

# The Use of Deoxycholic Acid for the Clinical Reduction of Excess Submental Fat in Indian Patients

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## ABSTRACT

**Copy:** The injectable adipocytolytic drug deoxycholic acid (DCA) is the first pharmacological intervention approved for the reduction of submental fat (SMF) and offers an alternative to invasive measures to improve the submental profile and the cervico-mental angle. DCA injection (ATX-101, Kybella [United States], Belkyra [Canada]; Kythera Biopharmaceuticals, Inc., Westlake Village, CA, acquired by Allergan, Inc.), are proprietary formulations of synthetically derived DCA that is FDA approved for improvement in the appearance of moderate to severe convexity or fullness associated with SMF.

**Aim:** As none of the aforementioned are available in India, we undertook this study to study the efficacy of generic DCA for SMF reduction in Indian patients.

**Methods:** 50 patients with confirmed Indian ethnicity and unwanted SMF were injected 3 mg/cm<sup>2</sup> of generic DCA into their SMF, with a 12-week follow-up period. In each session, 5 ml of 30 mg/ml DCA was injected. The sessions were spaced approximately 2 months apart. All these patients with reductions in SMF were reported using Clinician Reported SMF Rating Scale (CR-SMFRS) and Patient Reported SMF Rating Scale (PR-SMFRS) using the Validated Rating Scale for improvement in the appearance of their chin, the neck, and the cervico-mental profile. Also, for objective assessment of improvement in SMF, caliper measurements were used.

**Results:** One session was required in 2 patients, 12 patients needed 2 sessions, 32 patients needed 3 sessions, and 4 patients needed 4 sessions. Altogether, 90% patients showed at least a decrease of 1 point in (CR-SMFRS). Reduction in SMF as confirmed by caliper measurements was statically significant.

**Conclusion:** The findings show generic deoxycholic acid to be equally effective in the treatment for SMF in Indian patients.

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## BACKGROUND

Facial aesthetic surgical procedures such as face and neck lifts are consistently amongst the top 5 cosmetic surgical procedures performed annually.

Among such procedures, neck contouring is gaining popularity, and various novel technologies (Ultherapy, Merz Aesthetics, Merz North America; CoolMini, ZELTIQ Aesthetics, Pleasanton, CA; Thermi, Almirall Company, S.A.) are available to target this anatomic region.

Consequently, interest in rejuvenation strategies for the lower third of the face has surged, and patients increasingly are seeking ways to reduce submental fullness.<sup>1</sup>

Submental fat is considered aesthetically unappealing and can have a negative psychological impact on patients. Accumulated fat deposits treated invasively with surgery liposuction etc., can be associated with serious complications and substantial recovery times, evidence supporting effectiveness of noninvasive energy devices is also limited.<sup>2</sup> Lipolytic injectables (injection lipolysis, mesotherapy, or lipodissolve) are minimally invasive,

alternative approaches for reducing accumulated submental fat, wherein one or more compounds are injected into the submental fat.<sup>3</sup>

Amongst them, deoxycholic acid (DCA), a naturally occurring bile acid, emulsifies fat for absorption in the intestine with non-selective cell-lysis ability and acts by irreversibly disrupting the adipocyte membrane causing adipocytolysis.<sup>4</sup> DCA injections ATX-101, Kybella<sup>®</sup> in the United States and Belkyra<sup>™</sup> in Canada (Kythera Biopharmaceuticals, Inc., Westlake Village, CA, USA, an affiliate of Allergan, Dublin, Ireland) are proprietary formulations of synthetically derived DCA that is FDA approved for improvement in the appearance of moderate to severe convexity or fullness associated with submental fat.<sup>5</sup>

The efficacy and safety of DCA injections in the submental fat area was demonstrated in four phase 3 randomized controlled trials.<sup>4,6,7,8</sup>

DCA has a nonselective cell-lysis ability, however, affinity is lower in proteinaceous tissues versus fatty tissue. Therefore,

**FIGURE 1.** Showing various points for injections of DCA. At each point, 0.1 ml of DCA injected at a distance of 1 cm sq. area.



adipose tissue is more susceptible to DCA versus surrounding tissue.<sup>6</sup>

## METHODS

### Copy Study Design

This was a prospective, clinical study carried out at The Esthetics Clinics, India, between April 2017 and April 2018. Institutional Review Board Approval was obtained and written informed consent was taken from each patient.

### Patients

Fifty patients above 18 years of age, of Indian ethnicity, and who were seeking improvement in convexity/fullness associated with submental fat, were enrolled. Patients were excluded if they had other potential causes of submental convexity or fullness (eg, thyromegaly, cervical adenopathy, excessive skin laxity), infection at injection site, previous use of injectable lipolytic

agent, or previous aesthetic procedures in submental area, were using anticoagulants, or were pregnant or lactating. Caution was exercised in patients with changes in anatomy or landmarks, or who had scar tissue that may have impacted the ability to safely administer the DCA injections. In addition, patients were required not to change their dietary or exercise regime or start a weight reduction regimen during the course of study.

### Treatment

DCA (10 mg/mL) for subcutaneous injection is available as a sterile solution in a 5-mL clear, colorless vial, for single-patient use. Vials were stored at 20 to 25°C.

### Procedure

Before treatment, perceived changes in neck anatomy associated with submental fullness were assessed, and the preplatysmal fat within the treatment area was identified. Thereafter, the treatment area was marked with a surgical pen,

**FIGURE 2.** Validated grading for assessment of SMF.

Scale	0	1	2	3	4
Submental Convexity	Absent	Mild	Moderate	Severe	Extreme
Description	No localized submental fat evident	Minimal localized submental fat	Prominent localized submental fat	Marked localized submental fat	Extreme submental convexity
Representative Photographs					

and a 1-cm injection grid was applied to mark the injection sites (Figure 1). The needle (26 gauge) was placed with respect to the mandible to avoid injury to the marginal mandibular nerve (MMN; motor branch of the facial nerve) allowing DCA to be injected within the target SMF treatment area only DCA was injected subcutaneously in the SMF area using an area-adjusted dose of 0.1/cm<sup>2</sup> session comprised a maximum of 50 injections: 0.1 mL per injection (total, 5 mL/session), spaced 1 cm apart. Ice packs, oral analgesia, and topical local anesthetic were used before and after treatment as needed. Number of sessions were determined as per the aesthetic goals of patients.

### Efficacy Assessments

#### Subjective Assessment

Global Standard Photography was performed in all patients to evaluate and compare submental convexity/amount of SMF in all patients at baseline, 4 weeks, 8 weeks, and 12 weeks post each session.

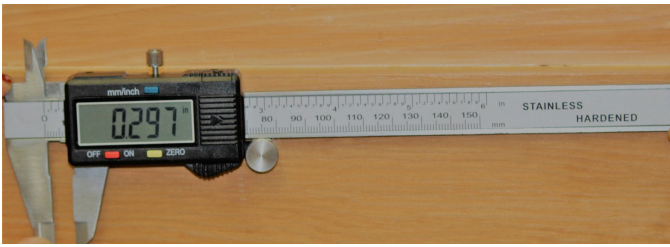
Both Clinicians as well as subjects assessed the improvement using Validated Grading Scale for SMF (Figure 2).<sup>9</sup>

The scoring scale by clinicians was called Clinician Reported SMF Rating Scale (CR-SMFRS) and was assessed by two neutral, blinded facial plastic surgeons. Likewise, patients assessed the improvement in a similar way and the scale was called Patient Reported SMF Rating Scale (PR-SMFRS).

#### Objective Assessment

It was performed using a digital caliper (Figure 3 and 4). Measurements were taken at baseline and compared with measurements at week 4, 8, and 12 post each session. Percentage reduction was calculated and graded as shown in Table 1.

Also, the patients were made to fill a short questionnaire regarding the improvement as shown in Table 2 and adverse events like pain, tenderness, and lumpiness and their duration were noted.

**FIGURE 3.** Digital caliper for objective assessment of SMF.**FIGURE 4.** Digital caliper for objective assessment measurement of SMF.

## RESULTS

All the Fifty patients' data was stored in Microsoft Excel 2007 version and we used Graph pad prism statistical software version: 6 for running the Statistical analysis. Komgrov normality test confirmed that the data was distributed normally, and we used one paired student t-test to evaluate the significance of the study.

### Patient Demographics and Baseline Characteristics

Overall 50 patients were treated: 26 males and 24 females. Mean patient age was 35.4 years. Age range was 20-63 years. Mean body mass index (BMI) was 31.1 (4.4; 17.3, 44.8) kg/m<sup>2</sup>.

### Procedural Outcomes

Overall, 50 patients had a total of 138 treatment sessions. 2 patients required only a single session. In the multiple-treatment-session group, most (32/48) patients had 3 sessions; 12 patients had 2 sessions, and 4 patients had 4 sessions (Table 3). The patient follow-up duration between treatments were standardized as 4, 8, and 12 weeks after the procedure was performed. The dose of DCA was also standardized to be 5 ml/session. The sessions were performed until the aesthetic goals of patients were achieved.

### Treatment Response

#### Clinician Reported SMF Rating Scale (CR-SMFRS)

Improvement by 1 point from baseline was seen in 44 (88%) patients. Of these, 2 (4%), 11(22%), 29 (58%), and 2 (4%) patients

**TABLE 1.**

Grading of Objective Assessment Using Caliper Measurements	
Percentage Reduction in Sub mental Fat	Grading
0	No Improvement
0-10%	1
11-20%	2
21-30%	3
31-40%	4
41-50%	5
51-60%	6
61-70%	7
71-80%	8
81-90%	9
91-100%	10

**TABLE 2.**

Patients' Self-Assessment Scale	
Questions	Possible Responses
Since the start of the study, I can see my submental fat reducing	Strongly agree / Strongly disagree
How would you grade the pain & swelling insubmental area after deoxycholic injections?	0- No Pain /Swelling 1- Very Mild Pain/ Swelling 2- Mild Pain/ Swelling 3- Moderate Pain/ Swelling 4- Severe Pain/Swelling 5- Very Severe Pain/Swelling
How many days does the swelling & pain persist?	0 Days 0-3 Days 3-7 Days 7-14 Days 14-21 Days Longer than 21 days

had 1, 2, 3, and 4 treatment sessions, respectively. Improvement by 2 points from baseline was seen in 6 (12%) patients. Of these, 1(2%), 3 (6%), and 2 (4%) patients had 2, 3 and 4 treatment sessions, respectively (Table 4a).

#### Patient Reported SMF Rating Scale (PR-SMFRS)

Improvement by 1 point from baseline in 47 (94%) patients. Of these, 2 (4%), 13 (26%), 30 (60%), and 2 (4%) patients had 1, 2, 3, and 4 treatment sessions, respectively. Improvement by 2 points from baseline in 3 (6%) patients. Of these, 1(2%) and 2 (4%) patients had 3 and 4 treatment sessions, respectively (Table 4b). The improvement in objective grading is demonstrated in Table 5.

Overall, local swelling, lumpiness, and tenderness over the injection sites were reported for a mean 20.7, 23.4, and 11.4 days, respectively. Eighty percent of patients had mild to moderate tenderness post injections. Ten percent of patients witnessed

TABLE 3.

## Total Sessions Required in Respective Number of Patients

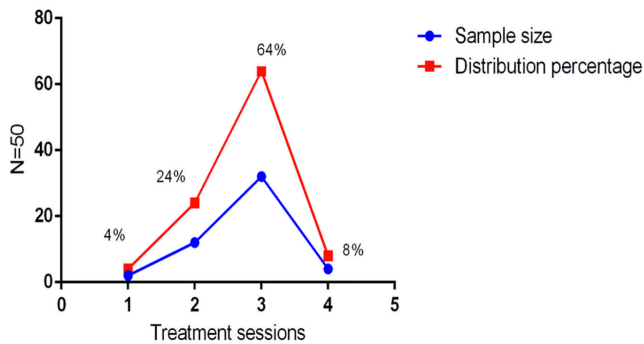


TABLE 4A.

## Clinician Reported SMF Rating Scale CR-SMFRS Score

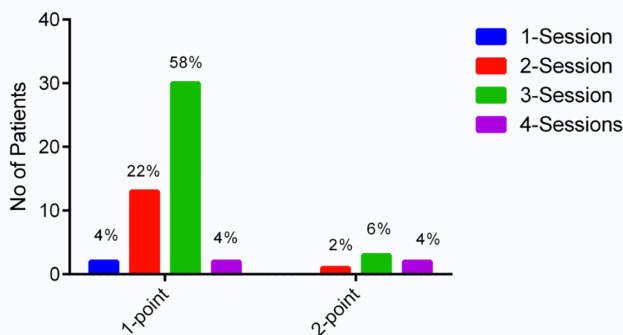


TABLE 4B.

## Patient Reported SMF Rating Scale (PR-SMFRS) Score

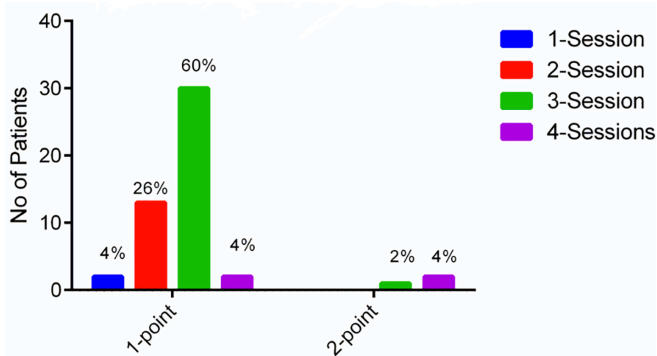
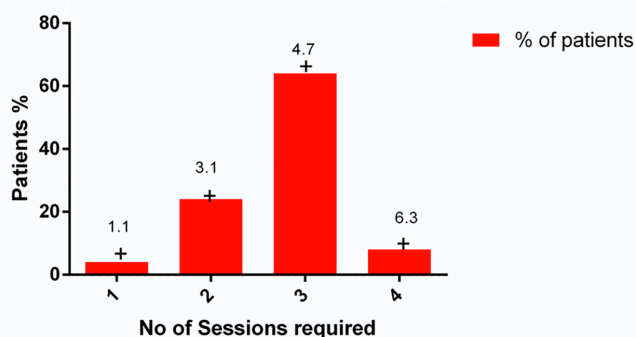


TABLE 5.

## Improvement in Objective grading of SMF



severe pain post injections. None of the patients had complications like marginal mandibular nerve paresthesia. Lumpiness was defined as a feeling of nodules between thumb and forefingers. Anecdotally, in patient review websites, lumpiness is always mentioned as a concern by most of the patients, which has not been reported by any clinical paper earlier.

## DISCUSSION

The focus of this study was to assess and evaluate the procedural and treatment outcomes after administration of DCA injections for treatment of accumulated submental fat, including durations of swelling, numbness, tenderness in Indian patients.

In the West, multiple clinical trials have been conducted to study the efficacy of DCA in the Caucasian population for clinical reduction of submental fat. This is the first study among patients of Indian ethnicity. Since FDA approved, ATX-101 (Kybella, United States), is not available in India, we used generic deoxycholic acid for treatment of submental fat reduction.

The shape and contour of the chin and neck play an important role in facial aesthetics. Due to a global aesthetic benchmark of well sculpted and chiseled face, excess fat within the submental area (double chin) can negatively affect facial aesthetics and body image.<sup>9</sup> Common treatments for submental contouring include invasive procedures such as surgical rejuvenation & targeted liposuction. Energy devices (lasers, radiofrequency, cryolipolysis, and ultrasound) may be used to improve submental skin laxity.<sup>10</sup>

Cryolipolysis has recently cleared FDA approval for use in the submental area (using the CoolMini™ applicator; Zeltiq Aesthetics, Inc., Pleasanton, CA) and may offer a less invasive alternative to surgery or liposuction for reduction of SMF.<sup>11</sup>

Injectable therapy with phosphatidylcholine/deoxycholate also offers a less invasive option for reduction of SMF, however, these products are produced by chemical compounding & are not regulated by the US Food and Drug Administration (FDA), Health Canada, or the CE commission.<sup>12</sup>

ATX-101 (DCA) injection is the first injectable drug approved by the FDA for improvement in the appearance of moderate to severe convexity or fullness associated with SMF.<sup>13</sup>

Since 2007, DCA has been the focus of an extensive preclinical and clinical development program, more than 1600 patients have been treated with it. One of the initial insights leading to development of DCA for reduction of SMF was generated by Rotunda and colleagues<sup>14</sup> who identified DCA as the active adipocytolytic ingredient in compounded phosphatidyl choline/sodium deoxycholate. Using cell viability and cell membrane lysis assays, significant cell death, membrane lysis, and disrupt-

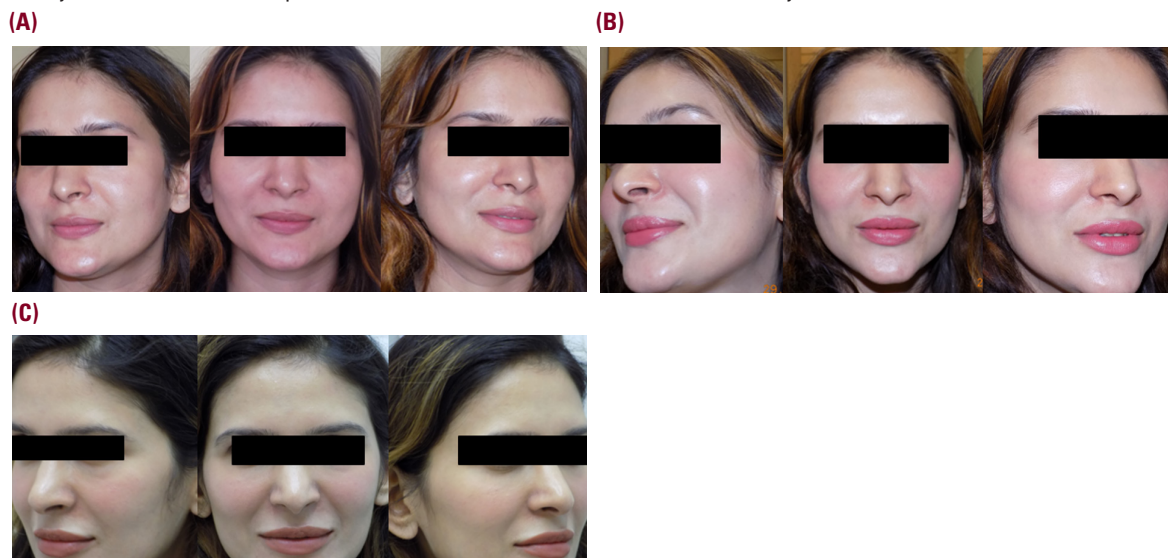
**FIGURE 5. (A)** Patient 1- Baseline images of a young female with moderate SMF who underwent 1 session of DCA injections **(B)** Results of patient 1, after 8 weeks of first session of DCA injections.



**FIGURE 6. (A)** Baseline images of patient 2, with extreme SMF, who underwent 3 sessions of SMF **(B)** Results of patient 2 after 8 weeks of first session of DCA injections. **(C)** Results of patient 2 after 8 weeks of second session of DCA injections. **(D)** Results of patient 2 after 8 weeks of third session of DCA injections.



**FIGURE 7. (A)** Baseline images of patient 3, with moderate SMF, who underwent 2 sessions of SMF **(B)** Results of patient 3 after 8 weeks of first session of DCA injections. **(C)** Results of patient 3 after 8 weeks of second session of DCA injections.



tion of fat architecture was observed in human keratinocyte cell cultures and porcine tissue samples treated with isolated sodium deoxycholate.<sup>15</sup>

As mentioned, endogenous DCA is a secondary bile acid that serves to emulsify and solubilize dietary fat, thereby aiding in its breakdown and absorption within the gastrointestinal tract. The initial mechanism of action proposed for DCA was that administration of exogenous DCA to subcutaneous fat (adipose tissue) within the submental area would lead to adipocyte lysis, the targeted destruction of fat cells, and ultimately a reduction in SMF.<sup>16</sup>

As DCA destroys adipocytes, administration of exogenous DCA would be expected to result in a reduction in the overall number of adipocytes within the treatment area (preplatysmal fat) and a durable treatment response over time. Support for this proposed mechanism of action was provided by a Phase I clinical study that evaluated the histological effect of ATX-101.<sup>17</sup>

In this open-label study, after ATX-101 injections, neutrophilic infiltration was observed on days 1 and 3, with lipid laden macrophages and mild septal inflammation of the adipocyte layer noted on day 7. By day 28, inflammation was nearly resolved while neovascularization, thickening of fibrous septae indicative of collagen production (neocollagenesis), and fat lobule atrophy were noted.<sup>13</sup> The effects of DCA were dose dependent & confined to the subcutaneous fat layer across all doses evaluated, with no changes observed in either the dermis or epidermis.<sup>18-20</sup>

Rotunda and colleagues<sup>14</sup> further demonstrated that when cultured cells exposed to high in vitro concentrations of DCA (42mM) die rapidly through membrane disruption. Because DCA destroys cells through a lytic mechanism, it seems unlikely that DCA would be cell type specific and that it should therefore also destroy non-fat tissue near the injection site.<sup>21</sup>

Various studies have previously shown that DCA may preferentially destroy fat because fat lacks specific proteins that bind DCA and neutralize its toxicity. Although the toxic effects of DCA on cultured cells may differ from effects on adipocytes in intact fat, results have suggested that adipocytes are not intrinsically more sensitive to DCA than other cells. DCA is endogenous, with an average adult human body containing approximately 0.5g (including DCA in circulation and biliary stores). Lastly, because of the rapid attenuation of DCA detergent activity by proteins and the transport of DCA to the endogenous bile acid pool, the activity of DCA is spatially limited, targeting the injected tissue, and hence, DCA is considered to be a biocompatible detergent with potential use as a therapeutic agent.<sup>14</sup>

Long-term follow-up of subjects from multiple Phase 2 and Phase 3 trials has demonstrated that the reduction in SMF and resulting improvement in the submental profile achieved with ATX-101 treatment is maintained in most subjects over time. Currently available data support a durable treatment response with maintenance of efficacy observed for up to 4 years after last treatment.<sup>22</sup>

Increased skin laxity is a potential concern when subcutaneous fat is removed from a targeted area such as the submentum. However, in the Phase 3 trials, despite the significant reduction in SMF, skin laxity was maintained or improved in the large majority of subjects treated with ATX-101 (as evaluated by the clinician using the Skin Laxity Rating Scale or Submental Skin Laxity Grade scale).<sup>23</sup> The absence of an observed worsening of skin laxity in most ATX-101 treated subjects suggests that skin retraction is occurring in the treatment area as fat is destroyed. It is apparent from clinical reports that a brisk inflammatory response, evident as erythema and edema, occurs after injection. Repeated inflammation may potentially lead to fibrosis, especially after multiple injections. Histological documentation of thickened fibrous septae and increased total collagen within the treatment area may partially explain this effect.<sup>24</sup> Overall, these results suggest that secondary or adjunctive procedures for skin tightening are not needed in appropriately indicated subjects after reduction of SMF with DCA.

Adverse effect like swelling occurs due to adipocytolysis, which leads to a mild inflammatory response and clearance of the lysed cellular material from the injection site. Lumpiness could be attributed due to induction of a mild inflammatory response after adipocytolysis, with macrophage recruitment and phagocytosis, through which cellular debris is cleared over time.<sup>23</sup> Plasma lipid levels show no meaningful increase over time after ATX-101 treatment.<sup>24</sup> DCA does not accumulate in adipose tissue, owing to rapid clearance facilitated by protein binding, which also attenuates the action of DCA in non-lipid-rich tissues such as muscle and bone.<sup>25</sup>

## CONCLUSION

This study showed that generic DCA is equally effective as Kybella for reduction of SMF. In Indian patients whose stubborn SMF persists very commonly, it presents a minimally invasive, tailorable alternative to liposuction and surgery for patients with moderate to severe submental fullness. As DCA destroys undesired fat within the treatment area, it leads to durable improvement in the appearance of the submental profile, and likely without the need for adjunctive treatments to address skin laxity.

## DISCLOSURE

The authors state no conflict of interests.

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Patients' Self-Assessment Scale

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