in the score range of 2–3 out of 10 for intramuscular injection.[62] In a large survey,[63] Canadian pharmacists described a mean anticipated patient pain score of 4 out of 10, versus a patient actual mean of 1.3 out of 10. An anticipated fingertip lancing pain score of 3.6 out of 10 was reported by the pharmacists versus a patient self-report mean of 1.6 out of 10. Finally, in two large Internet surveys of pain in insulin injection,[64] one for patients and one for HCPs, significant differences in perception of patient pain were seen. Patients reported mean injection anxiety scores of 1.5 out of 10 versus a mean score of 2.8 provided by the HCPs. Pain itself was reported at 2.2 out of 10 for patients versus the highest score among primary care providers of 2.9. In a ranking of injection-related problems, HCPs rated injection anxiety as the most frequent problem, whereas patients themselves ranked it as lowest. Sixty-two percent of primary care providers described their patient as less than satisfied with their insulin injections, whereas only 27% of patients actually rated themselves as low. Very similarly, among primary care providers in a managed care setting in Israel,[13] reasons for non-initiation of insulin in their uncontrolled patients were as follows: patient fear of hypoglycemia, stated by 79.7% (vs. 12% of patients); inability to cope with the pain of self-monitoring, 53.9% (vs. 5.4% of patients); and inability to cope with the pain of injection, 48.4% (vs. 12% of patients). Other reports have shown an equally concerning lack of awareness of their patients' injection anxiety, by being able to accurately identify only 50% of those with the problem.[65]

Similar impact of HCP apprehension on patient discomfort or distress is seen when family members are the HCPs or healthcare supporters. Although parents are generally considered more accurate predictors of their children's pain,[66] among mothers of newly diagnosed children with diabetes,[16] 30.4% rated their child's injection pain as moderate-severe, versus the reports of only 22.7% of children. Of experienced mothers, 13.6% continued to report distress with injections versus 9.5% of their children. Most important is that the mother's perception of their child's pain was highly correlated with that child's glycosylated hemoglobin level at 1 year. Mothers' potential influence on a child's pain and distress has been documented in other populations as well, including children receiving venipuncture[67] and in infants receiving vaccinations.[68]

Conclusions

Despite decades of experience and a prominent awareness of the importance of effective insulin therapy for optimal long-term diabetes health, insulin therapy adherence has been less than ideal. The most common patient challenge is injection anxiety, with additional barriers in self-confidence and the impracticality of the lifestyle of those with diabetes.

Comfort in insulin therapy has contributed significantly to injection anxiety. Injection comfort, however, has greatly improved over the past decade because of advances in needle design and manufacture and of further insights into effective insulin delivery. Needle length has reduced from a traditional length of 12.7 mm to the current standard of 4 mm, with unchanged efficacy, less unwanted tissue trauma, and greater confidence of accurate drug delivery to the subcutaneous space. Needle diameter has improved from 28-gauge to 32- and 33-gauge, with thinner walls permitting unimpaired insulin flow. Needle tips have improved in design with increasing bevel cuts, accomplished with reduced penetration force, without loss of stability. All three achievements have led to consistent gains in patient comfort.

The contextual factors in insulin injection—higher HCP perception of patient distress or pain in contrast with patient self-reporting—now represent the greatest potential area of further improvement. HCPs and family members harbor an exaggerated, anachronistic view of discomfort as a continuing barrier to injection. Further education and insight into the current positive patient experience may help HCPs and family caregivers provide a more supportive context for insulin injection and allow further focus on the remaining barriers to effective insulin therapy.

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Address correspondence to:
Ronnie Aronson, M.D., FRCPC, FACE
LMC Diabetes & Endocrinology
Suite 106
1929 Bayview Avenue
Toronto, ON, Canada M4G 3E8

E-mail: ronnie.aronson@lmc.ca