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The Impact of Obesity on Pain Perception During and After Subcutaneous Injections: A Cross-Sectional Analysis

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Abstract: (1) Background: The administration of subcutaneous (SC) injectables is among the most frequent procedures a nurse performs in daily practice. The needle for the injection must pass through the skin barrier to reach the SC space, where the drug will be deposited. This procedure can cause pain to the patient and local lesions. Local fat measurement can be performed by measuring the skin fold. Previous studies have found higher levels of pain in people with obesity receiving SC insulin, and this study thus aimed to measure pain levels *during* and *after* an SC injection of low-molecular-weight heparin (LMWH) and identify how age, gender, and obesity may modulate the level of pain *during* and *after* the procedure. (2) Methods: This was a cross-sectional study, and the variables included age, gender, body mass index (BMI), BMI quartile, abdominal skin folds (ASFs), ASF quartile, and pain level *during* and *after* injection. A caliper was used to measure ASFs, height and weight were used to calculate BMI, and the Visual Analog Scale (VAS) was used to measure pain. (3) Results: The sample amounted to 202 participants, which was not considered representative of the study population. The average age was 64.3 years, and females predominated (62.40%). Of these participants, 42.5% were obese, and 29.1% were overweight. The average pain levels were low *during* (1.4) and *after* injection (1.9), highlighting the absence of pain *during* injection in 29.7% and *after* injection in 34.2%. (4) Conclusions: Obesity was associated with increased pain, but when adjusted for age, the pain was no longer significant. Females and young participants showed a significant relationship with pain *during* injection. Age, gender, and obesity had a statistically significant relationship with pain level. Participants with obesity (according to BMI and ASF) showed the highest levels of pain *during* and *after* injection. *After* injection, there was an increase in pain in most cases, possibly due to the discomfort caused by the drug itself, an aspect considered in the drug's technical data sheet as a frequent adverse effect (>1/10 to <1/100). However, the drug volume does not seem to be related to pain in this study.

Keywords: obesity; pain; injectable; subcutaneous; analog pain scale; skin fold; enoxaparin

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1. Introduction

Obesity in the population is associated with increased morbidity and demand for health and social services, and this complex pathology is associated with the presence of chronic multisystemic proinflammatory disorder [1–3]. To diagnose this pathology, various techniques are available, many of which are easy to use and low in cost, including impedancemetry, plicometry, and body mass index (BMI) [4]. Focusing on this last parameter, where a relationship is identified between weight and height, a BMI $\geq$ 30 kg/m^2 is classified as obesity according to the World Health Organization (WHO) criteria [5].

The pathophysiology of obesity and factors such as age, ethnicity, culture, and gender may influence human-perceived pain sensitivity [3]. In addition, increased pain perception in adulthood is associated with the early onset of obesity [2], while studies have shown a

lower pain tolerance in people with obesity, as well as a propensity for anxiety, depression, and metabolic syndrome [1].

Pain is an unpleasant but vital sensory and emotional experience for survival (adaptive function) because it alerts an individual about possible damage or injury and, consequently, prompts the pain sufferer to take measures to protect and avoid complications [6]. Acute pain is processed in the periphery through the dorsal horn, generating the perception of pain; the structures involved in the transfer of information about the cognitive component of pain (attention, anticipation, and memory) may be affected in people with obesity due to neuroinflammation [1,3].

Pain perceived by humans can be (1) acute pain as a response to tissue injury, caused by the activation of peripheral pain receptors and their sensory nerve fibers, or (2) chronic pain, as described above, appearing as a response to tissue injury, but in this case, due to the persistent activation of nerve fibers. This pain may be due to a continuous injury or dysfunction of the peripheral or central nervous system. The skin has different nociceptors located in the most superficial layers, some with myelin fibers such as mechanical ones (skin displacement) and thermal ones (activated by heat > 45 °C or cold < 5 °C, and non-myelinated ones such as polymodal ones (activation by mechanical pressure, heat, cold, and irritating substances). Central sensitization modifies the way in which the nervous system processes painful stimuli, which can generate allodynia (response to a non-painful stimulus) and hyperalgesia (excessive painful response to a not-so-intense stimulus) [7–9].

Inflammation and bodily injury cause pain by reflecting central and peripheral sensitivity; in the latter, the hyperexcitability of nociceptive neurons causes cell damage, plasma extravasation, the activation of local afferent cells (sensory neurons), and the migration of inflammatory cells to the site of injury, releasing substances such as amines, lipids, cytokines, and transmitter peptides [7], aspects related to inflammatory markers that show a pronociceptive influence on the peripheral and central nervous system. In people with obesity, the excessive accumulation of adipose tissue can trigger neuropathic and nociceptive pain [10–12]. There is research suggesting that pain influences innate and adaptive immunity, with microglia and astrocytes implicated in the pathophysiology of pain. Receptors such as Toll-like receptor 4 (TLR4), present on glia and afferent neurons (nerve cells), are activated by lipids and trigger a cascade of signals that lead to the release of proinflammatory cytokines, such as interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α). These proinflammatory cytokines can sensitize pain receptors (nociceptors) and central neurons, thereby generating increased pain sensitivity and hyperalgesia (proalgesic) [2,10,12].

On the other hand, people with obesity may present altered sensitivity to leptin (they may have hyperleptinemia but present resistance), thus preventing an adequate regulation of appetite and energy metabolism, and may present physiological alterations such as those related to healing and pain [13–15], showing evidence between ty, leptin, and pain.

The skin, as the most extensive organ of the human body, also suffers the effects of obesity; xerosis increases, and the mechanical resistance of the skin decreases, worsening scarring [14]. There is some discrepancy between published studies on obesity and pain sensitivity; while some research suggests less pain sensitivity in areas with excess subcutaneous (SC) fat [16], other studies show the opposite [17,18].

The literature on the relationship between age and pain is also controversial. Some studies indicate that older people have a higher pain threshold, while others find no clear differences [19,20]; for this reason, tailoring interventions according to the age of the patient and the impact on perceived pain is a challenge for the scientific community [21]. Regarding the influence of age on pain perception, studies [3,22] on somatosensory (cold, heat, and vibration) and mechanical and thermal factors (pressure, heat, cold stimulation, cold pressure test) showed that older people experienced less pain. Lautenbacher et al. [22] stated that aging can decrease deep pain but not superficial pain. Studies with low-molecular-weight heparin (LMWH) found no relationship between age and pain intensity [23–25], while Terhrani et al. [26] carried out a quasi-experimental study with 167 participants wherein pain intensity was evaluated during the injection, and significant differences were

detected ($p < 0.05$) relating to age, with the average level of pain experienced being higher in participants aged between 61 and 70 years.

The literature indicates that the pain derived from injectables depends on numerous factors: the needle, the drug, the volume, the application site, the injection speed, the fold formation, and the use of buffers to optimize pH and stability, among others [27,28]. Regarding the volume of the drug, a larger volume usually causes more pain [29], but there is no evidence on what the recommended volume is to minimize pain. Pain and itching are recognized in the enoxaparin (ENP) technical data sheet as frequent adverse reactions (>1/10 to <1/100) [30]. Previous studies on the administration of SC LMWH have not detected an increase in pain in subjects with obesity [31,32], Others did find an increase in pain but with no significance [24,25,33]; however, other authors have detected a higher level of pain in situations of obesity [3], focused on the hypothesis that these individuals present higher levels of certain inflammatory markers, which can lead to a hyperalgesic state [34]. Studies in rats administered with ENP have shown that this molecule has local anti-inflammatory effects (fracture area) and systemic effects with a decrease in TNF-0, IL1, and IL-6 [35], and this decrease in inflammation could be associated with a reduction in pain.

The increase in obesity and overweight worldwide has been established. In 2022, one in eight people in the world was obese, 43% of adults > 18 years of age were overweight, 16% were obese, and 37 million children under 5 years of age were overweight [36]. In Spain (2022), 34.3% of the population over 18 years of age was overweight and 14.1% was obese, while in the population of the Canary Islands (Spain), 34.4% of the population was overweight and 14.8% was obese, and 17.8% of adolescents were overweight (INE, 2022) [37]. These data suggest that in the future, there could be an increase in the percentage of people with obesity among recipients of injectable drugs, considering that obesity is associated with other morbidities that require treatment; sometimes, these treatments are injectable, daily and at home, so it is necessary to look for strategies to minimize local pain and ensure adherence to treatment, an important aspect for survival.

The aim of this study was to measure pain levels *during* and *after* the SC injection of LMWH and to identify how age, gender, and obesity may modulate the level of pain *during* and *after* the procedure.

2. Materials and Methods

2.1. Study Design

This was a cross-sectional descriptive study.

2.2. Study Sample

This study was conducted at the Trauma Surgery Hospital Unit (TSHU) at the Insular Maternal and Child University Hospital Complex of Gran Canaria over a period of one year. The study population comprised patients admitted to the TSHU during that period, regardless of the admission process (emergency, scheduled, consultation).

The TSHU was selected due to being the hospital unit with the highest prescription of LMWH, in addition to the presence of patients with limited mobility in some cases, which may increase the probability of capturing patients who are obese or overweight.

The criteria established for the inclusion of participants in the study were as follows: on the list of new admissions to the TSHU; at least 18 years old; no previous diagnosis of any cognitive impairment (for example, Alzheimer's disease, dementia) nor disorientation experienced during the time of sample selection (e.g., derived from infections, treatment with opioids, among others); and having enoxaparin (ENP) in the medical prescription. In each case, having verified these criteria were met, the researcher checked for any functional limitations of the patient (e.g., lower limb fractures, orthoses) that would prevent their standing for weighing and measuring, or if able to carry it out, for any devices the patient was using that would modify their measure weight and/or height.

The selection of the sample participants was carried out following this process: (1) Every morning, the lists of newly admitted patients > 18 years old were reviewed. (2) It was verified that the pharmacological regimen included ENP (Clexane® [Sanofy Aventis, Barcelona, Spain] only—the decision to include only Enoxaparin–Clexane was influenced by being the only brand acquired by the hospital during the study). (3) It was verified that the patient did not have a diagnosis of cognitive disease or disorientation. (4) The patient was visited in the room by the researcher, and an assessment was made on their inability to stand and/or their utilizing a device that could be a bias when capturing height and weight. (5) The patient was visited in the room to be informed about the study and to be given the information sheet, data protection sheet, and informed consent. (6) Each participant was included in the study once they signed the informed consent.

A sample size of 287 randomly selected subjects was deemed sufficient for estimation with a 95% confidence level, a population percentage considered to be around 50%, and a precision of ±5 units. A substitution rate of 0% was anticipated. The GRANMO® calculator [Datarus, Barcelona, Spain] was used [38]. However, as the Results Section shows (Figure 1), this sample could not be reached.

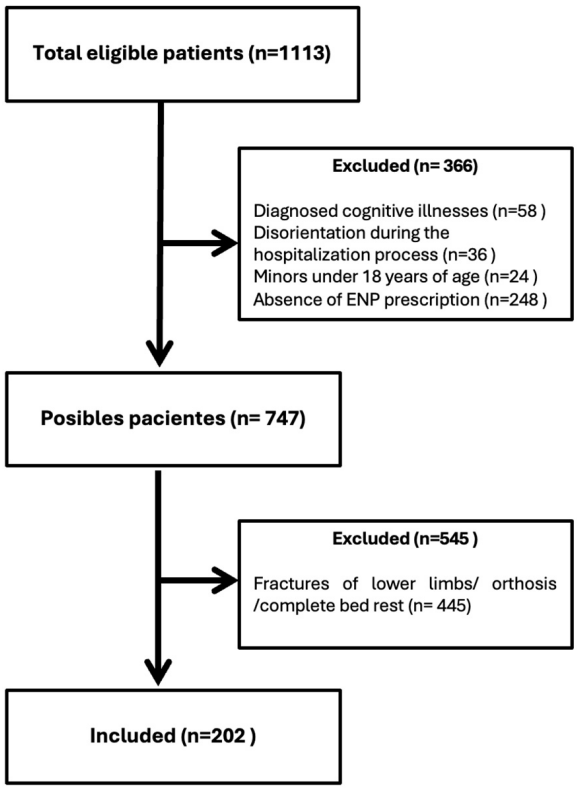

Figure 1. Inclusion/exclusion flow chart.

2.3. Variables

The variables incorporated into this study were as follows:

Independent variables: age, gender, weight (kilograms), height (meters), BMI (kg/m^2) [4], BMI categories (I-VI) [5], abdominal skin fold (ASF) value (millimeters), abdominal fold categories (I-IV), and dose of ENP (in milligrams). Dependent variables: level of pain *during* the injectable and level of pain *after* the injectable.

2.4. Measurement and Data Sources

The tools used to measure each variable were as follows: (1) the medical history of the participant, where information can be obtained on compliance with the inclusion criteria, as well as gender and age; (2) a plicometer (Holtain®; HOL-98610ND [Holtain Limited, Crosswell, UK) with a possible measurement range of 0–48 mm; (3) a quartile of the ASF

was calculated by dividing the maximum value of the fold (48 mm) into quartiles (ASF I 0–12; ASF II 13–24; ASF III 14–36; ASF IV 37–48 mm); (4) a scale–height (SECA-780) gauge with a measurement range of 0–130 kg and 0–200 cm; (5) BMI (kg/m^2) value [4]; (6) BMI category, according to the WHO (underweight < 18.5; normal weight 18.5–24.9; overweight 25–29.9; obesity type I 30–34.9; obesity type II 35–39.9; extreme obesity $\geq$ 40 kg/m^2 [5]); (7) a stopwatch and a mobile phone; (8) the Analog Pain Scale (EVA) [39], which has a 10 cm line, where the possible values are between 1 and 10; (9) all ENP prefilled syringes are single dose, with a 27G (0.4 mm) thick and 4/10 inch (1.016 cm) long needle. The volume of the drug in milliliters is proportional to the dose in milligrams (e.g., ENP 0.4 mL = 40 mg). The decision to include this type of LMWH in the study was influenced by the brand of medicine acquired by the hospital. The operator in charge of carrying out the measurements and collecting data was C.d.l.M.D.-G.

The measurement procedure consisted of the following steps: (1) after the participant's inclusion in the study, the researcher measured their abdominal skinfold [40] on three occasions and recorded the average value (Figure 2); the participant was weighed and measured in a standing position and their BMI was calculated; (2) the researcher observed five nurses administering the injection; (3) the researcher asked the participant what the level of pain was *during* the injection; and (4) the researcher started the stopwatch once the nurse removed the needle from the skin and, after 2 min, asked again what the pain level was *after* the injection. This process was repeated for three consecutive days, at 24, 48, and 72 h, so each participant received 4 injections.

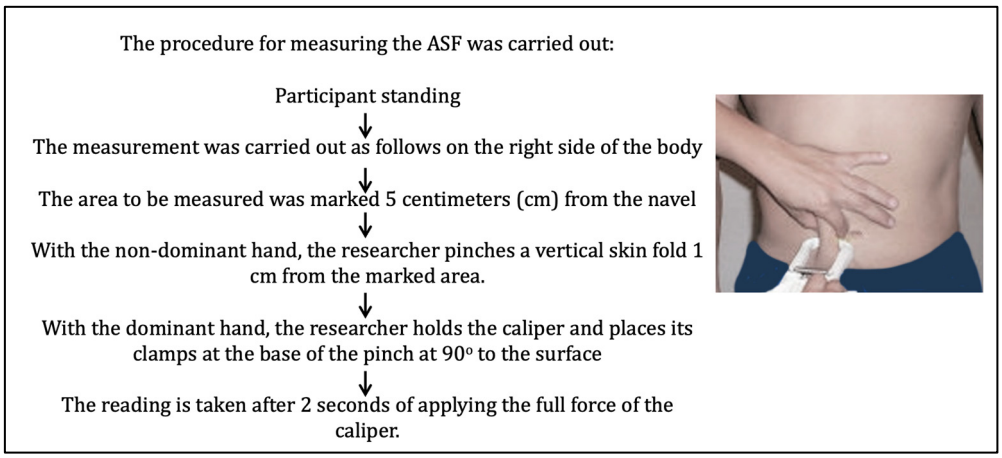

Figure 2. Procedure for measuring the ASF.

2.5. Statistical Methods

Once the data were collected and recorded, a statistical analysis was carried out using the Statistical Package for the Social Sciences for Windows 24.0 (IBM, Armonk, NY, USA) and the R program version 3.1.0 (R Development Core Team, Vienna, Austria), with the corresponding licenses. Descriptive statistics were performed, the Spearman coefficient was calculated to detect the degree of relationship between the variables, and a one-way non-parametric analysis of variance was performed. The operators in charge of carrying out the statistical analysis were C.d.l.M.D.-G. and a professional statistician.

2.6. Limitations

The limitations of this study include the following: (1) not reaching the expected sample in the sample calculation due to the limitation of a one-year study, thus preventing the generalization of results; (2) the predominance of women and older people; (3) the subjectivity of pain: the perception of pain varies between individuals, affecting the consistency of the results; (4) in the exploration of gender and pain, it is necessary to include other hormonal variables that may affect pain perception; (5) the measurement of pain that

depends on self-reports, which may introduce biases; (6) factors such as emotional state or previous experience with injections were not considered; and (7) the possible differences in pressure exerted by the nurses at the time of the injection.

3. Results

A sample of 202 participants (n = 202) was obtained, which did not reach the minimum expected sample of 287 participants to be considered representative. The reason for not achieving this sample was largely the impossibility of placing the patients in a standing position for measuring weight and height due to lower limb fractures, surgeries, or devices such as orthoses that were shown to be a bias for weight and/or height. Another aspect that limited the increase in the sample was the authorization for a year-long field study (data collection time included in the submitted project).

Sample characteristics: The mean age of the sample was 64.3 years (32–89), with a standard deviation (SD) of 15.0. Due to the characteristics of the hospitalization unit (traumatology), it was expected that the participants would be older; indeed, 25.7% of the sample were aged between 70 and 79 years, and 23.8% were aged 60–69 years. The majority of the participants were female (n = 126, 62.4%).

In terms of the anthropometric variables, the mean height was 165.6 cm within a range of 150–194 and an SD of 9.7. Regarding body weight, the sample had a mean weight of 79.5 kg with a range of 45.4–118 and an SD of 17.93. Once Quetelet's formula was applied with the above parameters, the sample had a mean BMI of 28.8 kg/m^2 with an SD of 5.1 and a range of 19.5–39.8. Based on the BMI values, the participants were categorized into six WHO categories [5] (Table 1), where type I obesity accounted for 36.1% of the sample, just over a quarter of the sample were of normal weight, and the remainder (72.2%) were overweight.

Table 1. Distribution of the sample according to the classification of obesity (from BMI) and gender. Frequency (n) and percentage (%).

Obesity Classification	Total n (%)	Male n (%)	Female n (%)
BMI I—Underweight < 18.5	0 (0.0)	0 (0.0)	0 (0.0)
BMI II—Normal weight [18.5–24.9]	56 (27.8)	12 (5.9)	44 (21.8)
BMI III—Overweight [25–29.9]	60 (29.7)	24 (11.9)	36 (17.8)
BMI IV—Obesity type I [30–34.9]	73 (36.1)	36 (17.8)	37 (18.7)
BMI V—Obesity type II [35–39.9]	13 (6.4)	4 (2.0)	9 (4.5)
BMI VI—Extreme obesity ≥ 40	0 (0.0)	0 (0.0)	0 (0.0)

When comparing these data with the country's records [37], a lower percentage of overweight can be seen in our data (29.7 vs. 34.3%, respectively); however, the sample presents obesity data of 42.5% compared with the state's 14.1%, possibly conditioned by pathologies, mobility limitations, and a more sedentary life.

In Table 2, the results of the ASF measurements are presented and categorized into low ASFs, moderate ASFs, high ASFs, and very high ASFs.

Table 2. Distribution of the sample by category according to ASF value (mm). Frequency (n) and percentage (%).

ASF	Total n (%)	Male n (%)	Female n (%)
Quartile I [0–12]	6 (3.0)	6 (3.0)	0 (0.0)
Quartile II [13–24]	50 (24.8)	11 (5.4)	39 (19.3)
Quartile III [25–36]	57 (28.2)	19 (9.4)	38 (18.8)
Quartile IV [37–48]	89 (44.1)	40 (19.8)	49 (24.3)

Regarding the doses of ENP received by the participants, the majority measured 40 mg (n = 183), 60 mg (n = 6), 80 mg (n = 9), and 100 mg (n = 4).

The mean pain sensation perceived *during* the ENP injection (202 subjects) was 1.4 with a range of (0–6) and an SD of 1.35, while for *after*-injection pain, the mean was 1.9 (0–8) with an SD of 2.1. The distribution of the sample according to the level of pain is represented in Table 3, where the absence of pain stands out, although this proportion represents only 30% of the sample compared with the remaining 70%, who experienced some level of pain.

Table 3. Distribution of pain level: *during* injection and *after* injection.

	Pain *during* Injection	**Pain *after* Injection**
Pain Level	**n (%)**	**n (%)**
Pain 0	60 (29.7)	69 (34.2)
Pain 1	58 (28.7)	45 (22.3)
Pain 2	56 (27.7)	21 (10.4)
Pain 3	12 (5.9)	22 (10.9)
Pain > 3	16 (8.0)	45 (22.3)

Table 4 shows the perception of pain *during* and *after* ENP injection according to BMI and ASFs. To explain the relationship between the participant's abdominal ASF and the level of pain perceived *during* and *after* the administration of ENP, the data in Tables 3 and 4 were reviewed, wherein the pain in the subjects can be observed (in absolute frequencies) for both time points (*during* and *after*) and for each quartile of abdominal ASF. The results highlight that pain *during* and *after* injection was null in 29.7% of the participants, and it was mild (1–3) in the majority of participants at 62.3% vs. 46%, respectively. The total sample included in ASF I experienced no pain *during*, while 62.8% of participants who had ASF IV experienced some type of pain, followed by 77.8% included in ASF II and 82.6% of ASF III. Regarding pain *after*, 67.7% of participants with ASF II experienced some degree of pain, followed by 68.5% of ASF IV and 81.8% of those included in ASF III, coinciding in the last two cases with the highest pain averages in the four injections (1.9 vs. 2.2, respectively). Regarding the level of pain based on the BMI category, 29.7% of participants did not experience pain *during*. However, regarding the presence of some degree of pain *during* for each BMI category, 65.7% in BMI IV presented some level of pain, with 70.6% in BMI III, 78.0% in BMI II, and 100% in BMI V, and these last two percentages would explain the highest average pain level (1.7 vs. 2.0, respectively). In pain *after*, 65.0% of those included in BMI III presented some type of pain, followed by 70.0% in BMI II, 67.1% in BMI IV, and again, 100% in BMI V, with an average of 4 injections of 2.4.

Table 4. Distribution of the perception of pain *during* and *after* ENP injection according to ASF categories and obesity (BMI). Frequency (n) and percentage (%).

	Pain during Injection				**Pain after Injection**			
Pain Level	ASF I	ASF II	ASF III	ASF IV	ASF I	ASF II	ASF III	ASF IV
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Pain 0	6 (3.0)	11 (5.4)	10 (5.0)	33 (16.3)	6 (3.0)	19 (9.4)	16 (7.9)	28 (13.9)
Pain 1	0 (0.0)	18 (8.9)	16 (7.9)	24 (11.9)	0 (0.0)	10 (4.9)	18 (8.9)	14 (6.9)
Pain 2	0 (0.0)	18 (8.9)	24 (11.9)	14 (6.9)	0 (0.0)	11 (5.4)	3 (1.5)	6 (3.0)
Pain 3	0 (0.0)	0 (0.0)	0 (0.0)	12 (5.9)	0 (0.0)	3 (1.5)	6 (3.0)	13 (6.4)
Pain > 3	0 (0.0)	3 (1.5)	7 (3.5)	6 (3.0)	0 (0.0)	7 (3.5)	14 (6.9)	28 (13.9)
Mean pain of the four injections	0.0	1.3	1.7	1.4	0.0	1.7	1.9	2.2

Table 4. *Cont.*

	Pain during Injection				Pain after Injection			
	BMI II	BMI III	BMI IV	BMI V	BMI II	BMI III	BMI IV	BMI V
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Pain 0	17 (8.4)	18 (8.9)	25 (12.4)	0 (0.0)	21 (10.4)	21 (10.4)	24 (11.9)	3 (1.5)
Pain 1	13 (6.4)	17 (8.4)	24 (11.9)	4 (2.0)	13 (6.4)	15 (7.4)	13 (6.4)	4 (2.0)
Pain 2	17 (8.4)	18 (8.9)	18 (8.9)	3 (1.5)	6 (3.0)	9 (4.5)	7 (3.5)	0 (0.0)
Pain 3	0 (0.0)	3 (1.5)	3 (1.5)	3 (1.5)	3 (1.5)	7 (3.5)	7 (3.5)	3 (1.5)
Pain > 3	9 (4.5)	4 (2.0)	3 (1.5)	3 (1.5)	13 (6.4)	8 (4.0)	22 (10.9)	3 (1.5)
Mean pain of the four injections	1.7	1.2	1.1	2.0	2.3	1.5	1.8	2.4

BMI categories I and VI were not available to sample.

As mentioned in the methodology, four injectables were assessed; therefore, four pain measurements were performed *during* and *after*, with Table 4 presenting the average pain based on the ASF, where the highest average pain *during* was found in ASF III. However, regarding pain *after*, the highest average was obtained by ASF IV (greater local subcutaneous fat) followed by ASF III.

Regarding pain levels during and after injection based on gender, Table 5 presents descriptive statistics, where a higher average pain level is observed in the female gender both during (1.6) and after (2.3) the ENP injection.

Table 5. Descriptive Statistics: gender a pain during and after.

	Valid	Mean	Std. Deviation	Minimum	Maximum
Gender	202				
Pain *during* (mean)	202	1.4	1.35	0.00	6.00
Pain *after* (mean)	202	1.9	2.1	0.00	8.00
Gender: female	126				
Pain *during* (mean)	126	1.6	1.5	0.00	6.00
Pain *after* (mean)	126	2.3	2.3	0.00	8.00
Gender: male	76				
Pain *during* (mean)	76	1.0	0.9	0.00	2.00
Pain *after* (mean)	76	1.3	1.5	0.00	5.00

Influence of obesity on the perception of pain: To identify the presence of significant differences between the perception of pain experienced by the subjects receiving ENP both *during* and *after* the injection, and depending on the degree of obesity (BMI) and the ASF value, the following correlation was performed using Spearman's test (Table 6).

Table 6. Spearman correlation between pain *during* and *after* injection compared with age, BMI, and ASF.

		1	2	3	4	5
1.	Age	1.00				
2.	BMI	−0.06	1.00			
3.	ASF value	−0.21 **	0.73 **	1.00		
4.	Pain *during*	−0.10	0.05	0.01	1.00	
5.	Pain *after*	−0.16 *	0.14 *	0.16 **	0.54 **	1.00

* Significant correlation at the 0.05 level. ** Significant correlation at the 0.01 level.

There is thus a positive correlation between pain *during* and *after* ENP application. Note that the correlation between pain *during* and *after* injection is 0.5, a value to be expected in repeated measurements on the same subject. This event could be explained by two factors: one due to the intensity and/or duration of *after*-injection pain on pain *during* the procedure, and the other by a possible superposition of *after*-injection pain on pain *during* the procedure. In Table 7, no relationship was found between BMI and pain *during*. However, there was a weak significant association between BMI and pain *after* ($p = 0.14$; $p < 0.05$), which seems to be more typical of the drug than the skin lesion. A significant association was also found between the ASF value and the level of pain *after*-injection ($p = 0.16$; $p < 0.01$).

Table 7. Categorical relationships between different variables (non-parametric).

	Pain *during*				**Pain *after* Minus Pain *during***			
	M ± SD	**Md**	**N**	**Range**	**M ± SD**	**Md**	**N**	**Range**
Age								
30–39	2.3 ± 1.3 ***	2	10	1–4	1.1 ± 0.9	1	10	0–2
40–49	1.2 ± 0.9	1	39	0–2	0.7 ± 1.7	1	39	−2–4
50–59	1.2 ± 0.8	1	18	0–2	0.6 ± 1.7	0	18	−1–3
60–69	1.7 ± 1.8	2	48	0–6	0.3 ± 1.8	0	48	−3–5
70–79	1.6 ± 1.5	1	52	0–5	0.5 ± 1.6	0	52	−2–4
80–89	0.9 ± 0.7	1	35	0–2	0.4 ± 2.1	0	35	−1–6
Gender								
Male	1 ± 0.9 **	1	76	0–2	0.2 ± 1.4	0	76	−2–3
Female	1.6 ± 1.5	1	126	0–6	0.7 ± 1.9	0	126	−3–6
ENP Dose								
40 mg	1.4 ± 1.4	1	183	0–6	0.5 ± 1.8	0	183	−3–6
60 mg	1 ± 1.1	1	6	0–2	0 ± 0.0	0	6	0–0
80 mg	2 ± 0.9	2	9	1–3	1 ± 2.3	0	9	−1–4
100 mg	1 ± 0.0	1	4	1–1	0 ± 0.0	0	4	0–0
Obesity (BMI)								
Normal weight	1.6 ± 1.7 *	1	56	0−6	0.3 ± 1.8 *	0	56	−2–6
Overweight	1.3 ± 1.2	1	60	0−4	0.2 ± 1.0	0	60	−2–2
Obesity Type I	1.2 ± 1.2	1	73	0−5	1 ± 1.9	0	73	−1–5
Obesity Type II	2.2 ± 0.9	2	13	1−3	0.2 ± 2.5	0	13	−3–4

* Significant at 0.05 level. ** Significant at 0.01 level. *** Significant at 0.001 level. M: mean; SD: standard deviation; Md: median; N: sample.

As shown in Table 7, the relationship between different categorical variables was analyzed, including age, gender, and obesity, with pain *during* and pain *after* injection. Since the *after*-injection pain variable is moderately related to the *during*-injection pain variable, the difference between these two was analyzed to assess a possible increase or decrease in *after*-injection pain. Table 7 presents the test of means between the BMI categories with respect to pain *during* and pain *after* minus pain *during* to determine if they are equal or different within the same category, identifying with an asterisk those that are significant. The asterisk is always inserted in the first category of the variable to indicate differences between categories but does not indicate the assignment of that difference to the first category.

The relationship between obesity and pain: As mentioned, Table 7 presents the test of means between the BMI categories with respect to pain *during* and pain *after* minus pain *during*. The presence of significant differences between the means of the different categories (age, gender, and BMI) is shown, exhibiting the highest level of significance in age, followed by gender and obesity. As discussed, there is a significant relationship between BMI and pain *during* and pain *after* minus pain during, but when looking at the nature of this relationship (Table 6), a correlation is only found between BMI and pain *after* ($p = 0.14$; $p < 0.05$). Since the variable pain *after* is correlated with the variable pain *during*, it could refer to the increase in pain *after* over *during*.

The relationship between age and pain: Table 6 shows a strong relationship between age and pain *during*. However, while no correlation is detected between age and pain *during* (Table 6), there is a correlation between age and pain *after*, with young participants having greater painful experiences ($p < 0.05$).

4. Discussion

Obesity is a complex condition that not only affects metabolic health but is also closely related to pain perception and management, influencing both acute and chronic pain in various ways. Previous studies have shown that obesity is associated with an increased risk of developing chronic pain and a lower pain tolerance [41,42]. Among these results, it is worth highlighting that participants with obesity reported higher levels of pain compared with those with a normal weight and that excessive adipose tissue may contribute to chronic inflammation, thus exacerbating pain perception [3,34]. The findings also suggest that the inflammatory and metabolic mechanisms associated with obesity may sensitize the nervous system, increasing the experience of pain [43].

The data from our sample of 202 subjects, with a higher percentage of women (62.4%) than men (37.6%), are consistent with those of other studies that have investigated pain perception and injectable medication administration. Several investigations have shown that women tend to participate in greater numbers in pain and medical treatment studies due to a higher prevalence of certain health conditions and a greater willingness to report pain and seek treatment [41,44]. In this regard, other studies have found that women tend to experience and report more pain compared with men, which may influence their greater representation in pain-related studies [45], and that women are more likely to seek medical care for chronic pain [46], which could explain the higher proportion of women in our sample. Therefore, the gender distribution in our study is not only similar to that observed in other studies but also reflects well-documented trends in pain research, treatment adherence, and their relationship to gender.

In our study, it was observed that patients with obesity reported higher pain levels both *during* and *after* SC injection, as shown by the mean pain scores for the four injections ($p < 0.05$), and these findings are consistent with studies using thermal and pressure stimuli, where obese individuals were more sensitive to pain, although this response may vary to different types and intensities of stimuli, depending on underlying subcutaneous fat levels [tash] [47]. The mean pain score *during* injection in our sample was 1.4 (SD 1.35), while the mean *after*-injection pain was 1.9 (SD 2.1). These results are similar to those obtained by other studies that found that patients with obesity experienced greater injection pain compared with their normal-weight counterparts [41,48]. Studies have shown conflicting results regarding the relationship between BMI and altered pain sensitivity in individuals with obesity [3,34,42,48], which relates to probable differences in methodologies and the critical limitation on the exclusive use of BMI to assess obesity. In our study, in addition to BMI, an abdominal skinfold measurement was used, and the significant correlation between BMI and *after*-injection pain in our study, although weak, supports the existing literature linking obesity with increased pain perception [31,49]. This is an issue to consider because pain experienced *after* SC injections can negatively affect individual comfort, generate anxiety, and lead to treatment rejection [33,50]. The average of four injections is a

methodologically sound strategy that facilitates a more precise and reliable estimate of the participants' pain experience.

On the other hand, our research also found that age and gender are factors that modulate pain perception. Based on Table 7, participants with the highest mean pain scores were found in the 30–39 category (2.3), both in terms of the pain during and the increase in pain after subtracting the pain during (1.1); however, no significant correlation was found between these last two variables. In Table 6, a negative correlation was found between age and pain *after*, where young people presented the highest pain levels, which is consistent with the observations of other authors [51] who documented that pain perception changes with age. Furthermore, females in our sample reported higher pain levels than males, which can be seen in the mean pain scores during (1.6 vs. 1.0, respectively) and after (2.3 vs. 1.3, respectively) in Table 5. This finding is consistent with previous studies suggesting gender differences in pain perception and tolerance [33,52].

In our study, a non-parametric statistical correlation test was performed (Table 6) that identified a positive correlation ($p = 0.54$; $p < 0.01$) between the pain *during* and the pain *after* as perceived by the participant. Among the possible interpretations could be the persistence of the initial pain at the time of evaluating the pain after, due to the sensitization of the nociceptors that generate a prolongation of the painful experience. Significant differences were identified in relation to the pain experienced by subjects receiving ENP *during* and *after* injection with BMI and ASF ($p < 0.05$). In addition, a significant positive correlation was detected between BMI ($p = 0.14$; $p < 0.05$) and ASF ($p = 0.16$; $p < 0.01$) with pain *after*. These findings suggest that SC fat may have an impact on pain perception *after* injection [47,53,54].

On the other hand, although no correlation was found between BMI and age ($p = -0.06$), a correlation was found, however, between ASF and age ($p = -0.21$). This aspect could be due to the types of fat distribution in obesity: while the BMI value does not provide specific information on the SC tissue in the abdominal area, the ASF value does provide this more specific information, showing a negative correlation between ASF and age, whereby younger participants have higher ASF. These results are in line with previous research suggesting that obesity and body fat distribution may influence pain perception [47,49,53,54].

Regarding age and the two types of pain, a significant negative correlation was found only in pain *after* ($p = -0.16$; $p < 0.05$), with younger participants showing greater pain *after*. Analyzing the previous paragraph, it can be understood that younger people exhibited higher ASF and greater pain afterward, which could explain the increase in abdominal adipose tissue as a chronic low-grade inflammatory process that actively influences the secretion of adipokines and proinflammatory cytokines, as well as the development of pathophysiological phenomena (metabolic syndrome and cardiovascular pathologies). These results are in line with previous research suggesting that obesity and body fat distribution may influence pain perception [47,49,53,54]. The current lines of research are advancing in the search for specific mechanisms relating to chronic inflammation caused by substance P (SP), a neuropeptide that acts as a potent mediator of neurogenic inflammation in organs and systems [55]. In addition, among the mechanisms mentioned are the degranulation of mast cells and the release of proinflammatory cytokines and vasoactive amine activators of sensory nerve endings [56], causing a localized peripheral sensitization of nociceptors in the local tissue environment [47]. There are studies aimed at the rehabilitation of patients with obesity wherein a reduction in body weight has occurred, leading to reports of greater pain control [57,58]. These aspects need to be further explored to improve our understanding and treatment of pain in patients with obesity.

In summary, our findings underscore the importance of considering individual factors such as age, gender, and body fat distribution when assessing and managing pain associated with SC injections. These results not only expand our understanding of how obesity and other variables affect pain perception but may also guide future research and clinical strategies to improve treatment adherence and patient quality of life.

5. Conclusions

Based on the objectives set out in this study, it is concluded that the percentage of participants who did not experience pain *during* the administration of SC ENP was lower than the percentage of those who experienced pain *after* (29.7 vs. 34.2%, respectively). Nevertheless, there was an increase in the mean pain *after* (1.4 vs. 1.9, respectively). The few participants who showed a level of pain greater than 3 only represented 16 subjects, with little representation in each pain level; for this reason, they were included in the category "pain > 3", becoming the category that presented the greatest increase in participants with this level of pain (16 participants).

Females perceived a higher mean level of pain, both *during* and *after*. Significant differences were identified between age groups and pain *during*, but it was the younger age groups that perceived the greatest pain, showing a weak negative correlation between age and pain *after*. Regarding obesity through BMI and ASF, it was found that the youngest had the highest local fat values (ASF), aspects that were also weakly correlated. Therefore, it was expected that the increase in local fat (high ASF) and pain *after* were somehow related, also showing a correlation.

Although the researchers included the ENP dose hoping to identify a relationship with the levels of pain perceived by the participants, this did not occur. The increase in dose and, therefore, the increase in volume, is associated with an increase in pressure in the SC tissue, where an increase in pain would be expected afterward. This may be due to a situation of pro-inflammation due to obesity and having a lower sensitivity to pain; however, attributing the perception of pain only to obesity is erroneous and simplistic when we know the multitude of factors that can influence pain (psychological, social, and cultural factors, among others).

This study demonstrates once again how obesity, age, and gender can influence the pain levels of patients receiving invasive procedures, variables that should be included in future studies exploring pain perception. Adequate intervention in patients prescribed long-term treatments is vital for adherence and survival.

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Abbreviations

Subcutaneous (SC); body mass index (BMI); abdominal skin fold (ASF); enoxaparin (ENP); low-molecular-weight heparin (LMWH); standard deviation (SD); mean (M); median (Md); sample (N).

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