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Nandrolone decanoate safely combats catabolism in burned patients: A new potential indication after recall

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ABSTRACT

Introduction: The hyper-catabolic state is a devastating pathophysiological response to severe injury, infection or burns. Nandrolone decanoate (ND) is a potent anabolic steroid have many clinical indications, but not investigated in burn injuries yet.
Patients and methods: A prospective randomized control study included 40 burned patients who were treated in Burn unit from burn injuries ranged from 20 to 40%. Both groups are objectively assessed, clinically and laboratory during treatment period till full recovery from burns' injury. Recall assessment of the drug safety after many years is achieved.
Results: ND showed highly significant results supporting its use in combating catabolic insults in burns patient. Both clinical findings and laboratory findings are correlated and highly support the use of ND in burns as new effective and safe long-lasting indication.
Conclusion: This study results showed preservation of lean body mass and protein partition, as well as the near normal nitrogen balance in burn patients. Study proposes that nandrolone decanoate could be used in safe and effective way to combat hypercatabolic impact in burn injury.

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1. Introduction

Severe burn injury is usually followed by a profound hypermetabolic response which persists after injury up to 24 months. Burn patient experiences an ebb phase immediately after injury then passes-through flow phase. Ebb phase lasts two to three days and decreases the metabolic rate and cardiac output, then flow phase starts.

The "flow" phase is of a hyper-metabolic response due to the released hormones of stress; catecholamine, cortisol and glucagon [1].

The hyper-metabolic response is characterized by hyper-dynamic circulation with an increasing of body temperature, oxygen and glucose consumption, CO_2 production, glycogenolysis, proteolysis and lipolysis. The response begins on the 5th day post-injury and continues up to 9 months to one year. It causes erosion of lean body mass, muscle weakness, immuno-depression, poor wound healing and major tissue breakdown. Inevitable gluconeogenesis results in nitrogen loss and lethal depletion of essential protein stores [2].

Hence methods to achieve normal nitrogen balance in severely burnt patients are required, because of an inevitable

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muscle breakdown and loss of lean body mass in spite of the nutritional support [3].

This fact led to investigation of many of non-pharmacological supports and pharmacological approaches to modulate the metabolic response [4].

Among used strategies are the use of hormonal therapy and anabolic steroids in order to achieve positive nitrogen balance. The growth hormone has a potent anabolic effect and improves wound healing, nitrogen balance, and decreases weight loss in hyper-metabolic patients suffering burns injury [5]. However, growth hormone is so expensive and has aggressive diabetogenic effect, antibody reaction and might be associated with increased incidence of leukemia or other morbidities [5].

Anabolic steroid hormones (ASHs) are used in major trauma and immunocompromised patients to stimulate appetite, increase muscle anabolism, protein synthesis and production of growth hormone and insulin like-growth factor [6]. They also enhance the immune system by triggering macrophages' activity and cell mediated immunity. They could improve the overall sense of wellbeing and eliminate the sense of fatigue [7].

The anabolic effect of steroid hormones is attributed to the process of re-uptake of the intracellular amino acid. ASH is converted by the enzyme 5α – reductase to 5α – dihyderotestosterone. Dihyderotestosterone binds to cytosol androgen receptors, initiating series of events leading to growth, differentiation and synthesis of a variety of enzymes and other functional proteins [8].

Oxandrolone [9] is an oral anabolic steroid showed a beneficial effect in combating muscle protein catabolism in burns, cachectic, critically injured adults and children patients. However, oxandrolone is not widely available in many countries but nandrolone decanoate (ND) is widely available injections and used for variable indications [6,7,9].

Nandrolone decanoate (ND) is proved and used as potent available anabolic steroid with minimal androgenic side effects. It already used after a major surgery and severe trauma but not yet investigated in burn injury.

Since the use of the growth hormone and oxandrolone are not applicable in many situations and countries, this study investigates the use of nandrolone decanoate (ND) in burn patients.

2. Pharmacological drug description

Nandrolone decanoate (ND) is an injectable anabolic preparation of testosterone analogue. The pharmacologically active substance is nandrolone. The decanoate ester gives a three-week duration of action with 6 days half-life [10,11].

It affects the androgen receptors of the muscular tissue superior to testosterone as it binds better [10].

The liver is the pathway for the degradation of ND, where it is converted into inactive androsterone and etiocholanolone then both are conjugated then excreted into the urine [12,13] (Fig. 1).

3. Patients and methods

A prospective randomized control study included 40 burnt patients who were treated in Burn unit. Sample size was calculated based on independent variables. On admission, immediate care and resuscitation were done for all patients. Protein intake maintained adequately at 1.5–2 g/kg/day in addition to adequate micronutrients in both groups.

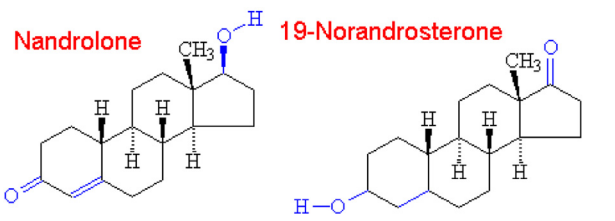

Fig. 1 – The steroid nandrolone and its metabolite 19-norandrosterone drawn by the Author based on the pharmacological information [10].

Study has been randomly divided by simple randomization into two arms (groups).

Group (A) twenty male patients received nandrolone decanoate injection in dose of 0.5 mg/kg/3 weeks, deep IM repeated till recovery. Surgical excision and grafting procedures were achieved in all patients.

Group (B) was the control one, in which twenty male patients suffering from burn injury not received nandrolone decanoate injection. Surgical excision and grafting procedures were achieved in all patients.

Caloric requirements for all patients were calculated. All patients were submitted to the same dietary regimens and the same equation for caloric requirement calculations using the same formula; **Energy** = basal metabolic rate (BMR) × activity factor × stress factor. BMR was calculated by Katch-McArdle formula [14] (BMR based on lean body weight) as the following: BMR = 370 + (21.6 × lean mass in kg). Physical activity is added by multiplying by an activity factor; for patients out of bed = 1.2. Stress factor in burn injury = 2.

Carbohydrates represented 50% of caloric needs gave 3.3 Kcl/g, while Fat represent 20% gave 9 Kcl/g and 30% protein gave 4 Kcl/g.

Both groups are objectively assessed clinically and by laboratory findings. Clinical evaluation included body weight measurement daily, lean body mass changes, incidence of infection, symptoms and signs of ND drug potential complications and progress of wound healing.

Lean body mass has been evaluated by body fat analyzer using bioelectric impedance or bioimpedance analysis (BIA) every two weeks.

Bioimpedance analysis is a noninvasive, simple and a commonly used approach for measurements of body composition and for assessment of clinical condition [15]. The hydration fraction of lean mass is assumed, then lean body mass (LBM) was calculated. Fat mass is derived by subtraction of lean body mass from body weight. Change in body weight of less than 1 kg was assessed by BIA to determine how much of the lean mass was.

Signs considered to diagnose infection were fever, redness, swelling, increased exudate, delayed healing, contact

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Table 1 – Summarizes demographics; ages, burn percentage and severities, causative agents, number of injections and number of anesthesia sessions for dressing, debridement and grafting.

	Group A							Group B						
No. of patients	Age/ year	Burn %	Deep comp. %	Causative agent	Body wt.	No. of Anas. “Dressing”	No. of Anas. “Grafting”	Age/ year	Burn %	Deep comp. %	Causative agent	Body wt.	No. of Anas. “Dressing”	No. of Anas.“Grafting”
1	20	25	15	Flame	70	1	1	35	25	15	Chemical	77	2	1
2	24		20	Flame	65	1	1	27	30	20	Flame	80	2	1
3	38	40	15	Flame	80	2	1	30	40	15	Flame	54	3	1
4	31	20	18	Chemical	76	1	1	35	20	18	Flame	68	2	1
5	30	30	20	Flame	67	2	1	24	30	20	Electrical	79	3	1
6	23	35	15	Flame	45	1	1	40	35	15	Flame	68	2	1
7	22	25	20	Chemical	80	1	1	35	25	20	Flame	69	2	1
8	22	40	20	Flame	60	2	1	28	40	20	Flame	71	4	2
9	21	40	18	Flame	58	2	1	29	40	18	Flame	68	2	1
10	33	25	18	Flame	76	1	1	28	25	18	Flame	66	2	1
11	22	35	15	Flame	71	1	1	29	35	15	Flame	87	2	1
12	30	30	20	Flame	63	2	1	31	30	20	Flame	75	3	1
13	36	30	25	Flame	78	2	1	20	30	25	Flame	76	2	1
14	24	35	25	Flame	64	2	1	30	35	25	Flame	94	3	1
15	40	40	15	Electrical	77	1	1	36	40	15	Flame	76	3	1
16	35	20	20	Chemical	84	1	1	24	20	20	Flame	84	2	1
17	28	20	15	Flame	74	1	1	30	20	15	Flame	87	3	1
18	20	30	20	Chemical	63	2	1	35	30	20	Chemical	67	3	1
19	28	25	15	Flame	71	1	1	28	25	15	Electrical	58	2	1
20	29	30	20	Flame	79	1	1	40	30	20	Chemical	87	3	2

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bleeding, odor, and abnormal granulation tissue. Wound healing stages (inflammation, proliferation and remolding) were monitored for proper timing, possible epithelization, percent of graft take and loss, incidence of infection, bleeding, abnormal wound findings in edges, floor or base.

Laboratory assessments done as basic values at time of admission then during follow up every two weeks till recovery. Laboratory assessments were monitored and evaluated to study both efficacy and the possible side effects of the drug. Laboratory assessments included CBC, fasting and post prandial blood sugar, Total proteins and albumin, liver and kidney functions, hormonal profile for testosterone level and gonadotrophin hormones (GnRh-LH-FSH bioassay). Laboratory assessments also included 24 h urinary creatinine, net Nitrogen loss, total proteins loss and Serum albumin loss. 24 h urinary creatinine is a reliable muscle breakdown indicator with an average normal range 0.13–0.22 m moll/kg/day. It was measured in all patients. Net nitrogen loss as another indicator for protein catabolism, was monitored in all patients. Normally protein execration is less than 0.15 g/24 h. Negative nitrogen balance was calculated by subtraction of nitrogen loss from nitrogen intake.

The inclusive criteria for patient's selection were, patients with 20–40% TBSA with a deep component of at least 15%, aged from 20 to 40 years old. As 20% burn patients are less vulnerable to huge catabolic impact and >40% burn patients are highly potential for the benefits from the drug ND, however 40% is the upper limitation because up to our Knowledge this study is the first article that reports ND potentiality as an anabolic support in burns. Inclusion criteria have been selected to avoid hormonal effect on children as well as on male patients above 40 years to avoid any possible androgenic effects on prostate. They were only males to avoid androgenic side effects on females.

4. Exclusion criteria

Females to avoid androgenic side effects. Patients have smoke inhalation injury, associated trauma to avoid multifactorial stress response. Any patients don't tolerate drug side effects in cases associated with medical problems as hormonal disorders, mental deficiency, patients on cytotoxic therapy, having polycythemia, cardiac, renal, hepatic, thyroid dysfunction, or diabetes mellitus were excluded. Infants, children and adolescences were excluded to avoid growth affection. Patients above 40 years excluded to avoid hormonal effect on the prostate.

Data have been collected as continuous measurements, ordinal and categorical. Data described by figures, plots and histograms. Statistics are analyzed by Minitab 19 program and the Chi square test was used in analysis.

The study was carried from September 2004 till august 2006. 13 years later, in 2019, patients were recalled many times during the treatment of post burn complications, and they have been reviewed for any incidence of drug complication. Informed consent was obtained from each patient. Institutional ethical approval is obtained for the study.

5. Results

In group 1, causative agent was thermal in 15 patients (75%), while 4 patients (20%) injured due to chemical agent and 1 patient (5%) has electrical flash injury. In group 2, causative agent was thermal in 15 patients (75 %), while 3 patients (15%) were injured by chemical agent and 2 patients (10%) were accidently exposed to electrical flash injury.

Table 1 summarizes ages, burn's percent, causative agents, number of injections and number of anesthesia sessions for dressing, debridement and grafting.

All over the period of the study, the average period for patient recovery from burn injury was about 5 weeks in the study group and 10 weeks in control group. So, the time to discharge and bed turnover were decreased by 50% in study group. Incidence of infection has minimized in study group to 10% of cases, while it happened in 25% of control group.

5.1. *Results of clinical findings*

Daily follow up of patients' body weight since admission till complete recovery revealed marked weight loss in group B (control group), while less body weight affection in group A (study group). Total weight loss (Total summation of losses for all patients), in group "A" was −29 kg (−2%) while in group B was −134 kg about (−9%)

Lean body mass represented about 70–80% of body weight on admission for all patients in both groups. LBM has been markedly decreased in control group "B" when patients were not injected with the anabolic hormone ND.

Average lean body mass loss (total summation of losses for all patients) was −21 kg, about (1.94 %) in study group, compared to 119.2 kg, about (−10.5%) in control group "B".

In study group the total sessions of anesthesia needed for dressing and surgical excision (for all patients) were 28 and for grafting were 20. While in control group the total sessions for

Table 2 – Summation of clinical evaluation.

Mean clinical evaluations	Group A (N = 20)	Group B (N = 20)
Average body weight loss	−29 kg (−2 %)	−134 kg (−9 %)
Average lean body mass loss	−24.2 kg (2.2 %)	−119.2 kg (−10.5%)
Average hospitalization period	5 weeks	10 weeks
Incidence of infection	2 cases (10 %)	5 cases (25 %)
Total sessions of anasesthia for dressing	28	50
Total sessions of anasesthia for grafting	22	22

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dressing and surgical excision were 50, and for grafting were 22.

Three cases of study group (15%) complained of prolonged morning erection. One case (5% of group A) complained of severe back pain and was controlled by non-opiate analgesia. Otherwise, there were not signs or symptoms reported for short term monitoring of ND complication. Table 2 and Figs. 2–7 summarize the clinical findings.

5.2. *Laboratory findings*

Normally the 24 h urinary creatinine is a reliable muscle breakdown indicator with an average normal range 0.13–0.22 m moll/kg/day.

In the study group "17" cases (representing 85%) were presented by negative nitrogen balance but didn't reach a double fold negativity. Only 2 cases reached double fold negative nitrogen loss. Although one case has gained a positive nitrogen balance. While in control group the best result was in 2 cases when negative nitrogen balance was double fold negativity. But the rest of cases (80%) of control group, were at least more than double to triple or 4 folds negative values.

Serum proteins changes were obvious in negative in control group where all cases showed decrease in total serum proteins (below 6 g/dl). Patients in this group had average lower values equal to 4.5 g/dl. While most of values in patients of study group (80%) showed a normal range of serum protein (6–8 g/dl) and the remaining 20% were just below normal 5–5.5 g/dl. Serum albumin findings were proportional to total protein negative results in both groups. Those negative Albumin findings mainly noticed at 3rd week while Serum pre-albumin negative findings have been noticed earlier.

Fasting blood sugar findings revealed slight elevation on the 3rd day of ND injection in study group only but returned to its normal level couple of days to week later.

Transient elevation of liver enzymes and lipid profile disorder were also noted in 75% of study group. Values showed double folding elevation of SGOT enzyme levels in all (100%) of study group. SGPT showed double folds elevation in (50%) of ND injected cases only. However, the elevations in liver enzymes were transient and improved within days leaving no significant impairment.

Releasing hormones including GnRh-LH-FSH bioassay didn't change or affect by feedback inhibition mechanism. Testosterone hormone was not changed in all patients of study group after 2 weeks of injection. It has found just below its normal level (10–15 nm/l) in 4 cases. The lowermost value reported is 7 nm/l in 3 case (15% of study group). Tables 3 and 4 and Figs. 8–10 summarize the laboratory findings.

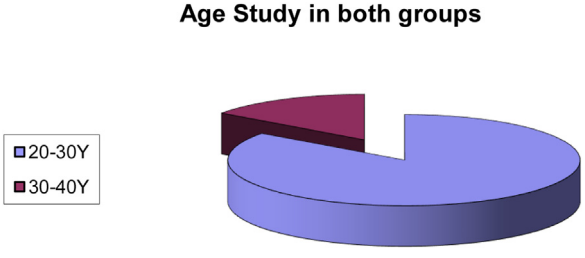
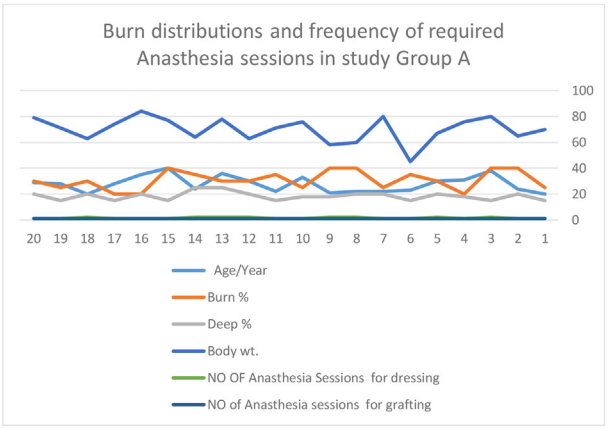
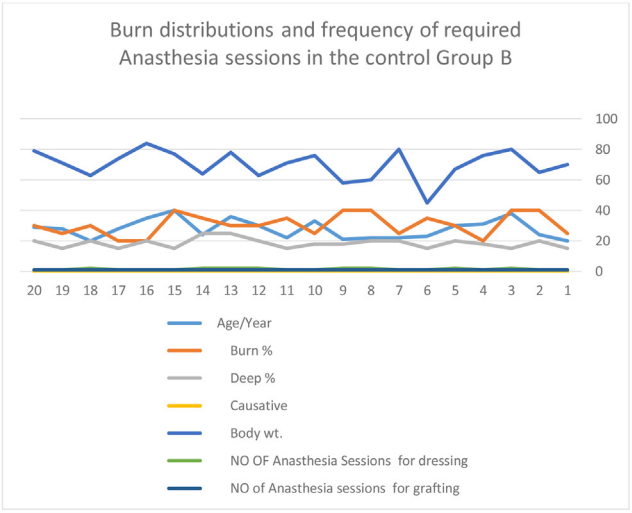


Fig. 2 – It shows median age in both groups.



A: Burn distributions and frequency of required Anasthesia sessions in study Group A



B: Burn distributions and frequency of required Anasthesia sessions in study Group

Fig. 3 – (A) Burn distributions and frequency of required anasthesia sessions in study group A. (B) Burn distributions and frequency of required anasthesia sessions in study group.

The above results showed efficacy and safety of ND drug in combating the catabolic effect of major burn trauma.

Long term follow up is checked by the author upon patient recall for any complication potentiality 13 years later. The response for recall in study group was 75% only while the remaining 5 cases were dropped out.

The checked 15 cases (75%) of the study showed no signs or symptoms of ND complications. Check has included any complications in hepatic, genitourinary, CNS, gastrointestinal, hematologic, breast, larynx, hair, skin, skeletal, fluid and electrolytes or metabolic/endocrine systems.

This study showed clinical correlation with laboratory findings that indicate the potential efficacy of ND in combating the catabolic insult in burnt patients. These results showed significant p value <0.001 regards the anabolic effect of ND

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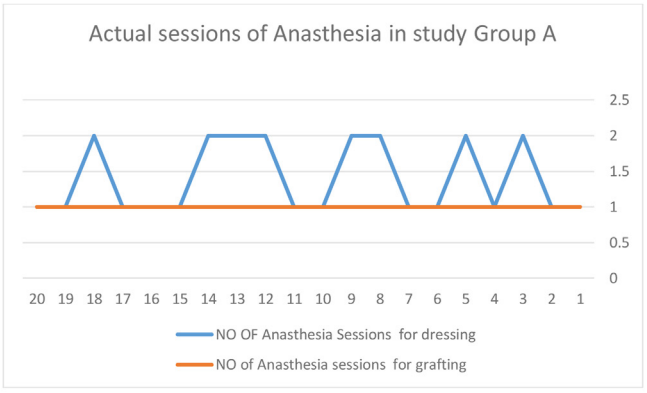
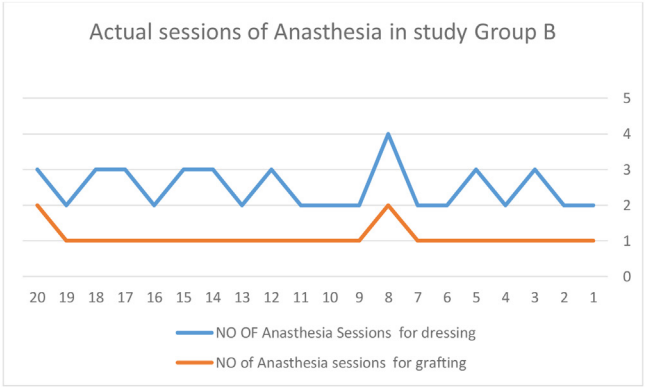
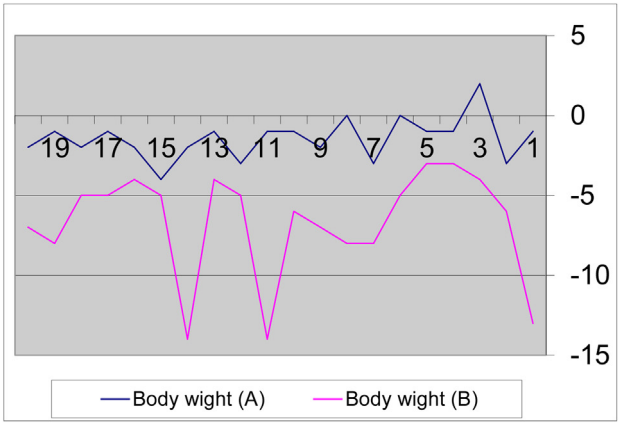


A: Actual sessions of Anasthesia in study Group A

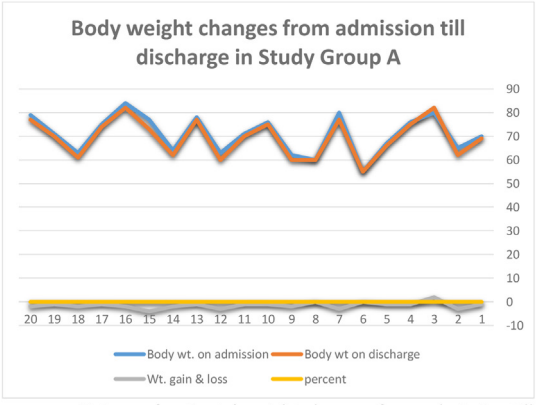


B: Actual sessions of Anasthesia in study Group B.

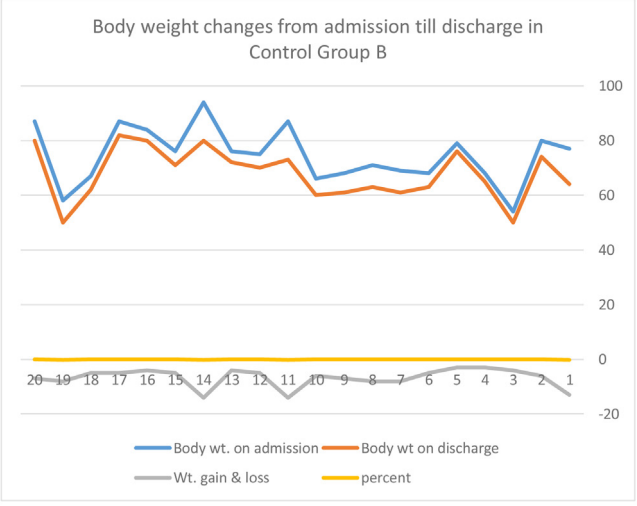
Fig. 4 – (A) Actual sessions of anasthesia in study group A. (B) Actual sessions of anasthesia in study group B.



A: Loss of patients' weight in Kilograms



B: Loss of patients' weight changes from admission till discharge in Study Group A



C: Loss of patients' weight changes from admission till discharge in Control Group B

Fig. 5 – (A) Loss of patients' weight in kilograms. (B) Loss of patients' weight changes from admission till discharge in study group A. (C) Loss of patients' weight changes from admission till discharge in control group B.

throughout its abilities to restore the body weight, lean body mass and nitrogen balance.

6. Discussion

Major percent of burn mortality and morbidity is due to catabolic insult of the injury. Catabolic response is devastating to burn victims and continues for one year after the injury [1]. Catabolic effect impacts wound healing, predisposes for infection, erodes lean body mass, impedes rehabilitation, and delays reintegration of burn survivors into society [2].

The problem is how to overcome the severe catabolic response in severely burnt patients. This is attributed to inevitable muscle breakdown and loss of lean body mass with subsequent negative nitrogen balance. Nitrogen balance could frequently happen in spite of nutritional support either by Enteral or Parenteral route [1–3].

So, investigating nutritional support [3] and other strategies [4–8] to prevent catabolism and to achieve positive nitrogen balance have become a major focus in care of severely burned patient.

Non-pharmacologic strategy includes early excision and grafting, proper treatment of sepsis, environmental thermal neutrality to keep room temperature in range of (31.5 ± 0.7 °C) [3,4]. It also includes continuous enteral feeding with high carbohydrate, high protein diet and micronutrients such as glutamine, arginine, and organic compounds (vitamins) [12]. Strategy of early implementation of patients in resistive exercise programs is also important [8].

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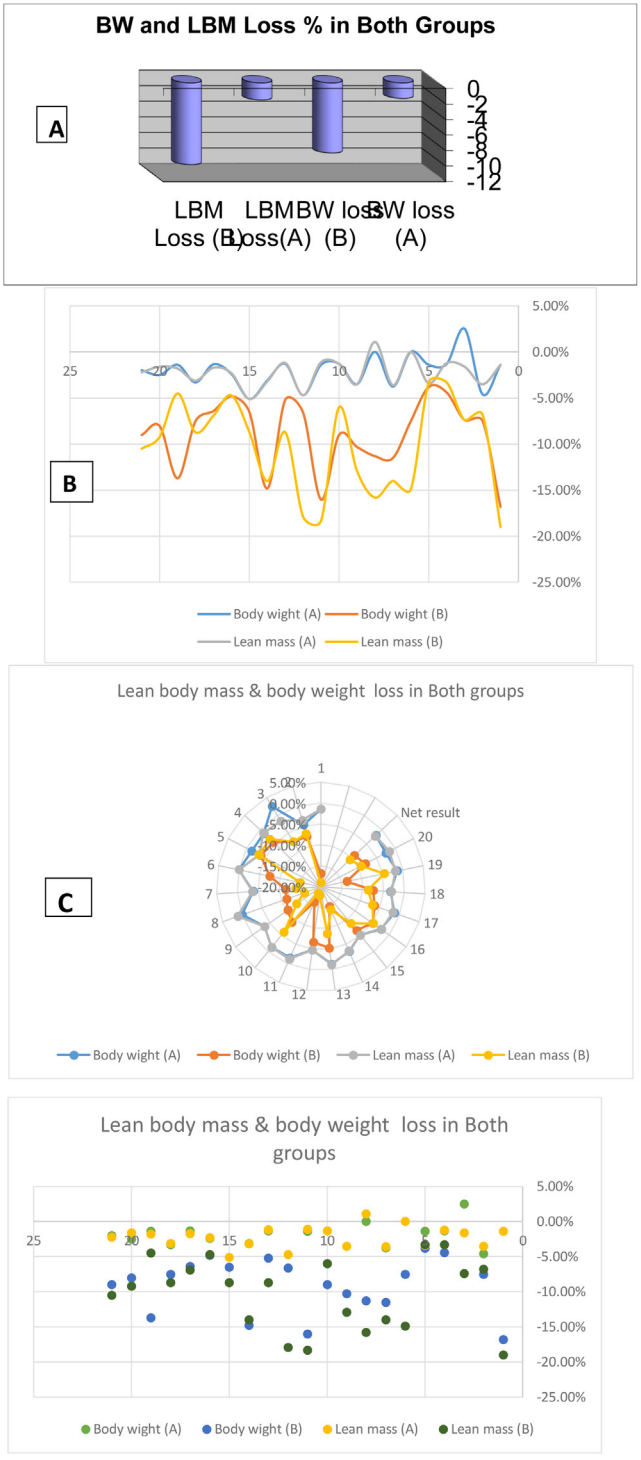

B: Lean body mass & body weight loss in both groups presented by dot plot chart

Fig. 6 – A, B, C: Lean body mass & body weight loss in both groups presented by graphs. (B) Lean body mass & body weight loss in both groups presented by dot plot chart.

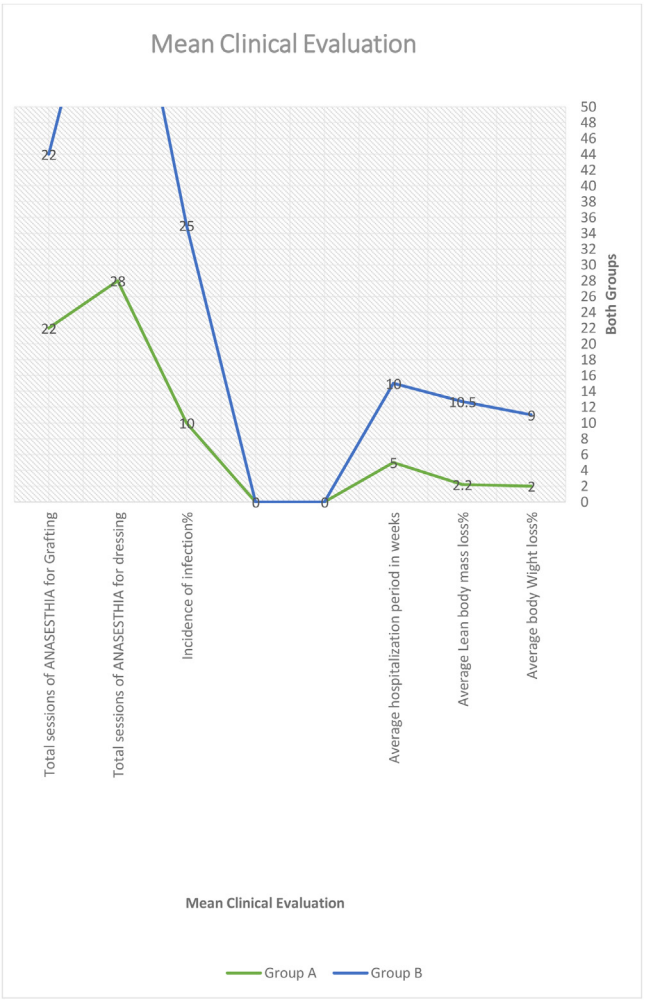

Fig. 7 – Mean clinical evaluation in both groups.

Many pharmacologic modulators [9–13] and anticatabolic strategies [16–22] are tried with variable success in many studies conducted to correct the post burn hyper-metabolic response. They investigated the use of low-dose insulin infusion, beta blocker propranolol, the recombinant human growth hormone and oral oxandrolone in combating the catabolism insult in burns [8,9,10,12].

In this study nandrolone decanoate (ND) injected in a dose of 0.5 mg/kg/3 weeks, deep IM showed highly significant results that supporting its use in combating catabolic insults in burns patient. Both clinical and laboratory findings are correlated and highly propose the use of ND in burns as new effective and safe indication.

ND received FDA approval in 1983 [16]. Many of previous studies have proved that; the anabolic-androgenic steroid ND is indicated therapy in pathological conditions presented by a negative nitrogen balance. It is also indicated for the treatment of osteoporosis and anemia [23,24]. But this study proposes for the first time a new indication for ND in burn injuries.

This study also represents second stage [21] assessment of the safety of ND administration in burn injuries during patients follow up for the treatment of post burns complications.

The low ND androgenicity is confirmed in clinical uses [24–27]. This comes with our study observations of its use in burns without reported symptoms or signs of high

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Table 3 – Summation of laboratory evaluation results.

Mean laboratory evaluations	Group A (N = 20)	Group B (N = 20)
Increased BL. sugar alterations	3 cases (15%)	3 cases (15%)
Double net nitrogen loss g/d	2 cases (10%)	20 cases (100%)
Increased 24 h urinary creatinine	4 cases (20%)	20 cases (100%)
Polythythemic changes	1 case (5%)	0%
Total proteins loss	4 cases (20%)	20 cases (100%)
Serum albumin loss	2 cases (10%)	18 cases (90)
Transient renal functions impairment.	0%	0%
Transient mild liver changes	15 cases (75%)	0%
Progressive liver dysfunction	0%	0%
Transient testosterone level changes	4 cases (20%)	Unchanged
Releasing hormones	Unchanged	Unchanged

Table 4 – Severity of nitrogen balance and incidences in both groups.

Net nitrogen balance	Group A	Group B
+ve nitrogen balance	1 case (5%)	0
–ve less than double folds	17 cases 85%	0
–ve double folds	2 cases 10%	2 cases 10%
–ve triple folds	0	12 cases 60%
–ve 4 folds	0	6 cases 30%

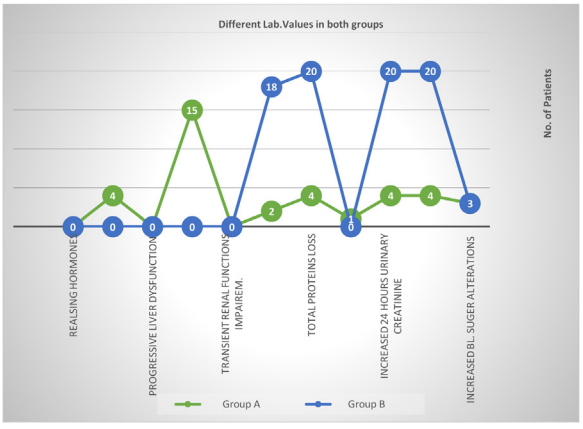

Fig. 8 – Different 6 laboratory values findings in both groups.

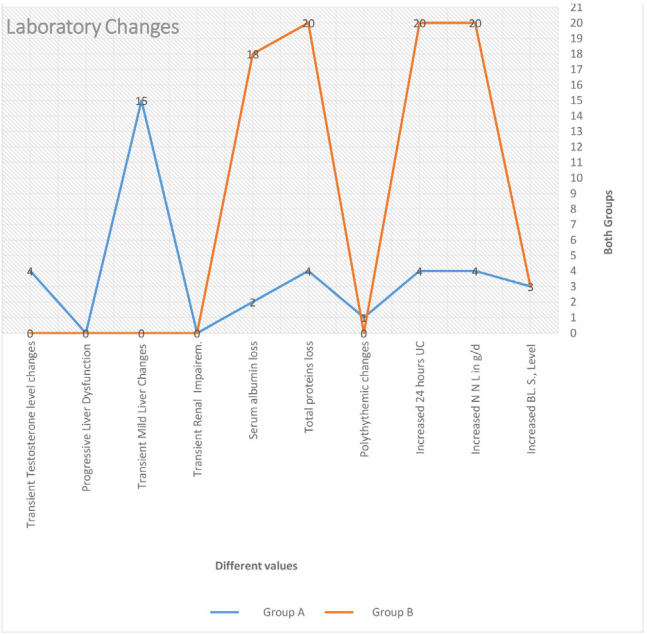

Fig. 9 – Comparisons of different 10 laboratory values in both groups.

androgenicity. The required dose in this study is minimal, although it's significantly effective.

This study results showed preservation of lean body mass and protein partition, as well as the near normal nitrogen balance in burn patients. These findings agree with many of other studies conducted on ND AS STRONG anabolic support for many other pathological conditions [24–31].

Schroeder et al. [32] conducted study which showed increase in the lean body mass and body weight after ND Adminstration for the treatment of wasting and cachexia in HIV infected individuals. Other studies reported ND as an effective treatment in chronic obstructive pulmonary disease [33] and renal failure [34] but not yet investigated in burn. So, this is the first sever tudy reports a positive anabolic support of ND in burnt patients with 20–40% TBSA burn injury.

HGH when compared to ND, GH has a major anti-insulin effect led to hyperglycemia, immune reaction, and may increase the leukemia incidence [35,36]. GH in those study is associated with increased mortality and morbidity. In contrary ND has neither a diabetogenic nor post injection reaction. It doesn't alter the WBCs count. In this study ND showed positive effect by shortening the length of hospital stay and decreasing of the morbidity and mortality rates. The time to discharge and bed turnover in this study decreased by 50% in study group. The average hospital stay is about 5 weeks in a study group A' while doubled to be 10 weeks in control group.

Incidence of infection also has minimized in study group to 10% of study. Also, frequency of anesthesia needed either for dressing or grafting have been significantly declined after use of ND. This may could be highly attributed to sparing of protein partition and relatively improvement of plasma albumin and subsequent better healing.

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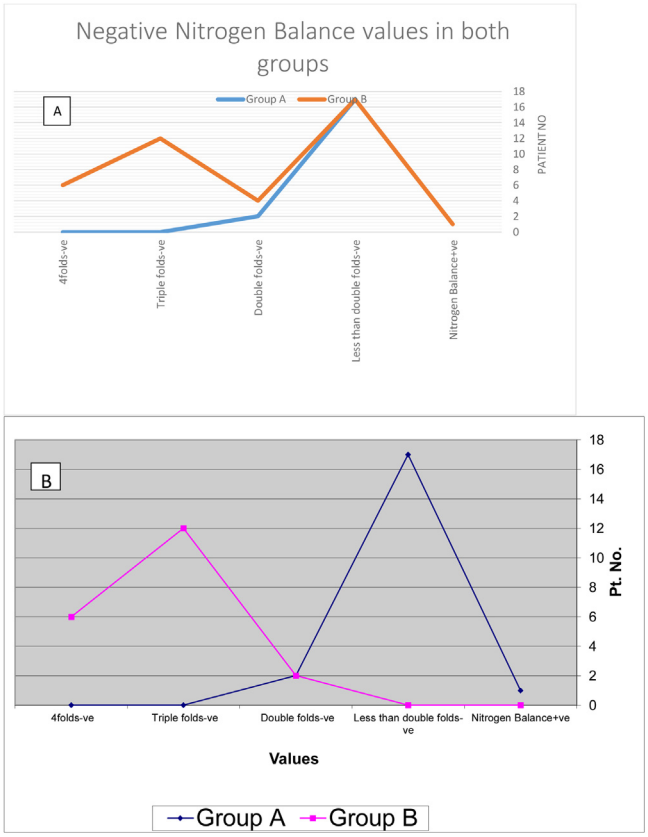

Fig. 10 – Comparisons of net negative nitrogen balance values in both groups.

Oxandrolone was fully used with success in restoration of body weight and lean body mass after burn injury with maintenance after discontinuation of the drug [37,38].

Mendenhall et al. in 1993 [39] reported the use of oxandrolone in severe burns. His study showed its less androgenic effect and less liver impact. This totally comes with our findings regards ND. When there was a little transient change in liver functions of burn patients after ND injections. Although total cholesterol and bilirubin were not change in both groups of this study, without any clinical manifestation of liver affection. In this study ND does not show GIT upset, gastric irritation, vomiting.

Another study, by Duncombe et al. [40] and associates, examined the effect of the treatment with ND in three different doses along period of 24 weeks (50 mg, 100 mg or 150 mg by IM once/twice weeks or placebo). Study evaluated; the prevention; delay of weight loss and drug effect on quality of life in male patients with HIV. Study concluded that ND increases patients' body weight in comparison with placebo or testosterone. All mentioned results in Duncombe et al. [40] correlate with this study regarding the outcome improvement of lean body mass and anti-catabolic effects following burn trauma.

A contraceptive investigation found 6 of 9 men received 200 mg of testosterone enanthate/week became a zoo-spermic and their gonadotropin levels suppressed after 16–20 weeks [41]. ND, unlike testosterone, does not undergo conversion to DHT, so there is no room for such comparison. In this study the releasing hormones including GnRh-LH-FSH bioassay didn't change or affected by feedback inhibition mechanism. New indication of ND could be emerged as one of the anabolic agents used in burn care [42,43].

No any reported complications of the treatment other than post burn scars and contractures in the study group, even with patient recall after 13 years ago.

7. Conclusion

Previous clinical studies have shown ND has been effective in treating of many medical diseases. But this study proposes that, nandrolone decanoate can be used with safety and efficacy to combat hyper-catabolic impact in burn injury.

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Conflict of interest statement

Authors have no conflict of interest.

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