Introduction

Omega-3 fatty acids (FA) frequently attract the attention of medical experts,scientists and consumers.the main omega-3 FAs are eicosapentaenoic acid(EPA),docosahexaenoic acid (DHA) and alpha-linolenic acid (ALA).EPA and DHA are mainly in fish and seafood,while ALA is present in flax seed,soy and walnut oils. The omega-3 FAs are essential for normal growth and are highly enriched in the cell membranes of the brain and the eye. They have several known anti-inflamatory mechanisms of action**(Barber et al.,1999).**

The physiologic manifestations of sepsis and other critical illness are believed to result from massive activation of the inflamatory cascade and excessive production of proinflamatory cytokines and lipid-derived inflamatory mediators**(Hotchkiss and Carl ,2003).**

Several studies have showed that EPA and DHA can inhibit the production of interleukin(IL-1) and tumour necrosis factor(TNF) by monocytes and the production of IL-6 and IL-8 and decreased expression of some adhesion molecules on the surface of monocytes,macrophages or endothelial cells after exposure to omega-3 FAs**(Novak et al.,2003).**

Supplementation of parenteral omega-3 (ω-3) fatty acids was proved to be safe and provides clinical benefits on the surgical intensive care unit(SICU) patients such as those undergoing coronary artery bypass graft(CABG) and liver transplantation after major surgery with less Production of endogenous cytokines and lower tendency of liver dysfunction and postoperative infection rate **(Han et al.,2012).**

Inclusion of fish oil in parenteral nutrition provided to septic patients is associated with marked changes in some cytokines, improvement of gas exchange and a trend towards reduced length of hospital stay **(Barbosa et al.,2010).**

Infusion of lipids enriched with omega-3 fatty acids in acute respiratory distress syndrome (ARDS) patients produces significant short term changes in eicosanoid values,which may be accompanied by an immunomodulatory effect **(Sabater et al., 2011).**

Aim of the work

This study will asses the safety and efficacy of fish oilcontaining formulas rich in omega-3 fatty acids in crtically ill patient.

Pathophysiology of systemic inflammatory response

The American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) introduced definitions for systemic inflammatory response syndrome (SIRS) , sepsis, severe sepsis, septic shock, and multiple organ dysfunction syndrome (MODS) **(Bone et al., 1992)**.

The idea behind defining systemic inflammatory response was to define a clinical response to a nonspecific insult of either infectious or noninfectious origin. systemic inflammatory response is defined as 2 or more of the following variables:

- Fever of more than 38°C (100.4°F) or less than 36°C (96.8°F)
- Heart rate of more than 90 beats per minute
- Respiratory rate of more than 20 breaths per minute or arterial carbon dioxide tension ($PaCO_2$) of less than 32mm Hg
- Abnormal white blood cell count (>12,000/μL or < 4,000/μL or >10% immature [band] forms)

Systemic inflammatory response is nonspecific and can be caused by ischemia, inflammation, trauma, infection, or several insults combined **(Fung et al., 2008)**.

Bacteremia, sepsis, and septic shock (figure 1):

Infection is defined as "a microbial phenomenon characterized by an inflammatory response to the microorganisms or the invasion of normally sterile tissue by those organisms." Bacteremia is the presence of bacteria within the bloodstream, but this condition does not always lead to systemic inflammatory response. Sepsis is the systemic response to infection and is defined as the presence of systemic inflammatory response in addition to a documented or presumed infection. Severe sepsis meets the aftermentioned criteria and is associated with organ dysfunction, hypoperfusion, or hypotension.

Sepsis-induced hypotension is defined as "the presence of a systolic blood pressure of less than 90 mm Hg or a reduction of more than 40 mm Hg from baseline in the absence of other causes of hypotension. Patients meet the criteria for septic shock if they have persistent hypotension and perfusion abnormalities despite adequate fluid resuscitation. MODS is a state of physiologic derangements in which organ function is not capable of maintaining homeostasis **(Dremsizov et al., 2006)**.

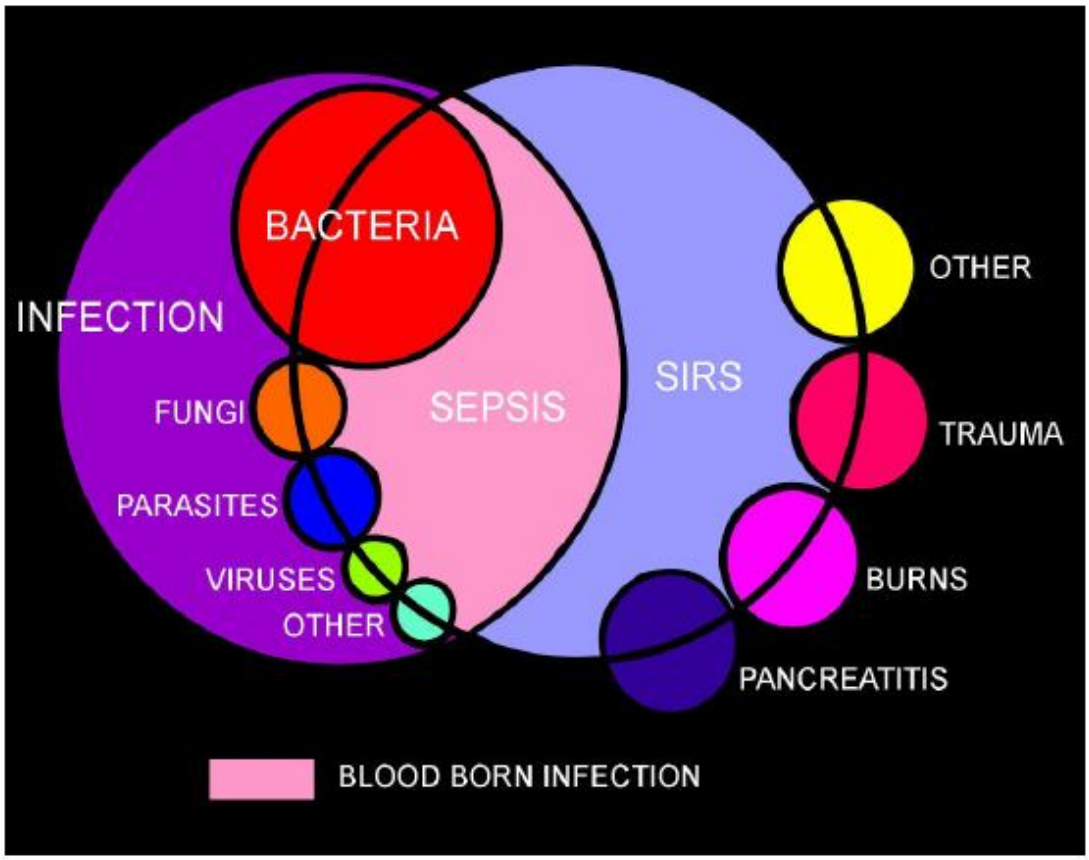

Figure (1): Venn diagram showing overlap of infection, bacteremia, sepsis, systemic inflammatory response, and multiorgan dysfunction**(Fung et al., 2008)**

Epidemiology:

The true incidence of systemic inflammatory response is unknown. However, because systemic inflammatory response criteria are nonspecific and occur in patients who present with conditions ranging from influenza to cardiovascular collapse associated with severe pancreatitis, such incidence figures would need to be stratified based on systemic inflammatory response severity **(Thoeni, 2012)**.

Rangel-Fausto et al. 1995 published a prospective survey of patients admitted to a tertiary care center that revealed 68% of hospital admissions to surveyed units met systemic inflammatory response criteria. The incidence of systemic inflammatory response increased as the level of unit acuity increased. The following progression of patients with systemic inflammatory response was noted: 26% developed sepsis, 18% developed severe sepsis, and 4% developed septic shock within 28 days of admission.

Pittet et al. 1995 performed a hospital survey of systemic inflammatory response that revealed an overall in-hospital incidence of 542 episodes per 1000 hospital days. In comparison, the incidence in the intensive care unit (ICU) was 840 episodes per 1000 hospital days.

The etiology of patients admitted with severe sepsis from a community emergency department was evaluated by Heffner et al, who determined that 55% of patients had negative cultures and that 18% were diagnosed with noninfectious causes that mimicked sepsis . Many of the noninfectious etiologies required urgent alternate disease-specific therapy (eg, pulmonary embolism, myocardial infarction, pancreatitis). Of the systemic inflammatory response patients without infection, the clinical characteristics were similar to those with positive cultures **(Heffner et al., 2010)**.

Comstedt et al. 2009 have demonstrated that 62% of patients who presented to the emergency department with systemic inflammatory response had a confirmed infection, while 38% did

not. Within the same cohort of patients, 38% of infected patients did not present with systemic inflammatory response.

Still, **Angus et al. 2001** found the incidence of severe systemic inflammatory response associated with infection to be 3 cases per 1,000 population, or 2.26 cases per 100 hospital discharges. The real incidence of systemic inflammatory response, therefore, must be much higher and likely depends somewhat on the rigor with which the definition is applied.

Sex-related demographics:

The sex-based mortality risk of severe systemic inflammatory response is unknown. Females tend to have less inflammation from the same degree of proinflammatory stimuli because of the mitigating aspects of estrogen. The mortality rate among women with severe sepsis is similar to that of men who are 10 years younger; however, whether this protective effect applies to women with noninfectious systemic inflammatory response is unknown **(Thoeni, 2012)**.

Age-related demographics:

Extremes of age (young and old) and concomitant comorbidities probably negatively affect the outcome of systemic inflammatory response. Young people may be able to mount a more exuberant inflammatory response to a challenge than older people and yet may be able to better modify the inflammatory state via the counter inflammatory response syndrome (CARS). Young people have better outcomes for equivalent diagnoses **(Thoeni, 2012)**.

Etiology:

The etiology of systemic inflammatory response is broad and includes infectious and noninfectious conditions, surgical procedures, trauma, medications, and therapies. The following is partial list of the infectious causes of systemic inflammatory response:

- Bacterial sepsis
- Burn wound infections
- Candidiasis
- Cellulitis
- Cholecystitis
- Community-acquired pneumonia
- Diabetic foot infection
- Erysipelas
- Infective endocarditis
- Influenza
- Gas gangrene
- Meningitis
- Nosocomial pneumonia
- Pseudomembranous colitis
- Pyelonephritis
- Septic arthritis
- Toxic shock syndrome
- Intraabdominal infections(eg, diverticulitis, appendicitis)
- Urinary tract infections

The following is a partial list of the noninfectious causes of systemic inflammatory response:

- Acute mesenteric ischemia
- Adrenal insufficiency
- Autoimmune disorders
- Burns
- Chemical aspiration
- Cirrhosis
- Cutaneous vasculitis
- Dehydration
- Drug reaction
- Electrical injuries
- Erythema multiforme
- Hemorrhagic shock
- Hematologic malignancy
- Intestinal perforation
- Myocardial infarction
- Pancreatitis
- Seizure
- Surgical procedures
- Toxic epidermal necrolysis
- Transfusion reactions
- Upper gastrointestinal bleeding
- Vasculitis
- Medication side effect (eg, from theophylline)
- Substance abuse - Stimulants such as cocaine and amphetamines

(Thoeni, 2012).

Pathophysiology:

Systemic inflammatory response, independent of the etiology, has the same pathophysiologic properties, with minor differences in inciting cascades. Many consider the syndrome a self-defense mechanism. Inflammation is the body's response to nonspecific insults that arise from chemical, traumatic, or infectious stimuli. The inflammatory cascade is a complex process that involves humoral and cellular responses, complement, and cytokine cascades. **Bone et al. (1992)** best summarized the relationship between these complex interactions and systemic inflammatory response as the following 3-stage process.

Stage I :

Following an insult **(figure 2),** local cytokine is produced with the goal of inciting an inflammatory response, thereby promoting wound repair and recruitment of the reticular endothelial system **(Bone et al., 1992)**.

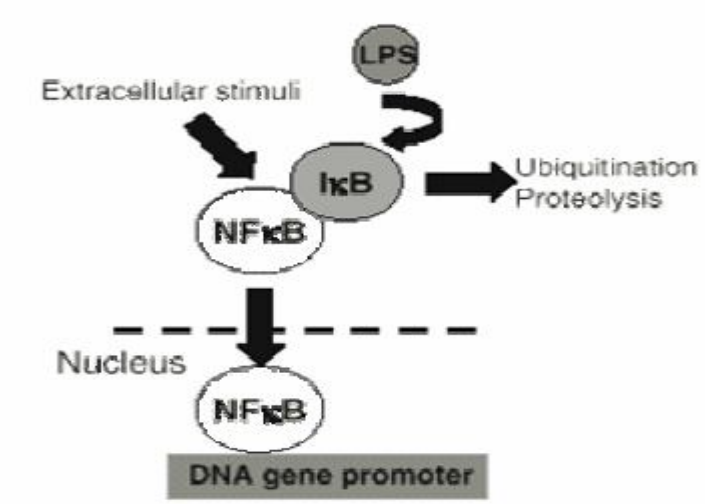

Figure (2): Initiation of SIRS:(DNA) deoxyribonucleic acid,(LPS) lipopolysaccharide, (NF-kB) (Nuclear Factor-Kappa B,(IkB) a regulatory protein that inhibits NF-kappa-B **(Bone et al., 1992)**

Stage II:

Small quantities of local cytokines are released into the circulation to improve the local response. This leads to growth factor stimulation and the recruitment of macrophages and platelets. This acute phase response is typically well controlled by a decrease in the proinflammatory mediators and by the release of endogenous antagonists; the goal is homeostasis **(Bone et al., 1992)**.

Stage III:

If homeostasis is not restored, a significant systemic reaction occurs. The cytokine release leads to destruction rather than protection. A consequence of this is the activation of numerous humoral cascades and the activation of the reticular endothelial system and subsequent loss of circulatory integrity. This leads to end-organ dysfunction **(Bone et al., 1992)**.

Multihit theory:

Bone et al. also endorsed a multihit theory behind the progression of systemic inflammatory response to organ dysfunction and possibly multiple organ dysfunction syndrome (MODS). In this theory, the event that initiates the systemic inflammatory response cascade primes the pump. With each additional event, an altered or exaggerated response occurs, leading to progressive illness. The key to preventing the multiple hits is adequate identification of the cause of systemic inflammatory response and appropriate resuscitation and therapy **(Bone et al., 1992)**.

The mediators of the trigger-response concept (figure 3):

After an injection of bacteria or endotoxin, certain cytokines appear briefly in circulating blood. The classical sequence is tumour necrosis factor (TNF) followed by interleukins 1 (IL-1), 6 (IL-6) and 8 (IL-8). These cytokines have been named the pro-inflammatory or alarm cytokines because they appear first. They, and other factors, mediate various responses including the activation of numerous cell populations and release of secondary cytokines and growth factors.

It is important to understand whether the same mediator is activated by different triggers and if different mediators are associated with different pathophysiological responses. Does the pathophysiological response to infection differ from the response to other triggers? There are certain differences: infection induces more TNFα than does physical trauma, which releases more IL-6 and IL-8 **(Bone, 1996)**.

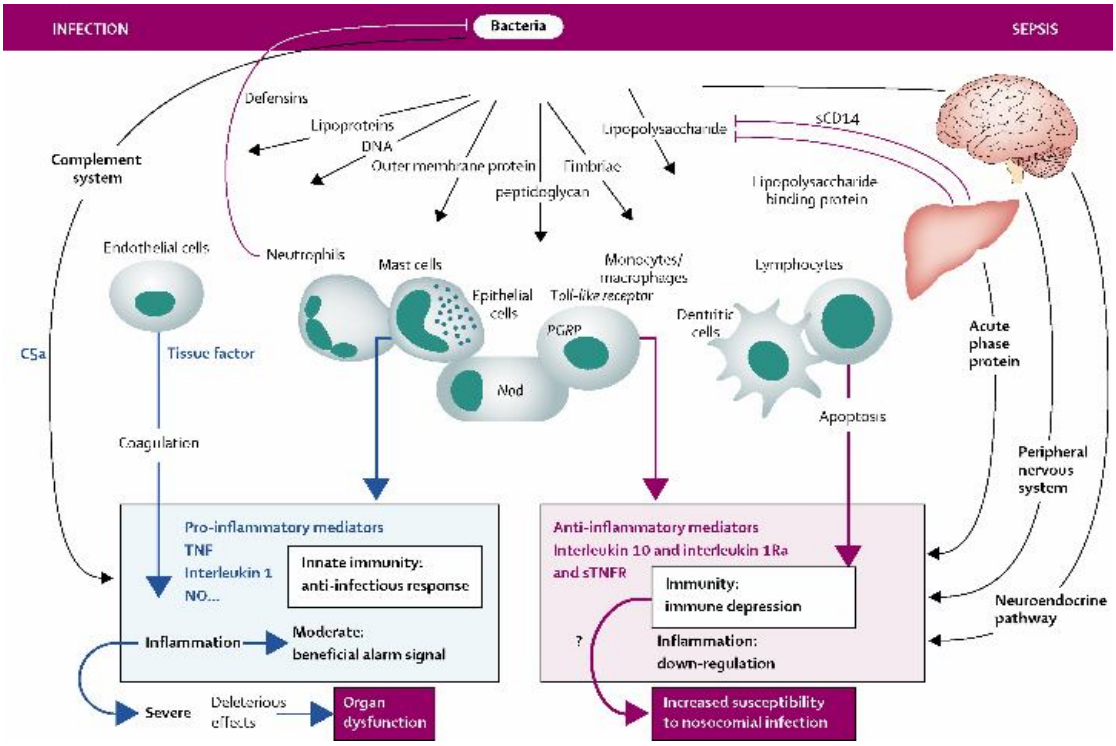

Figure (3): Organ dysfunction as a consequence of severe SIRS.(DNA) deoxyribonucleic acid (IL) interleukins,(TNF)tumour necrosis factor,(N0) nitric oxide,(C5a)activated complement 5**(Annane et al., 2005).**

Thus primary infection is associated with higher fever than in trauma, probably because of the different balance of mediators produced. Hypovolaemic and hypotensive patients, however, often initially suffer from hypothermia and leucopenia whether triggered by infection or trauma.

After resuscitation all such patients develop fever and leucocytosis. Initial differences in mediator patterns result in different clinical presentations, but within hours or days, it is clinically no longer possible to associate these responses with specific triggers **(Dinarello and Cannon, 2013)**.

Approaching the problem from a different standpoint, attempts to correlate measurements of circulating cytokines with pathophysiological changes and with prognosis have not been entirely successful. The concentrations of these mediators vary widely probably because they have short half-lives in the circulation and most are localized within the inflamed body compartment where they cannot readily be measured.

Patients admitted to intensive care with a diagnosis of acute sepsis, i.e. systemic inflammatory response following presumed infection, often do not have positive blood cultures providing unequivocal proof of invasive infection, nor do they have endotoxaemia **(Dinarello and Cannon, 2013)**.

Many do not have detectable TNFα or IL-1 in response to presumed invasive infection. Even elevated IL-6 or IL-8 concentrations in circulating blood are not found consistently. However, detectable bacteria, endotoxin or inflammatory mediators are associated with increased mortality **(Casey et al., 2013)**.

The acute phase response:

This may be seen as the primary part of the systemic inflammatory response. Tissue injury or bacteria at the site will activate complement and induce tissue macrophages, monocytes and other reactive cell elements such as mast cells, endothelial cells and platelets to produce various mediators **(Baumann and Gauldie, 2004)**.