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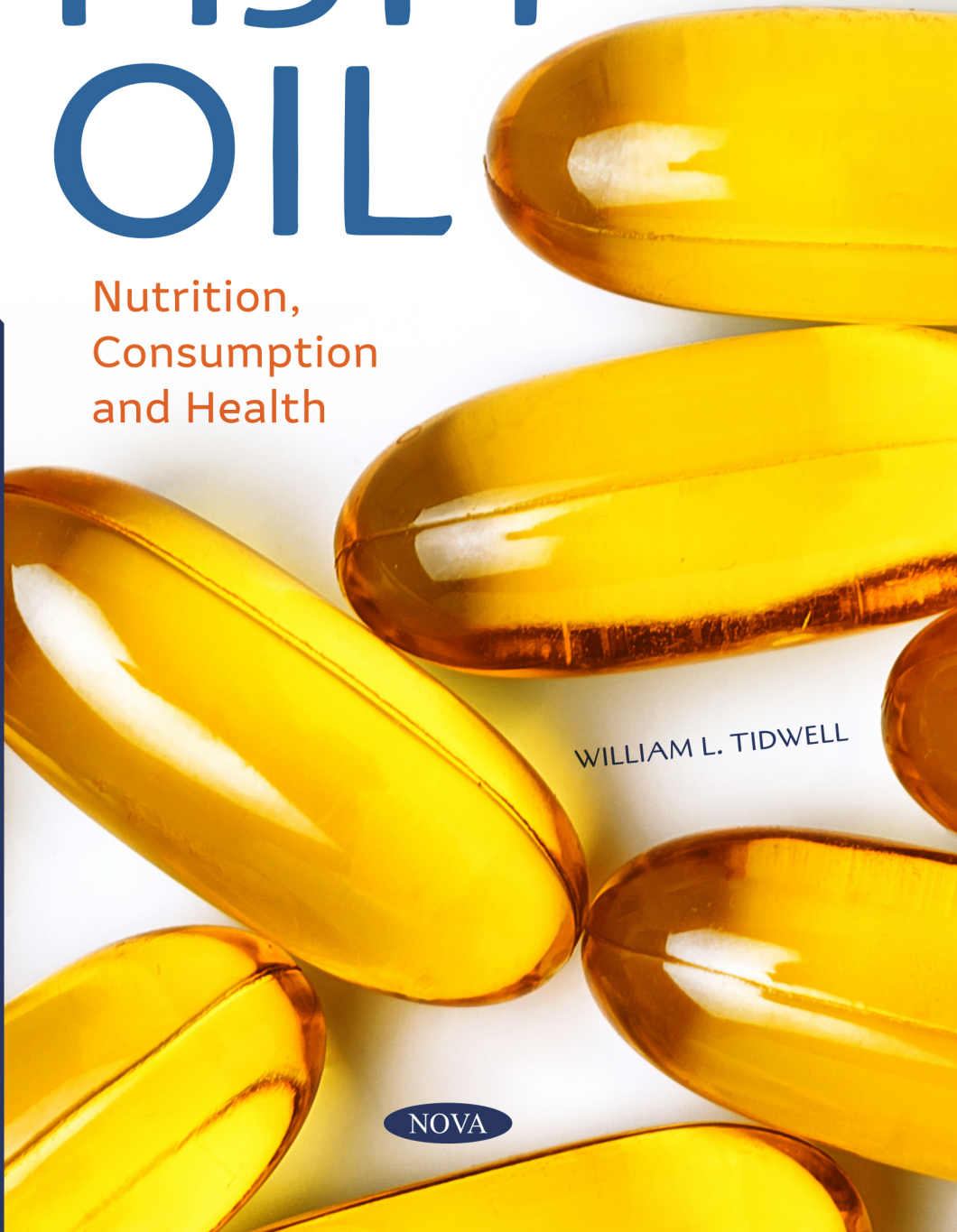
Nutrition, Consumption and Health



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Contents

Preface

This book includes five chapters that detail the consumption, benefits, and effects of fish oil. Chapter One discusses the impact of long-chain n-3 PUFA on changes in the inflammatory and chemotactic paracrine interactions between various immune cell populations (macrophages and T cell subsets) and adipocytes that contribute to obese adipose tissue dysfunction. Chapter Two summarizes the current literature on the role of epigenetic modifications on the association between fish oil consumption and reproduction performance. Chapter Three provides a comprehensive update on chemo-preventive and chemotherapeutic efficacy of fish oil alone or in combination with standard drugs against colorectal cancer development and progression.

Chapter Four discusses the development of various cell culture models to recapitulate obesity-associated adipocyte-immune cell paracrine interactions utilizing mature 3T3-L1 adipocytes or conditioned media from primary adipose tissue explants co-cultured with either purified primary immune cell populations or immune cell lines. Lastly, Chapter Five focuses on the significance and impact of dietary lipids on the growth, maturation, reproductive performance, and other aspects viz, immunity, fatty acid profile and lipid level requirements in diets of carps and their variants.

Chapter 1

The Effect of Dietary N-3 Polyunsaturated Fatty Acids on Obese Adipose Tissue and Skeletal Muscle

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Abstract

The global prevalence of obesity is rising. This represents a considerable public health challenge given that obesity increases the risk of developing a spectrum of co-morbidities that adversely impact human health. Chronic low-grade inflammation and metabolic dysfunction are central components of the obese phenotype that manifest both locally within tissues (e.g., visceral adipose tissue and skeletal muscle) as well as systemically (e.g., via the circulating adipokine and hormone profile). Therefore, identifying dietary interventions that can attenuate the severity of the obese phenotype is relevant from both an obesity prevention and intervention standpoint.

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In this chapter we will discuss the mechanisms through which long-chain n-3 polyunsaturated fatty acids (PUFA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), derived from fish oil improve the obese phenotype by attenuating visceral adipose tissue and skeletal muscle's inflammatory mediator production, paracrine interactions between either adipocytes or muscle cells and various immune cell populations (namely macrophages and T cell subsets), and metabolic dysfunction, such as impaired glucose metabolism.

Specifically, we will discuss the impact of long-chain n-3 PUFA on changes in the inflammatory and chemotactic paracrine interactions between various immune cell populations (macrophages and T cell subsets) and adipocytes that contribute to obese adipose tissue dysfunction. N-3 PUFA systemic influences on the circulating adipokine and/or hormone profile and improvements in glucose homeostasis in skeletal muscle will also be discussed.

Abbreviations

AA	arachidonic acid
ALA	α-linolenic acid
AMPK	adenosine monophosphate activated protein kinase
AT	adipose tissue
BAT	brown adipose tissue
BMI	body mass index
CD	cluster of differentiation
CLS	crown-like structures
CPT	carnitine-palmitoyl transferase-1b
CRP	C-reactive protein
CVD	cardiovascular disease
DAG	diacylglycerol
DHA	docosahexaenoic acid
DPA	docosapentaenoic acid
EPA	eicosapentaenoic acid
ERK	extracellular-signal-regulated kinase
F1	first generation
F2	second generation
F3	third generation
FFA	free fatty acid
Gal	galectin
GLUT	glucose transporter

GPR	G-protein receptor
HFD	high fat diet
HOMA-IR	homeostatic model assessment of insulin resistance
IFN	interferon
IKK	I kappa B kinase
IL	interleukin
IMCL	intramyocellular lipids
IRS-1	insulin receptor substrate
JAK	janus kinase
JAMA	junctional associated molecules A
JNK	c-Jun N-terminal kinases
LA	linoleic acid
LPS	lipopolysaccharide
MAPK	mitogen activated protein kinase
MCP	monocyte chemoattractant
MIP	macrophage inflammatory protein
Muc	mucin
NF-kB	nuclear factor kappa B
NK	natural killer
NLRP	NOD-like receptor family pyrin domain containing
PA	palmitic acid
PGC	peroxisome proliferator-activated receptor-gamma coactivator
PKB	protein kinase B
PKC	protein kinase C
PPAR	peroxisome proliferator-activated receptor
PUFA	polyunsaturated fatty acids
RANTES	regulated on activation normal T cell expressed and secreted
Reg	regenerating islet-derived protein
Relm	resistin-like molecule
SFA	saturated fatty acid
STAT	signal transducer and activator of transcription
SVF	stromal vascular fraction
T2D	type 2 diabetes
TAB	transforming growth factor-b activated kinase binding protein
TAG	triacylglyceride
TAK	transforming growth factor-b activated kinase

Th	T helper
TLR	toll-like receptor
TNF	tumor necrosis factor
TNFR	tumor necrosis factor receptor
WAT	white adipose tissue

Introduction

According to the World Health Organization 52% of adults and 18% of children are classified as overweight or obese based on body mass index (BMI) [1]. Obesity can be characterized by an increased accumulation of triacylglycerides (TAG) in the adipose tissue (AT) [2]. This accumulation becomes a concern when it begins to impact normal physiological functions [3]. Increases in fat mass impose added stress onto organs such as the heart and the lungs, while systemic changes in circulating cytokines impair normal immune and endocrine signaling [4]. All of this occurs when energy intake (dietary overconsumption of total calories) chronically exceeds energy expenditure, resulting in AT accumulation driven by adipocyte hyperplasia and hypertrophy [4, 5]. Consequently, obesity poses a significant burden on quality of life and increases the risk of developing other metabolic diseases such as type 2 diabetes (T2D), cardiovascular disease (CVD) and some types of cancer [6–9]. As adiposity increases, the adipokine profile (mediators produced within adipose tissue) shifts to an inflammation-promoting phenotype [10]. Not only do these changes in AT have a significant metabolic effect on the local AT environment, but peripheral tissues such as the skeletal muscle, liver, and pancreas are also affected [11–13]. Due to the highly dynamic nature of AT [14], adipocytes are particularly susceptible to changes in dietary behaviors, making them ideal targets for dietary interventions [15].

The two main families of dietary polyunsaturated fatty acids (PUFA) are n-3 and n-6 PUFA as identified by the position of the last double bond relative to the methyl end of the fatty acid chain [16]. The human body can synthesize all the fatty acids it requires except for α-linolenic acid (ALA; 18:3n-3) and linoleic acid (LA; 18:2n-6), which are essential fatty acids that must be consumed in the diet [17]. ALA is found in green leafy vegetables, flaxseeds and their oil, soybean oil, rapeseed oil and walnuts [18, 19], whereas LA, which is more highly consumed in Western diets, is found in most plant oils including those from corn, sunflower, and safflower oils [20, 21]. These dietary essential fatty acids serve as the precursors or parent fatty acids for the

synthesis of a series of longer chain n-3 and n-6 PUFA [17]. LA undergoes a series of elongation and desaturation reactions, to produce the longer and more unsaturated arachidonic acid (AA; 20:4n-6) [9]. The same elongation and desaturation reactions occur to convert ALA to eicosapentaenoic acid (EPA; 20:5n-3) and docosahexaenoic acid (DHA; 22:6n-3), however, the conversion efficiency of ALA to EPA and/or DHA in humans is very low (<5%) [19, 22–24]. The Academy of Nutrition and Dietetics suggests a combined intake of 0.5 g of EPA and DHA per day, however the average North American intake is substantially lower (0.1-0.2 g/day) [25, 26]. This indicates that current consumption rates in North America are severely low, consequently resulting in an unbalanced n-3:n-6 ratio [25, 26].

Transgenerational intervention studies providing lifetime dietary n-3 PUFA supplementation to the first (F1), second (F2) and third (F3) generation offspring results in reduced obesity severity in response to an obesogenic high fat and high sucrose diet in the F3 offspring consisting of reduced weight gain, fat mass and improved glucose homeostasis [277]. Dietary intake of long-chain n-3 PUFA (of varying intake durations) is associated with a broad spectrum of beneficial effects in obesity such as improved insulin signaling, partial reversal of insulin resistance, decreases in CVD risk factors and improvements in the inflammatory mediator profile [10, 25, 27–37], which will be explored in this chapter.

Changes in Obese Intestinal Health and Metabolic Endotoxemia

Although changes in AT function are a focal point of obesity it is important to consider the broader systemic changes that also occur in obesity. Importantly, there are gastrointestinal changes associated with obesity making it an intestinal-associated condition. The intestinal microenvironment of lean and obese individuals is dramatically different, and thus, the intestinal microenvironment contributes to critical aspects of the obese phenotype. The obese intestinal microbiome exhibits dysbiosis [38–46] and host epithelial barrier function is impaired [47, 48], resulting in a more permeable or “leaky” epithelial barrier that permits translocation of luminal contents (antigens, microbial metabolites or bacterial cell wall components) into the host circulation and tissues, which drives inflammatory mediator production and metabolic dysfunction [48–54].

The significance of obesity-associated gastrointestinal changes has been demonstrated with the transfer of microbiota from obese donors into germ free recipients [55–58] who subsequently develop the critical features of obesity. Moreover, microbiota transplant from lean donors into obese and/or T2D recipients can improve some critical features of the obese phenotype [59, 60], although further study is required. One of the most studied consequences of obesity-associated epithelial barrier permeability is the translocation of the Gram-negative bacterial cell wall component, lipopolysaccharide (LPS) across the epithelial barrier into the host circulation, termed metabolic endotoxemia [38, 61, 62].

LPS is a potent inflammatory stimulus that is significantly elevated in the blood of obese patients [48, 63] and rodents [49, 64] and is a ligand for Toll-like receptor (TLR)-2 and TLR4, which are expressed on both adipocytes and immune cell populations [65–68]. Downstream LPS signaling results in the activation of nuclear factor kappa B (NF-κB) and the production of inflammatory mediators that perpetuate the obesity-associated low-grade inflammation that leads to metabolic dysfunction and both AT and systemic insulin resistance, as shown in human, rodent and cell culture studies [49, 63, 69–79]. To demonstrate the functional relevance of LPS-TLR2/TLR4 signaling, continuous infusion of LPS in rodents recapitulates the effects of high fat diet (HFD)-induced obesity, including increased visceral AT mass, macrophage AT infiltration and accumulation, inflammatory mediator production and metabolic changes such as fasting glycemia and insulinemia [49]. Moreover, obesity severity is blunted in TLR4-deficient mice [49, 76]. Similarly, acute administration of LPS in humans results in increased levels of AT and circulating inflammatory mediators (e.g., tumor necrosis factor (TNF)α, interleukin (IL)-6 and monocyte chemoattractant (MCP)-1) prior to the development of insulin resistance [70].

In addition to LPS, saturated fatty acids (SFA; e.g., palmitic acid, PA) have also been shown to signal through TLR2 or TLR4 [69, 75, 76, 80] and activate NF-κB and inflammatory adipokine production in adipocytes and AT macrophages [69, 75, 77, 80–85]. Regardless of the ligand, TLR2/TLR4-mediated signaling results in activation of the transcription factor NF-κB, which in turn, regulates the expression of inflammatory and chemotactic adipokines [66, 86, 87]. Notably, in obese and T2D humans [63, 78, 88] and obese rodents [69, 89–91] the expression of TLR2 and TLR4 and the activity of NF-κB are increased, thereby underscoring the significant contribution of this signaling pathway to the development of the obese phenotype.