Resisted Exercise and Insulin Resistance Post Burn

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Chapter 1

Introduction

A burn injury represents the fourth most common type of trauma globally, though it is associated with the most devastating consequences. Severe burn injuries, encompassing 20% of the total body surface area (TBSA) in adults, present a unique challenge compared with other forms of trauma given the magnitude and persistence of systemic deregulation. Indeed, an extensive inflammatory response develops immediately following a severe burn to promote wound healing. This period, known as the "ebb" phase, is comparable with a fight-or-flight response and lasts for the first 72–96 h post injury **(Lippi et al, 2010).**

Despite a considerable decrease in the incidence of burns in the developed world, they remain one of the commonest forms of injury and account for a significant proportion of trauma cases in hospital emergencies worldwide. In the United States, up to 1.2 million people experience burn injuries each year, while there are 2 million fires reported. Most cases (75%) are mild and are treated on an out-patient basis. Severe burns, however, continue to cause devastating morbidity and significant mortality.

Emphasis in research on burn pathophysiology has shifted considerably over the last few decades. Hypovolemic shock, followed by wound infection, accounted for the majority of deaths from burns in the early part of this period. Consequently,

they were the main areas of burns research in the period leading up to the 1980s. Wound treatment, healing and scar problems were also prominent areas in the published literature at that time. The direct outcome of this earlier work was that various strategies to prevent hypovolemic shock were developed and incorporated into clinical practice. These involved phased fluid/colloid replacement regimens **(P.I. Jewo et al, 2015)**.

Following an initial sympathetic-mediated shock of a severe injury, the ebb phase is accompanied by a depression in the metabolic rate and reduced tissue perfusion. Thereafter, the systemic inflammatory response becomes uncontrolled and is further exacerbated by tissue and organ dysfunction, which drives the patient into a hyper metabolic state—a "flow" phase, which persists after wound healing and may last up to 36mo after initial injury (**Culnan et al, 2018**) .

Hyper metabolism is a classic yet highly complex and multifactorial challenge to overcome in patients with severe burns. The chronic increase of circulating stress mediators, such as catecholamines and glucocorticoids, drives a multiorgan hyper catabolic response resulting in lipolysis, glycogenolysis, and proteolysis leading to an insulin-resistant and lipotoxic state, which only worsens the hyper metabolic response in a futile cycle **(Knuth et al, 2021).**

If hyper metabolism cannot be curbed, the patient may succumb to sepsis and/or multi organ failure. Targeting skeletal muscle is central to mitigating hyper metabolism, as proteins and amino acids serve as a major fuel source following a severe burn. Mechanistically, this results from a substantial increase in muscle protein breakdown that grossly exceeds the rate of muscle protein synthesis **(Hollenberg et al, 2004)**.

The enormous energy demand, measured by resting energy expenditure, is a typical finding in burn patients, with the increase in metabolism (hypermetabolism) dependent on the size of burn. In patients with a TBSA of less than 10%, resting energy expenditure remains at physiological levels, but for TBSA in excess of 40%, this rate is twice as high during acute admission. Having reached the maximum value, the resting metabolic rate in severely burned patients gradually declines, amounting to 150%, 140%, 120% and 110% of baseline at the time of burn wound healing, 6, 9 and 12 months after thermal injury, respectively **(Wojciech Żwierełło et al, 2023)**.

Moreover, burn-induced muscle catabolism places a significant burden on the recovery process, as a 10%–30% loss impairs immune responses and delays wound healing, thereby increasing the risk of infection, and a 40% loss becomes fatal. Despite a mountainous effort to prevent muscle catabolism and wasting, we have yet to provide a safe and effective solution. Therefore, a better understanding of the pathophysiology and consequences of burn-induced skeletal muscle wasting is pivotal to alleviating hyper metabolism and reducing morbidity and mortality patients with severe burns **(Rowan et al, 2015).**

Hence, extensive burn injury produce clinical syndromes characterized in part by “insulin resistance, it is unclear if these insulin resistant states are identical. To test if the maximal biological effectiveness of insulin is altered in burned patients **(Cree et al, 2007)**.

The aim of our study is to assess the effect of resisted exercise on insulin resistance provide an overview of all procedures needed and current knowledge with

regard to HOMA IR test to evaluate the progression of insulin resistance post burn cases **(Hwang et al, 2016)**.

Severe burns cause a profound pathophysiological stress response and a radically increased metabolic rate that can persist for years after injury. Trauma and sepsis also result in hyper metabolism, although to a much lesser degree and for a significantly shorter duration .Immediately after severe injury, patients have a period of decreased metabolism and reduced tissue perfusion known as the “ebb” phase. Soon after, they enter the phase of hyper metabolic rates and hyper dynamic circulation, referred to as the “flow” state. This hyper metabolic state reflects an increase in whole-body oxygen consumption, and a patient is usually considered hyper metabolic when resting energy expenditure (REE) is more than 10% above normal. In the acute post burn injury phase, patients with a burn that covers greater than 40% of total body surface area (TBSA) have a REE between 40 and 100% above normal **(Audra Clark et al,2017)**.

Statement of the problem

Does resisted exercise affect insulin resistance post burn?

Purpose of the study

This study aims to

The main objective of the present study is to assess the effect of the resisted exercise on insulin resistance post burn.

Significance of the study:

1- Insulin resistance is a major problem post-burn which may led to serious complications.

2- The lack of knowledge and information in the published studies about the effect of resisted exercise on improving insulin resistance post-burn.

3- This study will be carried out to investigate the effectiveness of resisted exercise in improving insulin resistance in post-burned patients.

The hyper metabolic response to injury is characterized by increased blood pressure and heart rate, peripheral insulin resistance, and increased protein and lipid catabolism, which lead to increased resting energy expenditure, increased body temperature, total body protein loss, muscle wasting, and stimulated synthesis of acute-phase proteins. These responses occur in all trauma, surgical, or critically ill patients, but the magnitude with which they occur and their duration are particularly severe and sustained for burn patients **(Gerd G Gauglitz et al, 2022)**.

Delimitation

This study will be delimited in the following aspects:

Subjects

Sixty eight patients with insulin resistance post burn will participate in this study, they will be selected from government hospitals (general and insurance).

Will be randomly divided into two equal groups (group A, group B).

Their ages range from 18-35 years.

Equipment and tools:

Measurement:

Insulin resistance homeostasis model assessment [HOMA IR test].

Null hypothesis

There will be no effect for resisted exercise on insulin resistance post burn.

Basic assumption

It will be assumed that:

- All patients will be evaluated in the same way.
- All patients will be cooperative and follow instructions during the assessment procedures.
- The results obtained from this study will be of value in the physical therapy field.

Definition of terms:

The following terms will be defined and explained for a clear understanding of the terminology used in this study:

Insulin resistance

Insulin resistance is defined as the decreased tissue response to insulin-mediated cellular actions and is the inverse of insulin sensitivity. The term "insulin resistance," as generally applied, refers to whole-body reduced glucose uptake in response to physiological insulin levels and its consequent effects on glucose and insulin metabolism. Euglycemic hyperinsulinemic clamp studies have shown that insulin resistance is determined primarily by the response of skeletal muscle, with over 75% of infused glucose taken up by muscle and only 2–3% by adipose tissue **(Claire**

Levy-Marchal et al, 2010).

Chapter II

Literature review

Burns affect nearly 300 million patients annually worldwide, with an associated substantial mortality. In the USA half a million Americans per year get burned, with approximately 40,000 requiring hospitalization. Thermal injuries induce systemic bimolecular changes with profound physiological alterations, such as increased muscle and bone catabolism, hepatic steatosis, higher susceptibility to infections, multiple organ dysfunction, insulin resistance and sepsis. The hyper metabolic response, a profound increase in metabolic demand reflected by an elevated resting energy expenditure (REE), is the primary contributor to aforementioned complications, and can persist for up to 3 years after a severe burn.

The metabolic changes following burns are not dissimilar to other traumas but very different in terms of their extent and persistence; characterized primarily by an 'ebb' phase within 48 h where metabolism, cardiac output and oxygen consumption are all decreased. This is typically followed by a 'flow' phase at around 120 h post-burn, where these variables gradually increase and plateau. For instance, the acute response allows vital organs to conserve energy, and mild to moderate hyperglycemia provides fuel for the brain and immune system after trauma. Burn

injuries, however, stand out in their intensity and duration. The chronic persistence of the hyper metabolic response, which appears to be driven by catecholamine, stress hormones, and pro-inflammatory cytokines, far surpasses the ability of the patient to respond, and physiological exhaustion ensues. Augmented rates of glycolysis, lipolysis and proteolysis induce a loss of lean and total body mass which subsequently causes immune dysfunction, decreased wound healing and severe infections. Left untreated, the amalgamation of these systemic injuries leads to organ dysfunction, sepsis and death **(Christopher Auger et al, 2017)**.

Insulin resistance can be linked to diabetes, hypertension, dyslipidemia, cardiovascular disease and other abnormalities. These abnormalities constitute the insulin resistance syndrome. Because resistance usually develops long before these diseases appear, identifying and treating insulin-resistant patients has potentially great preventive value. Insulin resistance should be suspected in patients with a history of diabetes in first-degree relatives; patients with a personal history of gestational diabetes, polycystic ovary syndrome or impaired glucose tolerance; and obese patients, particularly those with abdominal obesity. Present treatment consists of sensible lifestyle changes, including weight loss to attain healthy body weight, 30 minutes of accumulated moderate-intensity physical activity per day and increased dietary fiber intake. Pharmacotherapy is not currently recommended for patients with isolated insulin resistance (G Rao, 2001).

The hypermetabolic response to severe burn trauma is associated with increased energy expenditure and energy substrate release from protein and fat stores. After burn, protein is catabolized, which leads to a loss of lean body mass and muscle wasting **(Hart, David W., et al, 2000)**.

Clinical features of Insulin resistance

Severe insulin resistance syndromes show variable metabolic traits and diverse clinical manifestations. Along with skin tags, acanthosis nigricans, a velvety hyperpigmented thickening of the skin, is an early sign and a common cutaneous manifestation of severe insulin resistance. Among women, ovarian dysfunction and hyperandrogenism are also common features. Hirsutism, polycystic ovaries, menstrual irregularities, or oligomenorrhea usually constitute the primary clinical manifestation in affected females. Hyperinsulinemia, in particular the synergy of insulin and gonadotropins, is implicated in the pathogenesis of polycystic ovary syndrome and ovarian hyperandrogenism. Other clinical features observed in some of the severe insulin resistance syndromes include dyslipidemia, namely hypertriglyceridemia; nonalcoholic fatty liver disease; adipose tissue loss; abnormal adipose topography; abnormal musculature; acromegaloid features; and other growth disorders **(Angeliki M. Angelidi et al, 2021)**.

Conditions Associated with Insulin Resistance:

Though the development of type 2 diabetes is the most obvious and direct consequence of insulin resistance and β (beta)-cell stress that proceeds unchecked, there are myriad other associations that healthcare providers should be aware of and screen for as indicated. Like insulin resistance, many of these conditions are more commonly seen in adulthood, but can certainly affect the pediatric population. Many of these disease associations and syndromes are not entirely surprising, given the multi organ effects of insulin even beyond glucose homeostatic mechanisms. Resistance to insulin-mediated control of circulating fatty acids may predispose to worsening dyslipidemia, a well-known risk factor for cardiovascular disease. Insulin, in addition, increases androgen synthesis and simultaneously decreases liver production of sex hormone-binding globulin, thus providing a mechanism for the reproductive disruption seen in PCOS. Consequently, insulin resistance itself is

associated with many well-known diseases and syndromes that incorporate other organ and system effects of insulin **(Melinda E. Chen et al, 2019)**.

Model assessments of insulin resistance:

Homeostasis Assessment Model (HOMA). The Homeostasis Assessment Model is a mathematical model which allows values for insulin sensitivity and β-cell function (expressed as a percentage of normal) to be obtained if simultaneous fasting plasma glucose and fasting insulin/C-peptide concentrations are known. Since insulin secretion is pulsatile, the optimal sample should be the mean of three results at 5-min intervals (0, 5, and 10-min samples). However, many researchers have used single basal samples for epidemiological studies. HOMA modelling is an appropriate method for assessing change in insulin resistance with time in individuals.

HOMA has proved be a robust method for assessing insulin resistance in groups of patients over long periods of time because the sampling is simple, and the result is available without complex computing as soon as fasting glucose and insulin values are available.

Estimates of insulin resistance from HOMA correlate well with estimates from the euglycaemic clamp ($Rs = 0.88$, $P < 0.0001$, $Rs = 0.85$, $P < 0.0001$). Although the coefficient of variation (CV) for HOMA was initially reported as 31%.

A potential source of confusion is that of terminology, which has sometimes allocated normal insulin resistance as 1 or 100%. Sensitivity has always been

described in percentage terms from 100% as the median norm. However, scales of percentages raise their own problems, since statements describing a percentage change can be ambiguous—a change on the scale from 50% to 60% is a 10% change in units but a 20% relative change **(T. M. Wallace, D. R. Matthews, 2002)**.

The changes in patient metabolism following a major burn may be seen for more than 12 months after the initial injury. The ensuing period of hypermetabolism and catabolism post-burn leads to impaired immune function, decreased wound healing, erosion of lean body mass, and hinders rehabilitative efforts delaying reintegration into normal society. The typical changes in metabolism are the development of a hyperdynamic circulation, increased body temperature, increased protein catabolism with peripheral protein wasting, increased lipolysis leading to fatty infiltration of the liver, increased glycolysis and insulin resistance. These changes are responsible for much of the morbidity and mortality seen with such an injury and as such are important targets for available treatments including: early excision and grafting; aggressive treatment of burn, early commencement of high protein, high carbohydrate enteral feeding, elevation of the immediate environmental temperature to 31.5°C (±0.7°C); and early institution of an aerobic and resistive exercise program. Several pharmacotherapeutic options are also available to further reduce erosion of lean body mass **(W. B. Norbury et al, 2006)**.

Since rehabilitation exercise training (RET) is considered the cornerstone of treating post burn patients, it has been proven that it has a great effect on restoring lean body mass, glucose, insulin resistance and protein metabolism. due to improvements in acute burn care over the last few decades, most patients with severe burns (up to 90% of the total body surface) survive. However, the metabolic

and cardiovascular complications that accompany a severe burn can persist for up to three years post injury. Accordingly, there is now a greater appreciation of the need for strategies that can hasten recovery and reduce long-term morbidity post burn. RET (including resistance exercise and aerobic exercise) is a vital maneuver to restore normal body metabolism and glucose sensitivity in burn survivors. Given that RET is a safe and efficacious treatment that restores function and reduces post burn morbidity, the purpose is that a long-term exercise prescription plan should be considered for all patients with severe burns **(Alen Palackic et al, 2021)**.

Chapter III

Subject, Materials and Methods

In this part of the study, the materials and methods will be presented under the following headings: subjects, equipment, procedures of the study and the statistical procedures.

Sample size

Sample size calculations will be performed using G*Power statistical software (version 3.1.9.2, Franz Faul, University Kiel, Germany) and will be revealed that the appropriate sample size for this study is N=68 patients, will be divided into two groups each consist of 34 patients, using the following assumptions: alpha level = 0.05, power = 0.90, effect size (Cohen's d) = 0.80, and two-tailed test.

Subjects

sixty-eight patients, who have upper limb, upper chest and upper back burn. Their ages will be ranged from 18-35 year old. Only patients around (20% - 40%) of total body surface area (TBSA) burned. The participants will be selected from government hospitals (General and insurance hospitals) and randomly distributed into 2 equal groups (group A, group B).

Design of the study:

In this study, the patients will be randomly assigned into two equal groups (34 patients for each group).

$1.1_{(a)}$ Group A: (Study group)

This group includes 34 patients who have insulin resistance and who will receive resistance exercise and routine medical treatment. The patients will receive 3 sessions per week for 12 weeks, time of the session is 30 minutes.

1.1(b) Group B: (Control group)

This group includes 34 patients who have insulin resistance and who will receive routine medical treatment.

1.2 Criteria for Patients selection.

The criteria for patients selection are classified into two various criteria:

1.2 (a) Inclusion criteria

- Patients ranged from 18-35 years of age.

- Patients has waist hip ratio around 0.8 in female and 0.95 in male.

- Patient has body mass index (BMI around 25 kg/m^2) (**J Obes Weight Loss Ther ,2015**).

- Patients has second degree thermal burn injury (superficial and deep partial thickness).

- Patients with around (20% - 40%) of total body surface area (TBSA) burned.

- Patients who are able to follow verbal commands.

- Patients will have upper limb, upper chest and upper back burn.

- Patients with normal hemoglobin A1C (5.6 %).

- Patients should take diet rich protein, omega 3 and should have good sleep.

- Patients passed two months post severe burns (**Melanie G. Cree et al, 2008**).

1.2 (b) Exclusion criteria

- Potential participants were excluded if they reported a leg amputation, anoxic brain injury, psychological disorders, quadriplegia, or severe behavior or cognitive disorders history of heart disease, stroke, diabetes mellitus, or any condition that would prevent them from engaging in an exercise study.

- Patients with liver disease, pancreatic disease or any disease affects metabolism.

- If they were already engaging in 2 or more planned exercise sessions per week.

- Patients with any medication to lower glucose levels. Blood pressure and medications to lower lipid levels **(Lance E. Davidson et al, 2009)**.

2. Equipment and Tools:

Equipment in this study will be divided into two main categories; therapeutic and measuring equipment.

2.1. Therapeutic Equipment:

Resisted exercise program will be done by using:

1- Sand bags.

2-Elastic bands.

3- Resistance machines.

2.2. <u>Measuring Equipment:</u>

The following tools are used to assess the insulin resistance:

-HOMA-IR analysis will be used to assess insulin resistance by taking

Blood sample using sterile syringe 5 cm **(Pilar Gayoso-Diz et al, 2013)**.

3. Procedures of the study:

The procedures of this study are classified into the following:

3.1 Measurement Procedures:

In this phase HOMA-IR analysis **measurements:**

All measurements will be taken before the treatment program, 6 weeks after the beginning of treatment program and 12 weeks after the beginning of the treatment program.

Assessment of insulin resistance:

- By doing HOMA-IR analysis.
- Participants were asked to fast for nine hours prior to coming in for blood testing. To maximize the validity of the glucose and insulin results, before the blood sample, participants filled out a fasting survey that asked specific questions addressing the last time they had consumed food or liquids. Included in the questionnaire were questions specific to the ingestion of less commonly thought of foods such as breathe mints, gum, tea, alcohol, or supplements to ensure that the participants were following the fasting protocol. Blood samples of 89-92 mL were collected (**McKayla J. Niemann et al, 2020**).

- HOMA-IR test was performed for both groups before the treatment program, after the 6 weeks of the treatment program and after 12 weeks of the treatment program to evaluate the progression of insulin resistance in both groups.

Scoring

The HOMA-IR is defined as [fasting glucose (mmol/L) × fasting insulin (μmol/L)/22.5] or [fasting glucose (mg/dL) × fasting insulin (μmol/L)/405].

The HOMA score of <1.9 was considered as indicator of "Insulin sensitivity"; 1.9 to 2.9 as indicator of "Low IR" and >2.9 as indicator of Significant IR (**Haamid Bashir et al, 2022**).

3.2 Therapeutic procedures:

Procedures for the exercise program:

- Resisted exercise will be done for patients with upper back, upper chest and upper limb burn.

- Resisted exercise will target muscle groups of lower limb.

- Resisted exercise will be done by using sand bags, elastic bands and resisted machines.

-Three-Repetition Maximum Test

The first and second sessions of actual training will be spent with patients being tested for a three repetition maximum to establish training loads that will be used

during the training period. The exercises will be performed included leg press, leg extension and leg curl. After an instruction period on correct exercise technique the patient will perform a warm-up to become familiar with the movement. Next, the weight will be progressively increased to which the patient can successfully perform four repetitions with correct technique. If four repetitions will be performed with correct technique a one minutes rest will be given and the weight will be increased. This will be repeated until the patient can perform three repetitions, with the fourth repetition not volitionally possible with correct technique, and the test will be terminated. The amount of weight lifted from the successful lift will be recorded as the individuals three repetition maximum. From this information, the basic 3 sets of 8-12 repetitions RM's were established.

Resisted Exercise Training Program

Rehabilitative exercise training will be performed as previously described. All exercises will be performed using free weights, elastic bands and variable-resistance machines. Modifications to exercises will be made when appropriate depending on the patient injury characteristics. The load will be gradually increased from 50-60% of 3RM at the beginning of the program up to 80-85% of 3RM (repetitions maximum) at the end of the program. All exercise sessions will be preceded by a 5-minute warm-up at <50% VO2peak. No strength training activities will be permitted outside the supervised training session; however, both groups will be encouraged to maintain normal daily activities **(Justin P. Hardee et al, 2014)**.

4- <u>Statistical procedures</u>:

- In this study, the mean, the standard deviation and the standard error will be calculated for all the patients (2 groups of the study) after the detected time of the study.
- The mean and the standard deviation will be used as a primary source of connecting facts about each parameter to measure central tendency.
- Repeated measure ANOVA test will be used to compare variables within each group to detect the level of significance in each group.
- Unpaired t-test to compare the variable between groups to detect significance level between two groups (comparison).
- The statistical package for social science (SPSS) will be utilized for data analysis and the level of significance set at 0.05 levels**.**

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