The Impact of Vegan vs Omnivorous Diets on Biomarkers of Inflammation in Muscle Recovery

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Abstract

Background: Although vegan diets are becoming increasingly popular in New Zealand and globally, the implications for health and muscle recovery following exercise remain unclear. Complete and timely recovery improves athletic performance and decreases injury risk. Nutrition plays a vital role in the pathogenesis of muscle recovery as it influences inflammatory and immunomodulatory responses through altering ROS and cytokine production. However, research on whether vegan and omnivorous diets equivalently facilitate these processes is limited.

Aim: To test whether individuals following a vegan diet present different levels of inflammation biomarkers in plasma after a bout of muscle damage-inducing exercise compared to individuals following an omnivorous diet.

Methods: Twelve 18-45 year old males were stratified as vegan or omnivorous in this cross-sectional study. Participants completed a muscle damage-inducing lower body exercise protocol and 4-day food record. Muscle damage marker CK, pro-inflammatory biomarkers IL-1β, TNF-α, CRP and anti-inflammatory biomarkers IL-6 and IL-10 were analysed from blood at baseline and 0h, 1h, 3h, 24h, 48h and 72h time points post-protocol to assess muscle damage and indicators of inflammation.

Results: Increased CK levels confirmed muscle damage as a result of the protocol, with omnivores displaying significantly higher absolute CK values to that of vegans ($F = 8.076$, $P = 0.036$). Plasma IL-1β absolute values among omnivores were also significantly higher ($F = 1.010$, $P = 0.034$). No significant difference in CRP or TNF-α absolute values ($F = 2.913$, $P = 0.110$ and $F = 1.106$, $P = 0.377$ respectively) or percentage change from baseline ($F = 0.958$, $P = 0.373$ and $F = 1.153$, $P = 0.358$ respectively) were found between diet groups, although TNF-α values among vegans remained higher across the time course. IL-6 and IL-10 levels were below detection levels. Dietary analysis showed vegans had significantly lower intake of trans fats ($P = 0.046$), cholesterol ($P = 0.014$) and significantly higher riboflavin ($P = 0.010$) compared to omnivores. There were also notable in differences in iodine and magnesium intake between groups.

Conclusion: Fluctuations in biomarkers may be attributed to variations in nutrient intake between groups. However, the inflammatory response to the protocol was mild and no significant difference in inflammatory biomarkers of muscle recovery following exercise was found between vegans and omnivores.

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Dedication

This thesis is dedicated to my late father and scientist Terry Leach who never stopped believing in me. You taught me to be kind, work hard and pursue my passions. You are my greatest inspiration and I hope I made you proud.

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LIST OF ABBREVIATIONS

Abbreviation	Full Form
ALA	alpha-linolenic acid
AMPK	5' adenosine monophosphate-activated protein kinase
ARA	arachidonic acid
ATP	adenosine 5’-triphosphate
Ca^{2+}	calcium
CK	creatine kinase
CKM	creatine kinase muscle type
CLA	conjugated linoleic acid
CRP	C-reactive protein
DHA	docosahexaenoic acid
DNA	deoxyribonucleic acid
DOMS	delayed onset muscle soreness
ECC	excitation-contraction coupling
ECM	extracellular matrix
EPA	eicosapentaenoic acid
ERK1/2	extracellular signal-regulated kinases 1 and 2
FAPs	fibro/adipogenic progenitors
GLA	gamma-linolenic acid
IBD	inflammatory bowel disease
ICAM-1	intercellular adhesion molecule 1
IFN-γ	interferon gamma
IGF-1	insulin-like growth factor 1
IKD	isokinetic dynamometer
IL-6	interleukin-6
IL-10	interleukin-10
IL-13	interleukin-13
IL-1α	interleukin-1 αlpha

IL-1β	interleukin-1 beta
IL-33	interleukin-33
IL-4	interleukin-4
IL-8	interleukin-8
IκB	inhibitor of nuclear factor kappa B
LA	linoleic acid
LDL	low-density lipoprotein
LPS	lipopolysaccharide
MAPK	mitogen-activated protein kinase
mRNA	messenger ribonucleic acid
MyoD	myoblast determination protein 1
Myog	myogenin gene
NADPH	nicotinamide adenine dinucleotide phosphate
NAFLD	non-alcoholic fatty liver disease
NF-κB	nuclear factor kappa B
NO	nitric oxide
NO_2^-	nitrite
NO_3^-	nitrate
NOX	NADPH oxidase
PGC-1α	proliferator-activated receptor-γ coactivator-1 alpha
PLA2	phospholipase A2
PPARγ	peroxisome proliferator-activated receptor gamma
PUFA	polyunsaturated fatty acids
ROS	reactive oxygen species
SD	standard deviation
SFA	saturated fatty acids
sIL6R	soluble interleukin-6 receptor
TGF-β1	transforming growth factor-beta1
Th2	type 2 helper T cell
TNF-α	tumour necrosis factor alpha
TGF-β	transforming growth factor beta
XO	xanthine oxidase

CHAPTER 1. PURPOSE

1.1 Background

Vegan diets are becoming increasingly popular with the shift toward sustainability, animal welfare and health seeing these diets emerge as a potential solution to unsustainable and unethical animal agricultural practices (Sabate & Soret, 2014). A vegan diet requires abstention from the consumption of all animal-derived foods and is usually accompanied by an associated philosophy of rejecting the commodity status of animals including exploitation and cruelty to animals, along with advocating for plant-based alternatives to meat (The Vegan Society, 2021). An omnivorous diet, in contrast, consists of both animal and plant-based foods (Boutros et al., 2020b; Menzel et al., 2020). On a global basis, veganism has moved from obscurity into mainstream diets and its prevalence in industrialised nations has increased exponentially. In the United States alone, veganism has seen a 30-fold increase over 15 years between 2004 and 2019 (Faye, 2019). A similar trend has been reported in the UK (Rocha et al., 2019) and New Zealand (Milfont et al., 2021).

It is undisputed that nutrition has a major influence on athletic performance, and veganism in sports has become a particular point of interest. A multitude of studies have already investigated both nutritional and pharmaceutical interventions to stimulate muscle anabolism, support recovery and provide athletes with a competitive advantage (Barnard et al., 2019; Eichelmann et al., 2016; Nieman et al., 2020). It has been suggested that high intakes of antioxidant and nitrate-rich fruit and vegetables improve muscle function and may assist the recovery process after exercise by preventing excessive inflammation and oxidative stress (Nieman et al., 2020; Rizzo et al., 2013). Diets rich in plant foods including vegetables, fruit, whole grains and nuts are high in anti-inflammatory nutrients such as polyphenols, carotenoids and flavonoids, which have been inversely related to markers of inflammation in blood (Galland, 2010; Holt et al., 2009). The anti-inflammatory action of these nutrients has been found to occur most notably through the regulation of nuclear factor kappa B (NF-κB), which plays a critical role in the production of critical cell signalling molecules known as cytokines (Calder, 2010). In support of these findings, there has been an increasing number of high-profile athletes advocating for plant-based and vegan diets with claims they are compatible with peak performance, improved endurance and elevated aerobic capacity compared with omnivorous diets (Katharina, 2020; Menzel et al., 2020; Nebl et al., 2019).

Although plant-based nutrition has gained increasing popularity and represents a growing social movement (Cramer et al., 2017), to date research about veganism and its impact on health and athletic performance is still in its infancy. There is inconsistent support for many of the health claims of vegan diets (Nieman et al., 2020) and there are concerns that poorly planned vegan diets may lead to nutritional deficiencies such as vitamin B_{12} and iron (Sakkas et al., 2020) and serious health issues including neurological impairment (Serin & Arslan, 2019). There is also a body of evidence suggesting omnivorous diets may be more beneficial (Barnard et al., 2019; Eichelmann et

al., 2016; Nieman et al., 2020), with literature indicating substantial advantages from efficacious doses of highly bioavailable nutrients such as omega-3, zinc and protein acquired from animal-based foods, particularly in the recovery phase following exercise (Berrazaga et al., 2019). Omega-3, which is primarily found in fatty fish, and zinc from seafood, meat and poultry, have been found to attenuate inflammatory and immunomodulatory responses to exercise (Mickleborough, 2013) through decreasing ROS and altering cytokine production (Calder, 2010; Silveira et al., 2018). The type of protein consumed may also be an important factor in post-exercise protein synthesis, with animal-derived proteins providing the full array of amino acids required for proper muscle repair (Tipton et al., 2004). Because of these conflicting studies, it has not been possible to make definitive conclusions about the role of vegan diets in the regulation of inflammation, athletic performance and recovery.

Skeletal muscle is a dynamic tissue with an extraordinary ability to regenerate after injury and to adapt in response to growth or exercise (Khodabukus, 2021). The regenerative capacity of muscle relies on a complex, highly-controlled inflammatory response that bridges initial muscle injury responses with muscle reparation (Yang & Hu, 2018). Muscle damage initiates a pro-inflammatory response, which is reciprocated by the activation of negative feedback mechanisms including secretion of anti-inflammatory mediators, inhibition of pro-inflammatory signalling cascades, and activation of regulatory cells that enable the muscle regeneration process (Calder, 2010; Mickleborough, 2013; Zhang & An, 2007). Various immune cells and cytokine signalling molecules orchestrate the inflammation response, facilitating the removal of cellular debris from the site of damage, preventing the spread of damaging substances to neighbouring tissue, activating muscle progenitor cells, and enabling synthesis and remodelling of connective tissue (Peake et al., 2017b; Yang & Hu, 2018). As such, inflammatory responses must be tightly regulated and self-limiting to avoid excessive damage to host cells, while enabling complete and timely regeneration and recovery.

While it is suggested that optimal nutrition after exercise can alter signalling cascades to support the regenerative capacity of muscle and effectively reduce adverse symptoms associated with intense exercise (Alghannam et al., 2018; Gleeson et al., 2004), several studies have reported that nutritional interventions have no effect on exercise-induced muscle damage or inflammation (Bongiovanni et al., 2020; Thompson et al., 2003). This may be in part because investigations have focussed primarily on individual nutrients such as protein, omega-3 and antioxidants in isolation, rather than evaluating the cumulative effects of nutrients that constitute habitual diets. Hence, a significant gap remains in our understanding of how dietary patterns impact the mechanisms underlying the initial muscle damage response and subsequent adaptations to exercise that support recovery.

The purpose of this research is therefore to understand whether vegan diets impact muscle inflammation in recovery from eccentric exercise compared to omnivorous diets, in a cohort of healthy males aged 18-45 in New Zealand.

1.2 Aims, Objectives and Hypothesis

1.2.1 Aims

This study aims to test whether individuals following a vegan diet present differences in muscle inflammation biomarkers after a bout of muscle damage-inducing exercise compared to individuals following an omnivorous diet. In order to do this, this laboratory-based study compares the time-course of plasma biomarkers of muscle damage and inflammation following a muscle damage-inducing protocol of the lower body in vegans versus omnivores.

1.2.2 Objectives

The following objectives were completed in achieving this study's aim:

1. To measure levels of plasma biomarkers of inflammation (IL-6, IL-10, IL-1β, TNF-α CRP) and muscle damage (Creatine Kinase; CK) from blood samples acquired at baseline, 0h, 1h, 3h, 24h and 72h following a muscle damage-inducing protocol of the lower body.

2. To investigate differences in biomarkers of muscle inflammation and nutrient intake between groups of vegans and omnivores.

1.2.3 Hypothesis

H_0: No significant difference in inflammatory biomarkers in muscle recovery will be found between those that follow a vegan diet compared to those who follow an omnivorous diet.

1.3 Thesis Structure

This thesis contains four chapters. Chapter 1 provides an outline of the scope and justification of the research, along with the study aim, objectives and hypothesis and researcher contributions. Chapter 2 provides a review of the literature on the current understanding of inflammatory processes involved in muscle damage and recovery and the impact of diet on inflammatory biomarkers. Chapter 3 provides a detailed outline of the study procedures and results, along with a discussion of the findings and conclusion. Chapter 4 provides an overview of the study's contribution to health, including findings about the impact of vegan diets on muscle recovery. A reflection on the study's strengths and limitations will also be summarised, along with final recommendations for future research.

1.4 Researcher Contribution

Researcher	Contribution
Tam Leach	Primary author of this thesis, data collection, recruitment, blood analysis, analysis of results and statistics, ethics submission, research design.
Anastasya Woolsey	Data collection, recruitment, ethics submission, blood analysis, research design.
Andrew Foskett	Provided the study concept, proofread and provided feedback on the thesis. Guidance for protocol.
Kaio Vitzel	Provided the study concept, proofread and provided feedback on the thesis. Guidance for protocol, blood analysis, statistical analysis.
Kaylyn Zhang	Undergraduate research lab assistant
Krutika Nanavati, Cameron Haswell, Owen Mugridge, Andrea Wei, Ayla Blaxall	Phlebotomists
Henry Jones	PhD student (Anatomy / Physiology) – blood analysis

CHAPTER 2: REVIEW OF THE LITERATURE

2.1 Introduction

While the relationship between nutrition, physical performance and muscle function is well established (Fritzen et al., 2019), research on vegan diets and their impact on muscle recovery is scarce. Muscular adaptations are known to be triggered by exercise (Hedayatpour & Falla, 2015) and variations in diet (Hawley et al., 2011) and since vegan diets differ in nutrient composition compared to omnivorous diets, it is feasible that physiological responses involved in muscle recovery following damage-inducing exercise may also be altered.

This literature review seeks to investigate the mechanisms involved in mechanical damage and subsequent repair of skeletal muscle following exercise. It discusses the highly coordinated immune and inflammatory responses involved in these processes, and how products of these systems can be measured as biomarkers and used to evaluate the progression of muscle recovery over time. The characteristics of vegan and omnivorous diets will be discussed, along with how our current understanding of the dietary profiles inherent to the respective diets impact inflammation and muscle recovery from exercise. These investigations underscore the importance of understanding how different dietary profiles impact the ability of skeletal muscle to recover.

2.2 Exercise-Induced Muscle Damage

Mechanical damage of muscle from exercise follows a clear sequence of events. As sarcomeres become stretched beyond myofilament overlap, the excitation-contraction coupling system becomes disrupted (Allen, 2001). This overstretching of muscle fibres causes damage to contractile proteins where the supporting sarcolemma membrane and t-tubules tear, the sarcoplasmic reticulum ruptures and uncontrolled calcium (Ca^{2+}) release is triggered (Proske & Morgan, 2001) (Figure 1). The subsequent steps involve necrosis of myofibrils, formation of a hematoma in the torn muscle space and cellular breakdown products from damaged fibres, which then leads to a local inflammatory response associated with tissue edema, pain and eventual recovery (Fernandes et al., 2011; Proske & Morgan, 2001; Tidball, 2011).

2.3 Reactive Oxygen Species (ROS)

Reactive oxygen species (ROS) are generated by a myriad of sources and are closely associated with muscle damage. At the point of injury, endothelial muscle cells and the leukocytes that migrate to the site of damage express large amounts of ROS-producing enzymes such as xanthine oxidase (XO) and phospholipase A2 (PLA2) which destroy foreign biomolecules (Hellsten et al., 1997; Kawamura & Muraoka, 2018; Steinbacher & Eckl, 2015). NADPH oxidase (NOX), another ROS-producing enzyme activated by signalling molecules known as cytokines (Panday et al., 2015), is present in t-tubules, sarcolemma and leukocytes (Michaelson et al., 2010; Zuo et al., 2004). As the overstretching of sarcomeres causes damage to muscle cells, intracellular components

including mitochondria also become damaged, which amplifies oxidative stress and further increases ROS levels (Sakellariou et al., 2014). Elevated ROS concentrations are problematic as they cause oxidative damage to lipids, amino acids and base structures comprising muscle cell membranes, contractile proteins and DNA, and accelerate the rise in intracellular Ca^{2+}, which promotes signalling cascades for apoptosis (Barbieri & Sestili, 2012). Thus, the initial muscle damage event is followed by a secondary damaging phase caused by ROS accumulation, as well as by protein degradation and apoptosis triggered by cytokines and Ca^{2+}. While these processes are detrimental to host cells, they are vital for optimal muscle repair as they function to degrade and remove damaged cell components and provide important signalling molecules for the progression of inflammation, muscle adaptation and repair.

2.4 Muscle Degeneration and Inflammation

The regulatory processes involved in skeletal muscle damage and repair have been extensively studied and shown to rely on a highly coordinated series of interactions between immune cells and muscle cells (Urso, 2013). This process involves the sequential and overlapping phases of degeneration, inflammation, regeneration, remodelling and repair (Figure 1).

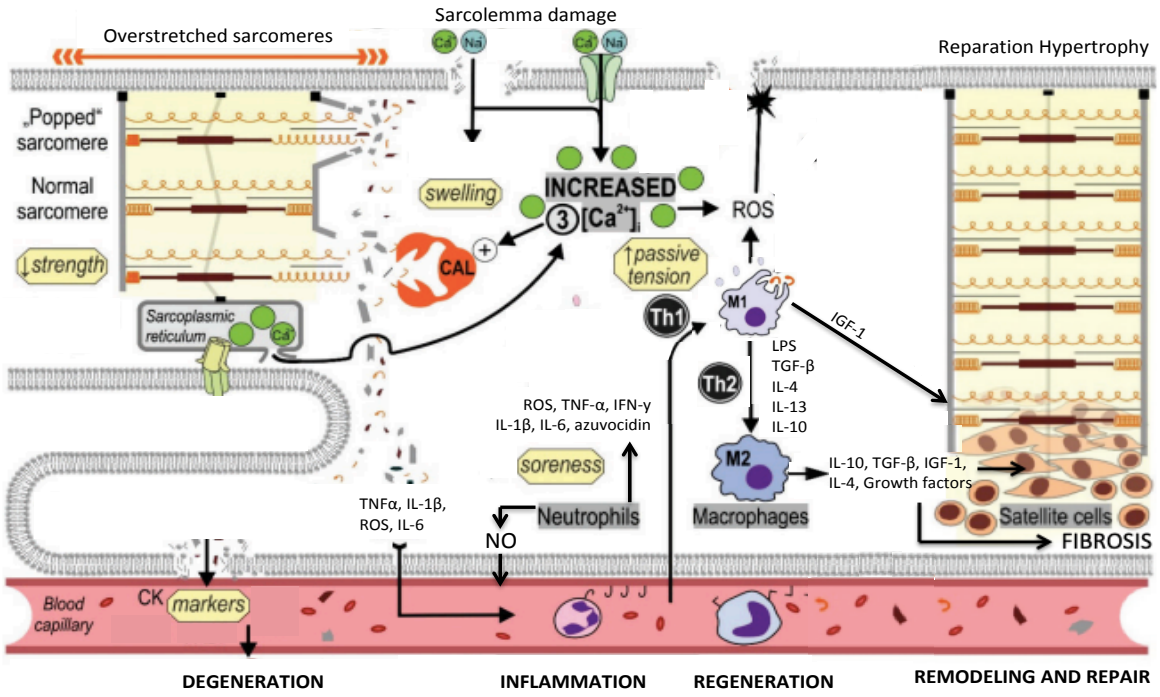

Figure 1. The regulation of skeletal muscle damage and repair. Summary of the interplay between cytokines and immune cells on the modulation of muscle recovery phases: degeneration, inflammation, regeneration and remodelling/repair. Figure adapted from Stozer et al. (2020).

2.4.1 Degeneration

The degeneration phase encompasses the initial event of sarcomere overstretching, the subsequent mechanical damage to muscle myofibrils and connective tissue, and the breakdown of damaged cell components (Toumi & Best, 2003). The overstretching of sarcomeres is thought to initiate a chain reaction of intracellular damage, where anchoring structures that connect myofibrils to the membrane are disrupted and sarcolemma and t-tubule damage ensues (Stozer et al., 2020). As a result, membrane permeability increases, which disrupts excitation-contraction coupling (ECC) and causes swelling and uncontrolled and persistent Ca^{2+} entry into the cell (Stozer et al., 2020). Elevated Ca^{2+} causes generalised degradation of cell components by promoting ROS production by mitochondria (Sorichter et al., 1995; Stozer et al., 2020), and activates tightly regulated and targeted degradation systems that recognise and rapidly degrade faulty or damaged proteins within cells.

There are multiple protein degradation systems activated by the influx of Ca^{2+} into the damaged cell, which work collaboratively with cytokines released from damaged muscle fibres and infiltrating immune cells. The autophagy-lysosome and ubiquitin-proteasome pathways are activated primarily by pro-inflammatory cytokines interferon (IFN) and tumor necrosis factor (TNF) (Haberecht-Muller et al., 2021; Sandri, 2013). Pro-inflammatory cytokines also activate Caspases, a family of protease enzymes that coordinate apoptosis, DNA fragmentation and degradation of cytoskeletal proteins (Du et al., 2004; Muhl & Pfeilschifter, 2003). Calpains (CAL) are another family of proteases expressed in skeletal muscle fibres that are associated with apoptosis and degradation of costameric proteins, and are activated by high concentrations of Ca^{2+} (Hyldahl & Hubal, 2014; Murphy, 2010). These processes ultimately work in a highly coordinated way to breakdown and remove damaged cell components after muscle injury and make way for the repair process.

2.4.2 Inflammation

Inflammation is a normal, protective, immune defence mechanism that localises injuries or infections and removes damaged tissue components so that the body can begin to heal. The initial inflammation response increases blood flow through vasodilation and increased permeability of blood vessels, supporting the accumulation of fluid, proteins and leukocytes from circulation to the site of injury (Muller, 2013). Inflammation has historically been viewed as detrimental to recovery as the physiological changes that occur correlate with a variety of diseases and disorders and contribute to muscle damage, impaired muscle function and delayed onset muscle soreness (DOMS) associated with intense exercise (Liu et al., 2017; Stozer et al., 2020; Toumi & Best, 2003). However, it is now generally accepted that inflammatory processes in response to infection and injury are integral to muscle repair and regeneration if tightly regulated (Peake et al., 2017a). For these reasons, pharmaceutical and nutritional interventions seek to accommodate an inflammatory response sufficient enough to facilitate repair and recovery, while avoiding an

excessive response that may unnecessarily exacerbate muscle damage and delay recovery (Depont et al., 2015; Smith-Ryan et al., 2020).

The pathogenesis of inflammation is a highly complex process, involving many cell types, signals and feedback loops. Cytokines are arguably the most crucial component in the inflammation phase, as they signal the action of other cytokines and immune cells to enhance or inhibit inflammation, thus upregulating or preventing inflammatory reactions. The initial phase of inflammation is orchestrated primarily by pro-inflammatory cytokines, which are released in a highly coordinated manner first by damaged myofibres and infiltrating neutrophils, and later by lymphocytes, macrophages, and dendritic cells (Peake et al., 2017a; Tidball, 2011; Zhang & An, 2007).

2.4.3 Neutrophils

At the point of muscle damage, pro-inflammatory cytokines; tumor necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1β) and interleukin 6 (IL-6) are released by myofibres, launching a chain immune reaction by signalling neutrophils, the first-line responders, to migrate from circulation into areas of injury (Wang, 2018; Ziemkiewicz et al., 2021). Neutrophils have a diverse repertoire of roles including primary defence against infections through production of proteolytic enzymes, ROS and nitric oxide (NO), and their release of pro-inflammatory cytokines activate the next line of defence, macrophages, to a M1 pro-inflammatory phenotype and directs their migration to the site of injury (Laumonier & Menetrey, 2016; Peake et al., 2017a; Tidball, 2017). Collectively, these inflammatory processes induce vascular changes, necrosis and degradation of the injured muscle cell, remove damaged muscle components through phagocytosis (Korthuis et al., 1988; Tidball, 2011) and amplify the initial inflammatory response (Louis et al., 2007; Pizza et al., 2002).

2.5 Regeneration, Remodelling and Repair

The phases of regeneration and remodelling involve processes that enable regrowth of muscle fibres and deposition of extracellular matrix (ECM) components that allow for proper muscle repair. The inflammatory process is vital for the activation and differentiation of satellite cells that enable regeneration, and for the stimulation of fibrogenic cells that produce, deposit and remodel the ECM.

2.5.1 Macrophages

The regeneration process is facilitated primarily by neutrophil-recruited macrophages and begins once most of the cellular debris has been removed by neutrophils and macrophages begin to infiltrate the site of injury (Epelman et al., 2014; Okabe & Medzhitov, 2014). Macrophages play a unique role in regulating both the inflammatory process and tissue repair (Wang et al., 2014), with a highly plastic and dynamic nature that readily adapt to alternate phenotypes in response to various stimuli (Biswas & Mantovani, 2010). Two main macrophage phenotypes have been

identified; M1 and M2, which play distinct but complementary roles in skeletal muscle healing. M1 macrophages display predominantly pro-inflammatory properties, while M2 facilitate pro-regenerative functions (Martins et al., 2020).

2.5.2 M1 Macrophages

In the early stage of muscle regeneration, monocytes are activated to the pro-inflammatory M1 macrophage phenotype by pro-inflammatory cytokines IFN-γ and TNF-α secreted primarily from neutrophils and T-helper 1 cells (Th1) (Vergadi et al., 2017; Verreck et al., 2004). This conversion causes a drastic increase in M1 macrophage levels at around 1–2 days following muscle injury as they migrate to the site of damage (Arnold et al., 2007; Peake et al., 2017a).

The typical characteristics of M1 include high production of NO and ROS that induce apoptosis of damaged cells and remove cellular debris from necrotic muscle tissue through phagocytosis, thus completing the work of neutrophils and paving the way for regeneration (Yoshioka et al., 2003). M1 macrophages secrete high amounts of TNF-α, IL-6 and IL-1β cytokines that stimulate catabolism of damaged tissues and upregulate pro-inflammatory responses (Korthuis et al., 1988; Rybalko et al., 2015). M1 macrophages may also have a role in functional muscle recovery by accelerating myofiber repair. This role has been demonstrated in studies showing early infiltration of M1 escalates the expression of insulin-like growth factor 1 (IGF-1) by muscle fibres (Rybalko et al., 2015; Siegel et al., 2011), which curbs degeneration, prevents excessive inflammatory responses and signals satellite cells residing on the surface of muscle fibres to exit their quiescent state and proliferate (Song et al., 2013; Yin et al., 2013a), giving rise to myoblasts that fuse with existing damaged myofibres or produce new ones (Hurme & Kalimo, 1992; Siegel et al., 2011; Yin et al., 2013b). These findings suggest that M1 macrophages are vital, not only for the complete clearance of necrotic debris from damaged muscles, but also for promoting tissue repair and remodelling through activation of satellite cells.

2.5.3 M2 Macrophages

The transition from the pro-inflammatory M1 phenotype to their pro-regenerative M2 counterpart is the next important step toward proper muscle regeneration. This switch attenuates inflammation and permits tissue repair by promoting growth factors, satellite cell differentiation, fibroblast proliferation and collagen synthesis (Burzyn et al., 2013; Laumonier & Menetrey, 2016; Lucas et al., 2010; Mills, 2012; Spadaro et al., 2017; Su et al., 2020). There is some controversy to the mechanisms underlying the M1 to M2 switch, although the prevailing hypothesis appears to be that M2 are derived from M1 macrophages that first acquire an inflammatory phenotype, and then mature into the M2 repair phenotype (Crane et al., 2014; Lin et al., 2009; Spiller & Koh, 2017), with the involvement of cytokines such as IL-10 and products of phagocytosis (Serhan et al., 2015). The cumulative effect of these processes is a significant increase in M2 macrophages at around 2-4 days following muscle damage (Arnold et al., 2007).

M2 secrete anti-inflammatory cytokines and growth factors IL-4, IL-10, IL-13, TGF-β and IGF-1 that are integral to effective and complete tissue regeneration (Perandini et al., 2018). Cytokines IL-4, IL-10 and IL-13 repress local inflammatory responses by inhibiting pro-inflammatory cytokines and propagating Th2 responses via the STAT6 pathway (Le Gros et al., 2008; Saraiva & O'Garra, 2010). M2 macrophage-derived IL-4 and IL-10 cytokines also increase expression of the myogenin gene (Myog) that induces satellite cell differentiation so that new myofibres can be formed (Arnold et al., 2007; Biswas et al., 2006). The secretion of TGF-β and IGF-1 by M2 promotes repair through inducing fibroblast proliferation (Lemos et al., 2015; Mantovani et al., 2013; Witherel et al., 2021) and IL-4/IL-13 promotes proliferation of fibro/adipogenic progenitors (FAPs) that support myogenesis via activation of STAT6 signalling (Heredia et al., 2013).

2.6 Biomarkers and their Time Course in Recovery

2.6.1 Interleukin 6 (IL-6)

IL-6 exerts both pro-inflammatory and anti-inflammatory actions (Munoz-Canoves et al., 2013), and is produced initially during exercise by working muscles in response to calcium-dependent stimuli (Febbraio & Pedersen, 2002). IL-6 elicits pro-inflammatory actions by attracting neutrophils to the site of damage (Scheller et al., 2011), which also secrete IL-6 once they have infiltrated (Kistner et al., 2022). IL-6 also contributes to neutrophil clearance, as neutrophils produce soluble IL-6 receptor (sIL6R) that induces apoptosis upon binding with IL-6 (McLoughlin et al., 2003; Scheller et al., 2011). This cytokine is further implicated in pro-inflammatory degradation processes, as it signals muscle cells to release chemokines that attract phagocytotic monocytes and T-lymphocytes to the site of injury and activates NOX in both neutrophils and macrophages (Rogeri et al., 2020; Scheller et al., 2011).

While IL-6 has traditionally been classified as pro-inflammatory, the current prevailing view is that IL-6 is predominantly anti-inflammatory. Aside from IL-6 being the primary inducer of acute phase proteins, many of which have anti-inflammatory properties, IL-6 also triggers expression of anti-inflammatory cytokine IL-10 by T-cells, and inhibits pro-inflammatory cytokines TNF-α and IL-1β production by macrophages (Eckardt et al., 2014). Studies have also linked IL-6 with other hypertrophy and regeneration processes, including the upregulation of MyoD, the pro-myogenic factor that signals satellite cells to proliferate and fuse into new myofibers via the IL-6/JAK/STAT3 pathway (Munoz-Canoves et al., 2013; Pedersen et al., 2001; Serrano et al., 2008). IL-6 is also linked with ECM formation through stimulation of IGF-1 and TGF-β1 production, which activate fibroblasts to secrete collagen molecules leading to muscle regeneration (Pedersen et al., 1998). The fact that IL-6 is synthesised by a host of cell types associated with muscle regeneration such as M2 macrophages, fibroblasts and satellite cells, further supports its primary role as an anti-inflammatory cytokine (Joe et al., 2010; Kami & Senba, 1998; Zhang et al., 2013).

2.6.2 Interleukin 1 beta (IL-1β)

In the early inflammatory cascade following muscle damage, IL-1β is released by infiltrating neutrophils, M1 macrophages, muscle endothelial cells and fibroblasts, with levels peaking at around 2 hours post-exercise (Cannon et al., 1991; Evans et al., 1986). IL-1β is classified as a pro-inflammatory cytokine as it is highly catabolic and is associated with several degenerative diseases (Laird et al., 2021; Schulze et al., 2002). IL-1β is secreted by damaged muscle endothelial cells and fibroblasts, upregulating the production of neutrophil chemoattractants CXC- and CCL-chemokines that elevate neutrophil concentrations at the site of damage (Larsen et al., 1989; Pyrillou et al., 2020). IL-1β is also secreted by neutrophils themselves and acts as a strong M1 macrophage-chemoattractant, so that macrophage levels also increase (Smith et al., 2008).

While IL-1β involvement in the recruitment of neutrophils and macrophages has been consistently demonstrated, its catabolic action is considered to occur most notably through upregulating IL-6 production by skeletal muscle cells (Lopez-Castejon & Brough, 2011; Luo et al., 2003). The release of IL-1β by circulating M1 macrophages also activates NF-κB and the mitogen-activated protein kinase (MAPK) signalling pathways, which promotes apoptosis and muscle catabolism through enhancing the expression of ubiquitin-conjugating enzymes, increasing muscle protein breakdown (Ji et al., 2022). Interestingly, IL-1β simultaneously inhibits the production of IGF-1 by muscle fibres during this process, so that muscle protein synthesis is also restricted until removal of cellular debris is complete (Authier et al., 1999).

2.6.3 Tumour Necrosis Factor alpha (TNF-α)

TNF-α is released predominantly by injured muscle fibres, neutrophils and M1 macrophages and has been recognised for its catabolic action in the initial response to muscle injury (Idriss & Naismith, 2000; Liao et al., 2010). In the context of exercise-induced muscle damage, TNF-α concentration typically increases in line with neutrophil levels (Pizza et al., 2005), peaking at around 4 hours following muscle damage (Peake et al., 2017a) and returning to baseline anywhere from 5 to 24 hours after exercise (Chazaud et al., 2009; Nieman et al., 2012; Ostrowski et al., 1999; Pokora et al., 2014; Ulven et al., 2015).

TNF-α is thought to propagate a pro-inflammatory response via activation of NF-κB and MAPK transduction pathways (Li, 2003; Salamone et al., 2001), which increases expression of pro-inflammatory cytokines IL-1β and IL-6 (Allen & Tresini, 2000; Yang & Hu, 2018). TNF-α also increases neutrophil adhesion (Li, 2003; Salamone et al., 2001), phagocytic capacity and ROS production (Nguyen et al., 2017), and contributes to oxidative stress and protein degradation in the initial response to muscle damage following exercise. Moreover, TNF-α stimulates NOX activation and ROS generation in damaged muscle fibres (Goossens et al., 1999; Li et al., 2005), and upregulates the ubiquitin-proteasome pathway (Karin & Ben-Neriah, 2000). Despite its catabolic actions, TNF-α may also have a role in muscle recovery, as it activates p38 MAPK to promote the migration of quiescent satellite cells and modulates the expression of MyoD (Warren

et al., 2002), a gene involved in the differentiation of muscle fibres (Chen et al., 2007; Peterson et al., 2011).

2.6.4 Interleukin 10 (IL-10)

IL-10 is classified as an anti-inflammatory cytokine that responds to pro-inflammatory signals to ameliorate the progression of local inflammation (Moore et al., 2001; Ostrowski et al., 1999; Philippou et al., 2012; Smith et al., 2000). IL-10 is a potent negative feedback regulator released predominantly by M2 macrophages and Th2 cells, and functions to suppress the production of pro-inflammatory cytokines IL-6, TNF-α, and IL-1β (Ostrowski et al., 1999; Smith et al., 2000). This is indicated by a surge of IL-10 with the transition of pro-inflammatory macrophages to their anti-inflammatory M2 counterparts 24-48 hours post exercise (Peake et al., 2017b; Smith et al., 2000).

There are two dominant means by which IL-10 mediates inflammatory responses. The first is through down-regulating class II MHC antigen presentation to Th1 cells, so that Th1 proliferation is inhibited, along with their production of IFN-γ and TNF-α (Steen et al., 2020). Since IFN-γ and TNF-α are essential factors in the activation of M1 macrophages, M1 concentration subsequently plummets, along with their pro-inflammatory products, IL-6, TNF-α, IL-1β and NO (Steen et al., 2020). The second way IL-10 counteracts inflammation is through inhibition of apoptotic signalling pathways, specifically the p38 MAPK pathway via STAT3-dependent signalling, which prevents ongoing muscle catabolism after injury (Murray, 2006; Zhu et al., 2015). Additionally, IL-10 has been shown to activate the PI3K/Akt cascade that attenuates caspase-3 expression, thus preventing degradation of DNA and cytoskeletal proteins (Du et al., 2004; Moore et al., 2001; Muhl & Pfeilschifter, 2003; Zhu et al., 2015). Collectively, these findings have placed IL-10 as a key mediator of the anti-inflammatory response, marking the transition from a pro-inflammatory state to one that is reparative.

2.7 Characteristics of a Vegan Diet

A vegan diet is defined as abstaining from the consumption of all animal-derived foods and products that involve exploitation or cruelty to animals during the manufacture process (Taylor & Twine, 2015). Vegan diets are typically rich in fruit, vegetables, whole grains, soy and nuts, which provide rich sources of carbohydrates, dietary fibre, magnesium, folic acid, antioxidants, vitamins and phytochemicals (Haddad et al., 1999). Soy and nuts tend to be the primary sources of polyunsaturated fats and protein (Burns-Whitmore et al., 2019). Vegan diets have been found to have a low ratio of saturated fatty acids (SFA) and low-density lipoprotein (LDL) cholesterol, both of which are abundant in animal foods and have been linked to adverse health outcomes (Austin et al., 2021). These characteristics of the vegan diet have been linked to significant cardio-protective effects and lower levels of inflammation (Appleby & Key, 2016; Davey et al., 2003; Haddad et al., 1999; Larsson & Johansson, 2002). There is also evidence to show high intakes of antioxidants such as polyphenols that are typical of plant-based diets may have benefits for

performance and recovery (Fuhrman & Ferreri, 2010; Venderley & Campbell, 2006). Several high-profile athletes including soccer player Alex Morgan, tennis player Venus Williams, boxer David Haye and All Black rugby player TJ Perenara have reportedly adopted veganism for its proposed performance benefits and/or for animal welfare reasons. However, the quality of vegan diets varies substantially among individuals and there are also many unanswered questions about how diet and disease are connected.

One of the main concerns with vegan diets is that many nutrients vital to immune and muscle function are difficult to acquire in adequate amounts from plant-based foods (Venderley & Campbell, 2006). Plant-based foods have low concentrations and/or bioavailability of B_{12}, vitamin D, iron, zinc, calcium, iodine, omega-3 and protein, and nutrient deficiencies are not uncommon amongst vegans (Davey et al., 2003). Some data also indicate that vegans consume less energy overall than omnivores (Clarys et al., 2014; Davey et al., 2003), which can lead to compromised immunity, reduced muscle mass and strength, and impaired training adaptation (Loucks, 2004). Although other research has shown no significant difference in total energy intake between vegans and omnivores (Selinger et al., 2022). Empirical research validating the health claims of vegan diets is also limited and to date, epidemiological studies have not provided convincing evidence for the protective effects of vegan diets, nor their role in performance and recovery.

2.8 Characteristics of an Omnivorous Diet

Omnivores are defined as generalised feeders who eat food consisting of both animal protein and vegetation (McArdle, 2021). Omnivores consume a variety of meat and dairy foods, as well as plant food groups (Kim et al., 2022). While an array of diet types comprises omnivorous diets, there are potential benefits for incorporating animal-derived foods. Many micronutrients involved in muscle repair mechanisms are found in high quantities in animal-derived foods, but are low in plant foods (Pohl et al., 2021). These include vitamin D, omega-3 and zinc which have antioxidant functions and other vital roles in muscle recovery (Boldyrev et al., 2013; Rawson et al., 2001). The consumption of protein- and creatine-rich lean meat also appears to have significant benefits for muscle function (O'Connor et al., 2017), although saturated fat, a common component of meat, has been implicated in inducing inflammation and impairing muscle recovery (Lowery, 2004), thus the benefits of meat consumption for muscle recovery remain unclear.

2.9 Differences Between Vegan and Omnivorous Diets

One of the largest nutritional studies investigating differences in nutrient intake between meat-eaters and vegans is known as the UK EPIC–Oxford study (Davey et al., 2003). In terms of macronutrient distribution, the study found that vegan diets tended to be higher in carbohydrates and lower in protein than omnivorous diets. Total fat intake was similar between groups, although omnivores had substantially higher saturated fat intake, while vegans had higher omega-6 polyunsaturated fatty acid intake from oils, nuts and grains. Vegans also had approximately 14% lower total energy intake than omnivores. More recently, Selinger et al. (2022) conducted a

comprehensive meta-analyses of observational and clinical health studies of vegans and omnivores among general healthy populations. Consistent with the EPIC study, carbohydrate intake was substantially higher among vegans and protein intake was lower, while in contrast to the EPIC study, Selinger et al. (2022) found total fat intake was substantially lower among vegans and energy intake remained relatively the same between groups (Figure 2).

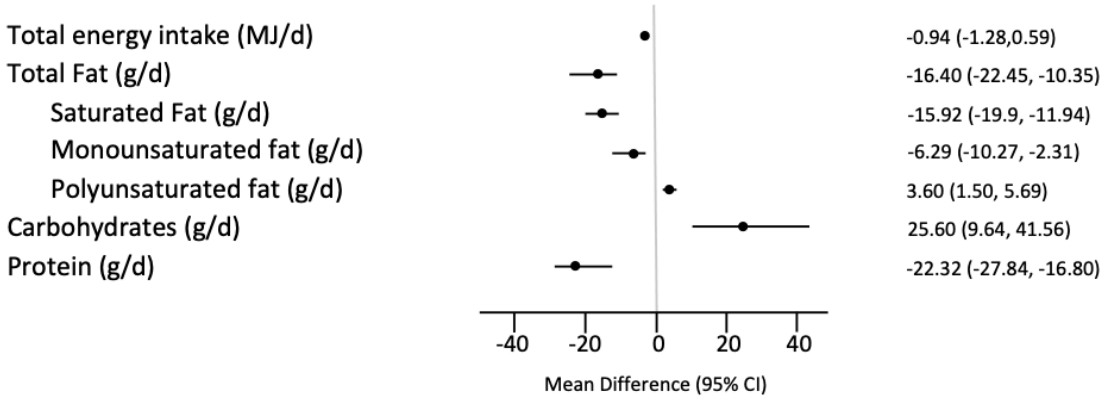

Figure 2. Differences in energy and macronutrient intake between vegans and omnivores**.** Vegans were shown to have significantly lower total fat intake with a mean difference (MD) of -16.40 g/d compared to omnivores, comprising of saturated fat (MD -15.92 g/d), monounsaturated fat (MD -6.29 g/d) and polyunsaturated fat, which was slightly higher among vegans (MD 3.60 g/d). Protein intake was significantly lower in vegans with a MD of -22.32 g/d compared to omnivores. The low intakes of fat and protein were compensated by high carbohydrate intake among vegans with a MD of 25.6 g/d, resulting in similar energy intake between groups (MD -9.94 g/d). Adapted from Selinger et al. (2022).

3.0 Macronutrients in Inflammation and Muscle Recovery

3.0.1 Protein

Dietary protein is arguably the most important nutritional factor in muscle recovery, as it is required for normal immune function and regeneration of damaged muscle tissue (Kreider & Campbell, 2009). There is evidence to indicate that individuals engaged in intense training have increased dietary protein requirements and that higher protein intake correlates with reduced inflammation (Hruby & Jacques, 2019; Nicastro et al., 2012). These benefits have primarily been attributed to an increased need for essential amino acid substrates to support muscle repair, anabolism and anti-inflammatory processes following muscle damage (van Vliet et al., 2015). For this reason, animal-derived proteins have been ranked as superior for facilitating muscle recovery since they typically contain more complete essential amino acid profiles (Kerksick et al., 2021; Tessier & Chevalier, 2018). Leucine, an essential, branched chain amino acid, has gained particular interest in anti-inflammatory processes, as it is considered a nutritional stimulus for attenuating proteolysis and can be transaminated to glutamate, a substrate highly consumed by macrophages (Nicastro et al., 2012). Leucine, like other essential amino acids, can be found in both plant and animal protein sources, although it is both more highly bioavailable and abundant in protein of animal origin (Kerksick et al., 2021).

Research comparing the effects of animal-based and plant-based protein on muscle function and recovery following exercise has so far predominantly supported animal-based proteins, as they have been shown to elicit the greatest response (Draganidis et al., 2017; Farup et al., 2014; Hartman et al., 2007; Phillips et al., 2009; Wilkinson et al., 2007). Possibly the most comprehensive study comparing protein sources is by Nieman et al. (2020), who conducted a double-blind randomised trial comparing the effects of whey protein with pea protein supplementation on muscle recovery in non-athletic, healthy males after exercise. The results showed whey protein significantly attenuated markers of muscle damage (DOMS, CRP and exercise performance), while the changes observed from pea protein were not significantly different to the water control. Other authors have demonstrated further benefits from animal-derived protein supplementation. Draganidis et al. (2017) conducted a study on 11 healthy, untrained men, investigating the effect of a whey and casein milk protein supplement for 8 days following exercise-induced muscle damage compared to a placebo. The results showed the milk protein attenuated proteasome activity, reduced oxidative stress, lowered NF-κB phosphorylation, reduced muscle discomfort and accelerated muscle strength recovery. Farup et al. (2014) showed whey protein supplementation was also able to accelerate satellite cell proliferation during recovery from exercise. However, it is not clear how these latter study results compare to plant-based alternatives.

In contrast, there has been an accelerated interest in the benefits of plant proteins for muscle recovery. Xia et al. (2018) provided untrained men with an oat protein supplement for 2 weeks prior and 4 days following exercise-induced muscle damage and reported significant reductions in muscle soreness, swelling and levels of IL-6, CK and C-reactive protein (CRP). Although other studies have reported protein ingestion has no significant impact on muscle recovery regardless of protein source. Saracino et al. (2020) provided a cohort of healthy, recreationally active, middle-aged men with a pre-sleep supplement of whey protein, rice with pea, or placebo over a 5-day period following muscle damage. The Saracino et al. (2020) study measured CK, IL-6 and IL-10, as well as maximal voluntary contraction force and muscle soreness at various time points and found no significant differences between groups for any outcome measure.

While there may be conflicting views on the impact of different protein sources on muscle recovery, the studies conducted thus far contain several limitations. Researchers have almost exclusively used short periods of protein supplementation, with various levels of dosing, and it has not been unequivocally determined whether longer periods of supplementation at higher dosage maintain recovery equivalence between protein sources. Further, there is a distinct lack of studies investigating whether long-term habitual protein intake can affect muscle recovery in healthy populations.

3.0.2 Carbohydrates

Vegan diets have been promoted for their high intakes of complex carbohydrates compared to omnivores (Pohl et al., 2021; Rogerson, 2017). Carbohydrate supplementation during endurance exercise has been found to modulate cytokine responses, most notably by decreasing IL-6 levels

(Nehlsen-Cannarella et al., 1997; Stellingwerff et al., 2011). However, the influence of carbohydrate on muscle in the post-exercise recovery phase has not been well investigated. While increased carbohydrate intake may be necessary to promote glycogen resynthesis for refuelling (Alghannam et al., 2018), the research consensus appears to be that increased intake of carbohydrate has no direct impact on markers of muscle damage or cytokine production in recovery. Miles et al. (2007) conducted a double-blind, crossover protocol where a carbohydrate supplement was prescribed to 8 participants for 2 days post exercise-induced muscle damage and found that blood glucose, IL-6, CRP, cortisol, CK activity and maximal force production were not remarkably different from the placebo. Badenhorst et al. (2016) reported similar findings, where a high carbohydrate diet was ineffective in attenuating post-exercise IL-6 responses. From the research conducted thus far, increased carbohydrate intake generally appears to neither promote nor impair immune and muscle repair responses, and therefore is unlikely to play a significant role in muscle recovery processes outside of replenishing glycogen stores.

3.0.3 Antioxidants

Foods that contain antioxidants, most notably, polyphenols, have been upheld for their ability to attenuate oxidative stress by neutralising ROS (Stahl & Sies, 2003). Polyphenols are a large family of organic compounds naturally occurring in plants, which comprise flavonoids, anthocyanidins, resveratrol, curcumin, tannins, lignans, and phenolic acids, and have gained particular interest due to their increased antioxidant activity (Rudrapal et al., 2022). Phenolic compounds have a unique chemical structure of free hydroxyls and conjugation of side chains to aromatic rings that enables them to interact with ROS and terminate chain reactions before cell viability is impaired (Kumar & Pandey, 2013). Through this mechanism, polyphenols are able to modulate pro-inflammatory processes through blocking the activation of ROS-induced TNF-α and NF-κB-dependent pathways (Derosa et al., 2016; Kim et al., 2009; Noorafshan & Ashkani-Esfahani, 2013). Interestingly, trials using other forms of antioxidant supplementation such as isolated vitamin C and E, have not consistently shown the same improvements in exercise-induced oxidative stress or markers of inflammation (McLeay et al., 2012; Peake et al., 2007), suggesting polyphenols may have unique anti-inflammatory properties.

While whole plant foods may have the potential to mitigate the effects of excess inflammation and promote muscle recovery though their anti-inflammatory constituents, the effects cannot necessarily be extrapolated to habitual diets. For example, the dosage of curcumin, a constituent of turmeric, required to elicit anti-inflammatory effects could not realistically be reached through dietary sources alone, considering that turmeric as a spice contains only around 5% curcumin (Zeng et al., 2007), and that curcumin in its raw form does not itself lead to health benefits due to its poor bioavailability, rapid metabolism, and rapid elimination and enhancing agents must be added (Hewlings & Kalman, 2017).

3.0.4 Fat

There are substantial variations in the type and quantity of total fat between omnivorous and vegan diets, which likely translate to differences in inflammation biomarkers between the two groups. Of all the fatty acid classes, polyunsaturated fatty acids (PUFA) are considered to be the most influential to inflammatory responses (Calder, 2011). Since PUFAs are an integral component of cell membranes, they influence membrane fluidity and maintain protein function homeostasis, thus regulating cell signalling processes, cellular functions and gene expression involved in inflammatory processes (Calder, 2011; Das, 2006).

PUFA are classified into omega-3 [sub-classes alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)] and omega-6 fatty acids [sub-classes linoleic acid (LA), arachidonic acid (ARA), gamma-linolenic acid (GLA) and conjugated linoleic acid (CLA)], according to the chain length and location of double bonds in their chemical structure (Agostoni & Bruzzese, 1992). While both omega-3 and omega-6 forms of PUFA are considered essential for normal cell membrane function, high intakes of omega-6 stimulate pro-inflammatory pathways through activation of NF-κB activity, while omega-3 derivatives inhibit NF-κB activity and exert anti-inflammatory actions (Patterson et al., 2012). Over the past few decades, both vegans and omnivores have increased their omega-6 to omega-3 intake ratio (Clarys et al., 2014; Davey et al., 2003), although vegetarian and vegan diets reportedly have significantly higher omega-6 intake (Kornsteiner et al., 2008; Pinto et al., 2017; Welch et al., 2010). The striking omega-6 increase from both groups coincides with a parallel increase in chronic inflammatory diseases such as non-alcoholic fatty liver disease (NAFLD), cardiovascular disease, obesity, inflammatory bowel disease (IBD), rheumatoid arthritis, and Alzheimer's disease (Patterson et al., 2012).

Omega-3 PUFAs have long been upheld for having anti-inflammatory properties that enhance recovery and preserve strength after muscle-damaging exercise (Jouris et al., 2011). Omega-3 is acquired primarily from fatty fish and in smaller amounts from nuts, seeds and their oils (Jouris et al., 2011). Omega-3 supplementation has been shown to down-regulate pro-inflammatory cytokines TNF-α and IL-6, and blunt ROS production by various immune cells (Heileson & Funderburk, 2020; Kyriakidou et al., 2021; Mickleborough, 2013). EPA and DHA omega-3 have gained most attention, exerting their anti-inflammatory actions through several mechanisms, including blocking the activity of NF-κB through decreased phosphorylation and subsequent degradation of IκB in human monocytes and M1 macrophages (Karin, 1999; Weldon et al., 2007; Zhao et al., 2004). This mechanism has been found to directly inhibit IL-6 and IL-8 production in cultured human endothelial cells (Calder, 2013). EPA and DHA also upregulate resolvins that inhibit neutrophil infiltration at sites of inflammation so that their production of ROS, IL-1β and TNF-α is reduced (Serhan et al., 2008). These findings are supported by reports of high intakes of omega-3 alleviating symptoms of DOMS and enhancing muscle recovery time (Jouris et al., 2011; Rawson et al., 2018). It is worth noting that benefits have been more consistently seen with

omega-3 acquired through diet, primarily from fatty fish, rather than from supplementation (Gray et al., 2014; Tsuchiya et al., 2016).

There are, however, concerns around high intakes of other types of fat, particularly saturated fat (SFA) found primarily in animal foods (Davey et al., 2003). SFAs are considered problematic due to a well-studied link between SFA intake, high triglyceride levels and detrimental inflammation profiles (DiNicolantonio & O'Keefe, 2017). Haversen et al. (2009) demonstrated the pro-inflammatory actions of SFA in one *in-vitro* study using human macrophages and found that palmitate, a long-chain saturated fatty acid, induced mRNA expression and secretion of TNF-α, IL-8 and IL-1β by M1 macrophages. Other *in-vitro* studies have found palmitate also suppressed protein synthesis (Perry et al., 2018), reduced myoblast and myotube growth and caused apoptosis (Mishra & Simonson, 2005). Consistent with these findings, Woodworth-Hobbs et al. (2017) found palmitate induced myotube protein degradation that was subsequently ameliorated with DHA treatment. However, the deleterious effects of fat consumption are not universally accepted (Lowery, 2004) and literature on saturated fat in relation specifically to recovery from exercise is extremely limited. Therefore, the relationship between saturated fat and muscle recovery has yet to be fully determined.

3.1 Micronutrients in Inflammation and Muscle Recovery

3.1.1 Nitrates

Exogenous nitrate (NO_3^-) is acquired primarily through ingestion of green leafy vegetables and vegetable and fruit juices such as beetroot juice, carrot juice and pomegranate juice (Hord et al., 2009). Through a recycling process known as the nitrate-nitrite-NO pathway (Lundberg et al., 2008), nitrate-rich food is digested and absorbed, and then taken up by the salivary glands and reduced to nitrite (NO_2^-) by commensal anaerobic bacteria in the mouth (Hezel & Weitzberg, 2015). NO_2^- is then reabsorbed into circulation and converted to bioactive nitric oxide (NO) in blood and tissues (Hezel & Weitzberg, 2015). Skeletal muscle is the primary site of nitrate storage, where it is reduced to NO as needed physiologically or in conditions such as inflammation (Wylie et al., 2019). NO is multifaceted in the inflammatory immune response depending on its source and concentration (Dunstan et al., 2006). At high concentrations NO enhances inflammatory responses and apoptosis in skeletal muscle after damage (Nakazawa et al., 2017). However, NO also functions as a crucial signalling molecule and has strong antioxidant properties (Hummel et al., 2006). NO is also a vasodilator and is thought to contribute to improved muscle contractile function by promoting ATP synthesis in mitochondria and modulating blood flow and glucose uptake (Lee et al., 2019; Stamler & Meissner, 2001).

Nitrate-rich beetroot juice has been studied for its potential as a pre-exercise ergogenic aid, with several studies revealing it may be an effective supplement for performance enhancement in athletes (Bond et al., 2012; Hoon et al., 2014; Maughan et al., 2018), due to its vasodilatory effects and decreased ATP cost in muscle force production (Lee et al., 2019). While the role of beetroot

juice in muscle recovery is less well understood, beetroot juice has been considered as a recovery aid following muscle-damaging exercise due to its high antioxidant capacity and rich nitrate content, which has indirect antioxidant effects through supressing the accumulation of leukocytes, the main producers of ROS after muscle-damaging exercise (Clifford et al., 2016a). Earlier findings also showed leukocyte migration significantly reduced after 7 days of dietary and intravenous nitrate administration following intestinal injury (Jadert et al., 2012). The mechanism was thought to involve modification of transmembrane protein P-selectin and cell surface protein intercellular adhesion molecule 1 (ICAM-1), which decreases the attachment of leukocytes at sites of tissue injury (Jadert et al., 2012). There have also been reports that beetroot juice supplementation attenuates some aspects of muscle damage such as muscle soreness (Clifford et al., 2016b), and promotes adaptive skeletal muscle remodelling to exercise through activation of peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) (Roberts et al., 2017), 5' adenosine monophosphate-activated protein kinase (AMPK) signalling cascades (Mo et al., 2012) and stimulation of muscle-resident satellite cells (Anderson et al., 2018).

Conversely, other studies have reported that inflammatory responses are unaffected by NO, with no change in ROS, CK, IL-6, TNF-α or IL-8 observed between those consuming beetroot juice compared to a placebo in recreationally active male participants following exercise (Clifford et al., 2016a). Authors have attributed the observed differences between groups to phytonutrients other than nitrate, or interactions between them, arguing that coingestion of betacyanins and polyphenols in beetroot juice increases the capacity for NO synthesis from NO_2^-, thus increasing NO bioavailability (Gago et al., 2007). Moreover, chlorogenic acid, another constituent of beetroot juice, has been found to promote NO release by human saliva, further enhancing its absorption (Peri et al., 2005). Therefore, it has yet to be determined whether equivalent doses of nitrate ingested through different supplementation sources elicit comparable physiological adaptations to exercise.

3.1.2 Zinc

Zinc is an essential micronutrient found in its most absorbable form in seafood, meat and poultry, and in smaller amounts in legumes (Thompson et al., 2020). Zinc is most known for its critical roles in the central nervous system, growth and development, bone metabolism, immune function and tissue healing (Roohani et al., 2013). Zinc acts primarily as a cofactor, assisting over one hundred enzyme systems (Thompson et al., 2020), and is an essential component for maintaining cell membranes and gene signalling (Maywald et al., 2017), as well as for collagen-building enzymes during proliferation and remodelling of muscle after injury (Gammoh & Rink, 2017). Zinc is also part of the catalytic centre of one of the most important enzymes of the antioxidant defence system, superoxide dismutase (Krzysciak et al., 2010), thus it has an important role in controlling oxidative stress to allow for the repair of damaged muscle fibres.

Zinc's critical involvement in the immune system includes its influence in the production and signalling of inflammatory cytokines (Zhou et al., 2010). The human body has an increased

demand for zinc in inflammatory conditions (Foster & Samman, 2012) and there is a well-established link between low-grade systemic inflammation and mild zinc deficiency (Gammoh & Rink, 2017). Studies show that plasma zinc concentration declines rapidly following tissue damage, which precedes a prominent increase in TNF-α and IL-6 levels (Gaetke et al., 1997). This has also been demonstrated elsewhere, where participants with low dietary zinc intakes were found to have elevated levels of IL-1α, IL-1β, and IL-6 (Costarelli et al., 2010; Foster & Samman, 2012; Gammoh & Rink, 2017). The large body of evidence showing zinc deficiency leads to a weakened immune response, elevated inflammatory responses and impaired recovery rates, especially in tissues with high demand such as skeletal muscle (Hernandez-Camacho et al., 2020; Jinno et al., 2014) has profound implications for muscle recovery following intense exercise, particularly for vegan athletes whose diets may not provide sufficient levels of zinc.

3.2 Summary

The process of inflammation and muscle recovery following exercise-induced muscle damage follows a predictable sequence of events. Intense exercise overstretches sarcomeres, initiating a cascade of inflammatory responses. Damaged endothelial cells and infiltrating leukocytes release ROS-producing enzymes and causes uncontrollable release of Ca^{2+} from ruptured sarcoplasmic reticulum and sarcolemma into the cytosol, activating signalling cascades for apoptosis and protein degradation. These processes initiate a highly coordinated series of interactions between immune cells and muscle cells involving the sequential phases of degeneration, inflammation, regeneration, remodelling and repair, which are carefully orchestrated by cytokines. Pro-inflammatory cytokines TNF-α, IL-1β and IL-6 are released by muscle and immune cells following muscle damage, which signal the activation of processes that degrade and remove damaged cell components. This is followed by a reciprocal release of anti-inflammatory cytokines such as IL-10 that facilitate repair and regeneration. The relative concentration of these biomarkers can be detected in blood and used to understand the progression and time course of inflammation and recovery.

Studies on diet and supplements have already demonstrated their impact on many aspects of health, with differences in vegan and omnivorous diets uncovering some interesting findings. While the popularity of veganism is on the rise, there are concerns about the potential for nutrient deficiencies and the implications for immune function and muscle recovery. Several nutrients are acquired in their most absorbable and abundant forms from animal-derived foods, many of which play integral roles in inflammatory responses and muscle recovery through altering pathways involved in proteasome activity, oxidative stress, satellite cell activation and extra cellular matrix assembly. However, the evidence is contrasting. Some studies have shown no correlation between the intakes of these nutrients on the recovery of muscle, while others have demonstrated promising results from plant-based alternatives. Further, vegan diets have been shown to be higher in several antioxidants associated with reduced muscle recovery time. Despite the ongoing debate, there are major limitations in the studies conducted to date. Research has not yet unequivocally evaluated whether nutrients from plant sources have equivalent effects on muscle

recovery to that of animal sources. Additionally, studies have almost exclusively investigated the impact of supplementation, rather than the quality, quantity and effects of habitual diets and further research is needed to gain a better understanding about the effects of diet on muscle recovery.

CHAPTER 3. RESEARCH STUDY MANUSCRIPT

3.1 Abstract

Aim: To test whether individuals following a vegan diet present different levels of inflammation biomarkers in plasma after a bout of muscle damage-inducing exercise compared to individuals following an omnivorous diet.

Methods: Twelve recreationally active males aged 18-45 years old participated in a cross-sectional study. Participants were stratified as vegan or omnivorous based on self-reported dietary habits and completed a muscle damage-inducing lower body exercise protocol. Muscle damage marker CK, pro-inflammatory biomarkers IL-1β, TNF-α, CRP and anti-inflammatory biomarkers IL-6 and IL-10 were analysed from blood specimens collected at baseline and 0h, 1h, 3h, 24h, 48h and 72h after exercise to assess muscle damage and the time-course of post-exercise inflammation. Results were analysed using two way within-subjects ANOVA, repeated measures tests. Participants completed a 4-day food record to evaluate dietary influences on biomarkers.

Results: Increases in CK levels confirmed muscle damage as a result of the exercise protocol, with omnivores displaying significantly higher absolute CK values to that of vegans ($F = 8.076$, $P = 0.036$). Plasma IL-1β absolute values among omnivores were also significantly higher ($F = 1.010$, $P = 0.034$). No significant difference in CRP or TNF-α absolute values ($F = 2.913$, $P = 0.110$ and $F = 1.106$, $P = 0.377$ respectively) or percentage change from baseline ($F = 0.958$, $P = 0.373$ and $F = 1.153$, $P = 0.358$ respectively) were found between diet groups, although TNF-α values among vegans remained higher across the time course. IL-6 and IL-10 levels were below detection levels. Dietary analysis showed vegans had significantly lower intake of trans fats ($P = 0.046$), cholesterol ($P = 0.014$) and significantly higher riboflavin intake ($P = 0.010$) compared to omnivores. Daily intake of iodine and magnesium were below recommended levels for vegans and omnivores respectively.

Conclusion: While variations in nutrient intake may account for observed changes in inflammation biomarkers between groups, overall, vegans did not show significant differences in biomarkers of muscle recovery following exercise compared to omnivores.

3.2 Introduction

Research about veganism and its impact on health and athletic performance is still in its infancy and it has not been possible to make definitive conclusions about the role of vegan diets in the regulation of inflammation and muscle recovery. While it is suggested that adequate nutrition after exercise can support the regenerative capacity of muscle (Alghannam et al., 2018; Gleeson et al., 2004), a significant gap remains in our understanding of how dietary patterns impact the mechanisms underlying the initial muscle damage response and subsequent adaptations to exercise that support recovery.

The use of blood biomarkers presents huge potential for highly accurate evaluation of exercise-induced muscle damage and recovery. However, the current understanding of muscle damage and recovery from exercise in terms of biomarkers is limited and there is still no consensus about their variability or the magnitude of their appearance and clearance from blood after exercise. Complicating the issue, cytokines are numerous with diverse functions and while they are typically classified as being either pro- or anti-inflammatory, based loosely on their predominant action, many have roles in both (Smith et al., 2000). Further, cytokines respond to many stimuli and are frequently released by different cell types at various time points in recovery (Zhang & An, 2007). The blood levels of muscle damage markers such as creatine kinase (CK) also vary among individuals (Monastero & Pentyala, 2017). This makes it difficult to evaluate the extent of muscle damage and the progression of inflammation using the presence of CK and cytokines alone. However, the generally accepted method among researchers for assessing the progression of muscle damage and inflammation is by repeated measures of an individual's CK and cytokine levels, and comparing their normal baseline to various time points in recovery (Cerqueira et al., 2019; Neme Ide et al., 2013; Peake et al., 2017a). It is also well accepted that multiple biomarkers together with functional measures of muscle strength, can provide an accurate assessment of the trajectory of muscle damage, inflammation and recovery (Bessa et al., 2016; Liu et al., 2017; Yang, 2018).

This laboratory-based study aims to test whether individuals following a vegan diet present different levels of muscle damage and inflammation biomarkers after a bout of muscle damage-inducing exercise compared to individuals following an omnivorous diet. To pursue this aim, a cross-sectional study was conducted in healthy males aged 18-45 years old. The time-course of recovery of muscle biomarkers following a muscle damage-inducing protocol of the lower body was compared between vegans and omnivores, alongside their 4-day detailed habitual diet record.

3.3 Methods

3.3.1 Participants

Twelve recreationally active males [mean age 30 years (± 12 years), mean weight 79.4 kg (± 23.0 kg), mean height 1.780m (± 0.116 m)] were recruited through university lectures, poster advertisements, social media and newsletters to participate in the study. Participants were screened over the phone and invited to be included in the study if they met the following inclusion criteria: male, aged between 18–45 years old, recreationally active (defined as performing moderate intensity exercise ≤2 days/week), had followed either a vegan or omnivorous diet for at least 2 years; the minimum duration shown to impact inflammatory biomarkers in subjects following vegan diets (Haghighatdoost et al., 2017). Exclusion criteria included: chronic diseases such as cardiovascular disease and diabetes, taking prescription medication and/or anabolic steroids that may interfere with inflammatory biomarkers or physical ability, cigarette smoker, orthopaedic limitations or musculoskeletal disorders, involved in heavy strength training or other high-force activities including near maximal or maximal eccentric force generation. Females were excluded from the study as hormones involved in menstrual cycles have been shown to influence inflammation biomarkers (Romero-Parra et al., 2020). Information sheets were provided to those interested (Appendix A1). All participants completed a health-screening questionnaire (Appendix A2) prior to taking part in the study and written consent was obtained (Appendix A3). The study was approved by the Massey University Human Ethics Committee (SOA 22/10).

Participants were classified as vegan or omnivorous based on self-reported dietary profiles determined during the initial screening process. Vegans were defined by the consumption of only plant-based foods. Omnivores were defined as consuming animal products ≥3 times per week (Boutros et al., 2020a; Menzel et al., 2020). Self-reported physical activity levels were determined during the health-screening questionnaire. Participants were asked to abstain from consuming alcohol, caffeine, dietary supplements or medications immediately prior and during the experimental period and asked to refrain from intense lower-limb exercise for 24h prior to the start of the damaging protocol until the completion of testing.

3.3.2 Study Design

Participants were recruited for a cross-sectional study to compare inflammatory biomarkers in the recovery of a single bout of muscle damage-inducing exercise. Six vegan and six omnivorous recreationally active healthy men aged 18–45 who were unaccustomed to the exercise were included in the study (vegans: 32.83 ± 5.95 years, 74.59 ± 13.22 kg, 1.79 ± 0.06 m; omnivores: 28.14 ± 6.77 years, 84.23 ± 12.30 kg, 1.77 ± 0.07 m) (Appendix B1). Inflammatory and muscle damage biomarkers were analysed from blood specimens collected at baseline and selected time points post exercise to assess recovery rate and the results of the two groups were compared (Figure 3). Sample size was based on similar studies investigating muscular strength and recovery

(Hevia-Larraín et al., 2021; Page et al., 2022; Wells et al., 2003). Based on these studies, 20 participants per group would be required to achieve 80% (β) power and 5% (α) significance.

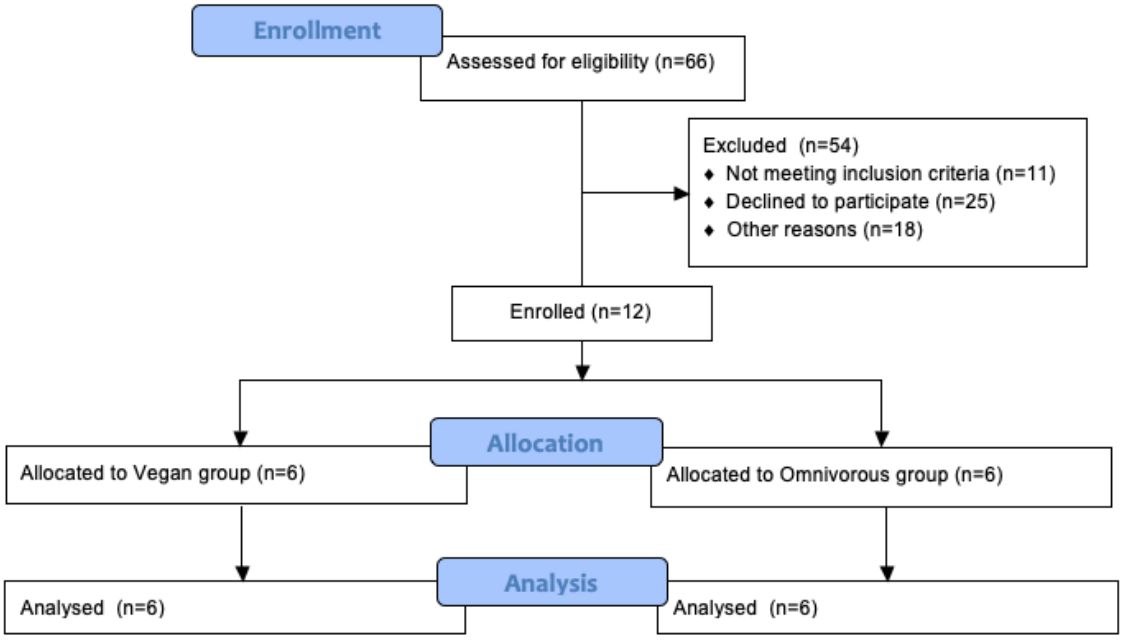

Figure 3: CONSORT flow diagram of the study: sample size and participant classification

3.3.3 Experimental Protocol

Participants were asked to attend a familiarisation session prior to starting the trial, where study procedures were explained, consent form signed (Appendix A3) and health screening questionnaire completed (Appendix A2). Height and weight were measured using a stadiometer and electronic calibrated scales respectively, and BMI was calculated ($kg.m^{-2}$). Participants were asked to complete a 3-day food diary for any days considered to be typical dietary intake, along with a 1-day food diary for all food and beverages consumed on the day of the muscle damage-inducing protocol (Appendix A4 and A5). Nutrient analysis was conducted from food records using Foodworks Professional (Xyris software package 2007) (Appendix B2). The time of day for testing was standardised, with participants commencing the trial between 8:00am and 11:00am.

On Day 1 of the trial, baseline blood samples were taken before participants were asked to perform a muscle damaging protocol of the legs. Completion time was recorded as 0h. Blood samples were taken immediately following the protocol (0h) and at 1h and 3h time points. Further blood samples were taken at 24h, 48h and 72h time points respectively (Figure 4).

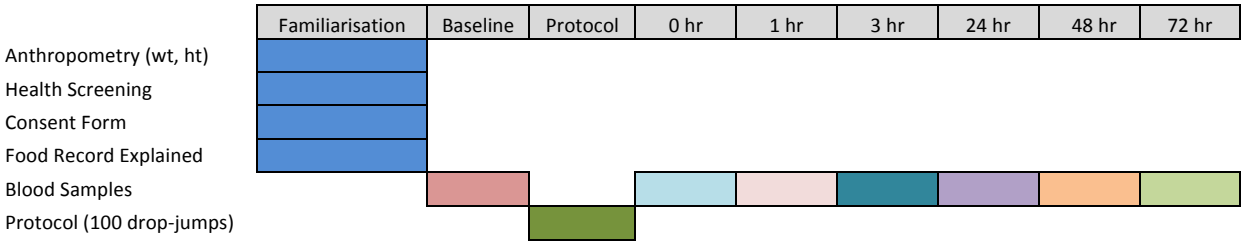

Figure 4. Experimental protocol schedule. wt: weight; ht: height.

3.3.4 Muscle Damaging Protocol

The muscle-damaging exercise protocol consisted of 100 drop-jumps from a 0.6 m high box. Each jump was separated by a 10 s interval and each 20 jumps by a 2 min rest period. Participants were instructed to jump from the box, landing on the ground with both feet, and immediately descending to a ~90° knee angle followed by maximal effort vertical jump. Participants were demonstrated the technique prior to performing the protocol and corrective feedback was provided throughout. Verbal encouragement was given to each participant to ensure maximal effort. This protocol has previously been demonstrated to induce significant muscle damage (i.e. increased muscle soreness, loss of muscle function) in the lower limbs (Howatson et al. 2009, 2012).

3.3.5 Blood Tests

Blood (8.5 ml) was obtained from the median cubital vein or a branch of the basilica vein at the antecubital fossa via venepuncture. Samples were collected into 10 ml vacutainer tubes treated with heparin as an anticoagulant. Plasma was separated by centrifuge for 10 mins at 3120 rpm within 30 mins of collection. Samples were aliquoted immediately into a duplicate series of aliquots and stored at -80˚C for later analysis. Using commercial ELISA kits (ThermoFisher Scientific, Waltham, MA, USA) inflammatory biomarkers IL-1β, IL-6, IL-10, TNF-α and CRP were measured (kit numbers: IL-1β #88-7261-22; IL-6 #88-7066-22; IL-10 #88-7106-22; TNF-α #88-7346-22; CRP #BMS288INST). CKM was measured using ELISA kit #ab185988 (Abcam, Cambridge, UK).

3.3.6 Statistical Analysis

IBM SPSS version 25 (IBM Company, Armonk, NY, USA) was used for all statistical analyses. The values of all variables were presented as the mean ± standard deviation. Two way within-subjects ANOVA, repeated measures were used to evaluate differences in biomarker concentrations at selected time points following a bout of exercise according to diet type (vegans vs omnivores). Unpaired 2-tailed t-tests were used to evaluate differences in nutrient intake between groups using Microsoft Excel. All p-values were reported significant at $P \leq 0.05$.

3.4 Results

3.4.1 Creatine Kinase (CK)

Plasma CK concentrations remained consistently higher across the time course in the omnivore group compared to the vegan group, with a significant difference observed between groups (F = 8.076, P = 0.036). However, there was no significant change in absolute values across time points (F = 2.124, P = 0.177). A similar trend in CK levels was seen for both vegans and omnivores with levels rising at 1h post-exercise and peaking at around 24h (100.4% and 104.3% change from baseline respectively), although the percentage change between vegans and omnivores was not found to be significant when compared to baseline levels (F = 0.099, P = 0.766) (Figure 5).

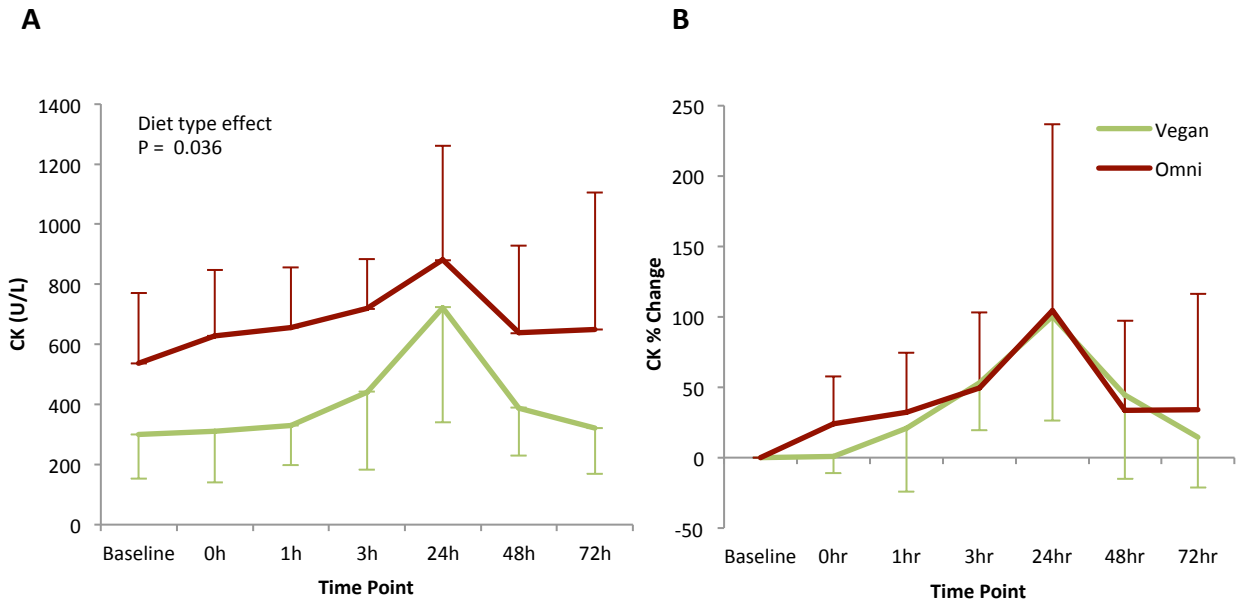

Figure 5. Plasma CK values over the time course of muscle damage-inducing exercise. Panel A: Absolute Values: Diet type effect: F = 8.076, P = 0.036; Time effect: F = 2.124, P = 0.177; Interaction between diet and time: F = 0.206, P = 0.825. Panel B: % change from baseline: Diet type effect: F = 0.099, P = 0.766; Time effect: F = 3.451, P = 0.091; Interaction between diet and time: F = 0.355, P = 0.772. STATS method: two way within-subjects ANOVA, repeated measures. Values presented as mean ± SD. Vegan N = 6; Omnivore N = 6.

3.4.2 C-reactive Protein (CRP)

Absolute CRP concentrations among both vegans and omnivores remained largely unchanged across time points (F = 2.913, P = 0.110), with a slight increase at around 24h post-exercise in the omnivorous group. The absolute change between diet groups was also found to be not significant (F = 0.023, P = 0.886). While relative changes in CRP levels from baseline were not different between diet groups (F = 0.958, P = 0.373), there was an increasing trend, with a 118.4% peak from baseline among the omnivorous group at 24h and a 44.4% peak from baseline at 48h among the vegan group (F = 3.607, P = 0.100) (Figure 6).

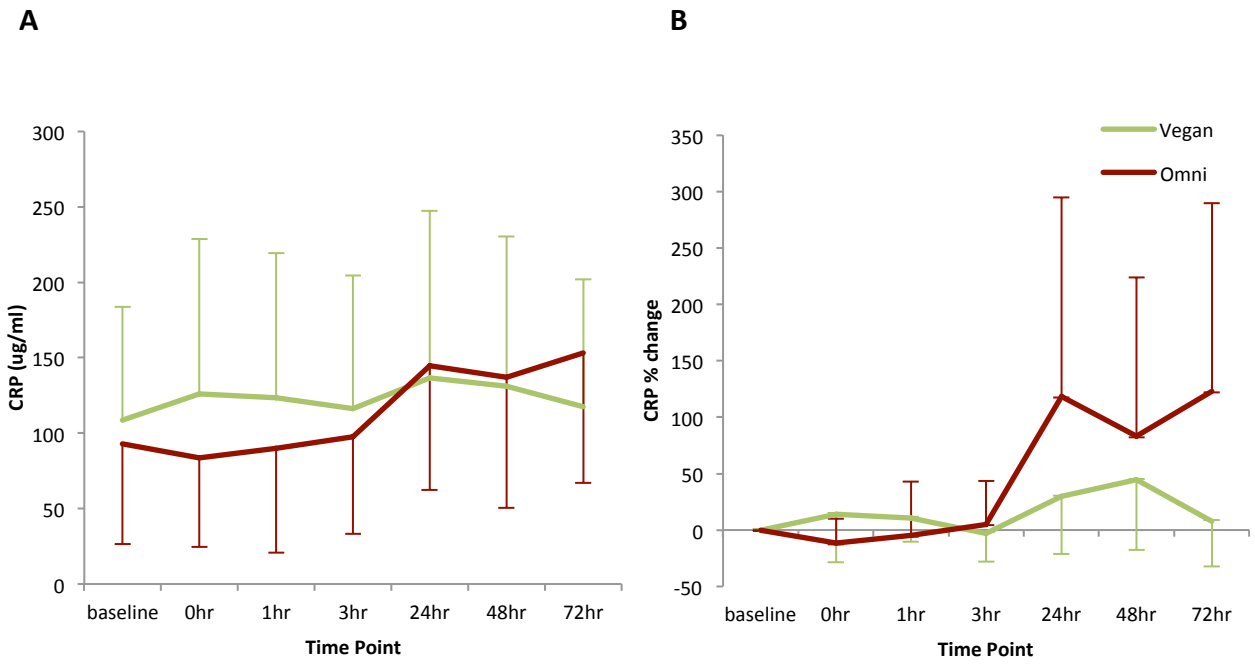

Figure 6. Plasma CRP values over the time course of muscle damage-inducing exercise**.** Panel A: Absolute Values: Diet Type effect: F = 0.023, P = 0.886; Time effect: F = 2.913, P = 0.110; Interaction between diet and time: F = 2.452, P = 0.153. Panel B: % change from baseline: Diet type effect: F = 0.958, P = 0.373; Time effect: F = 3.607, P = 0.100; Interaction between diet and time: F = 2.452, P = 0.153. STATS method: two way within-subjects ANOVA, repeated measures. Values presented as mean ± SD. Vegan N = 6; Omnivore N = 6.

3.4.3 Tumor Necrosis Factor alpha (TNF-α)

While plasma TNF-α among vegans trended higher to that of omnivores, absolute concentrations did not change significantly across time points (F = 1.106, P = 0.377) or between vegans and omnivores (F = 2.916, P = 0.149) as a result of the damage-inducing exercise (Figure 7). Vegan TNF-α levels peaked immediately following the exercise (39.3% increase), while omnivore TNF-α levels peaked later at 24h (31.7% increase). However, no significant change from baseline was observed across time points (F = 1.153, P = 0.358) or between vegans and omnivores (F = 0.050, P = 0.831).

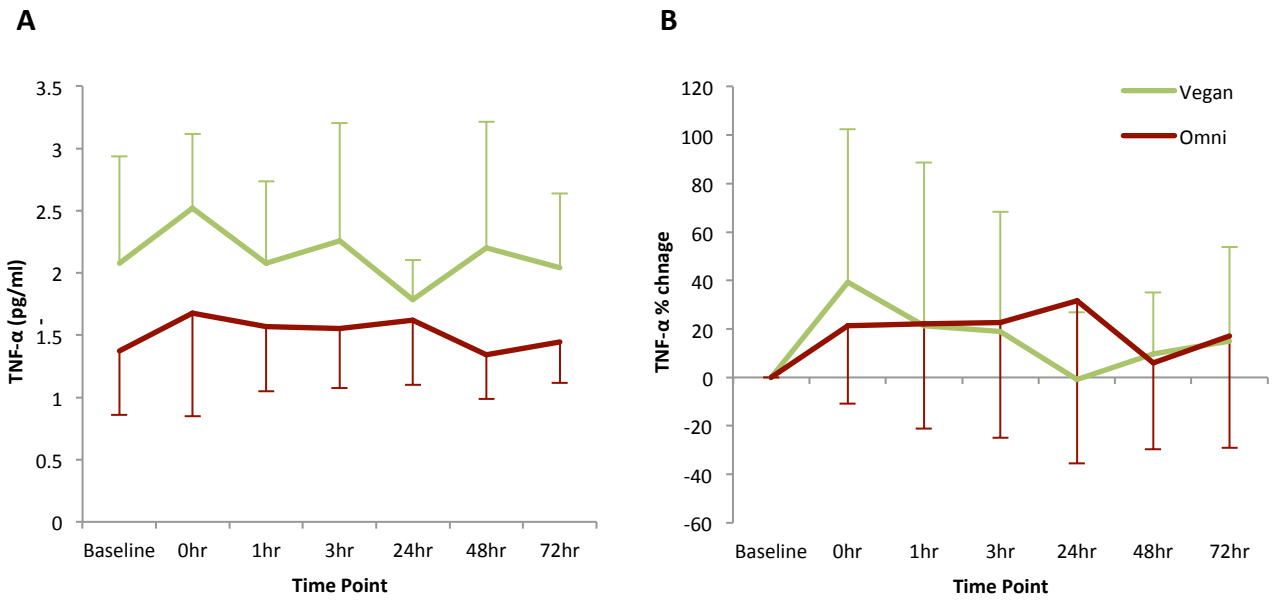

Figure 7. Plasma TNF-α values over the time course of muscle damage-inducing exercise. Panel A: Absolute Values: Diet type effect: F = 2.916, P = 0.149; Time effect: F = 1.106, P = 0.377; Interaction between diet and time: F = 0.788, P = 0.473. Panel B: % change from baseline: Diet type effect: F = 0.050, P = 0.831; Time effect: F = 1.153, P = 0.358; Interaction between diet and time: F = 0.614, P = 0.579. STATS method: two way within-subjects ANOVA, repeated measures. Values presented as mean ± SD. Vegan N = 6; Omnivore N = 6.

3.4.4 Interleukin 1-beta (IL-1β)

Plasma IL-1β absolute values among omnivores were significantly higher to that of vegans (F = 1.010, P = 0.034), although concentrations did not change significantly across time points (F = 0.580, P = 0.741) as a result of the muscle damaging protocol (Figure 8). Omnivores showed an initial increase from baseline at 0h (108.9 % increase), while vegans demonstrated a marginal decrease at this time point (39.6% decrease). A IL-1β peak at around 3h was observed among omnivores (371.8% increase), followed by a sharp decline, while vegans showed little change across time points. No significant percentage change from baseline was observed between vegans and omnivores (F = 0.730, P = 0.628).

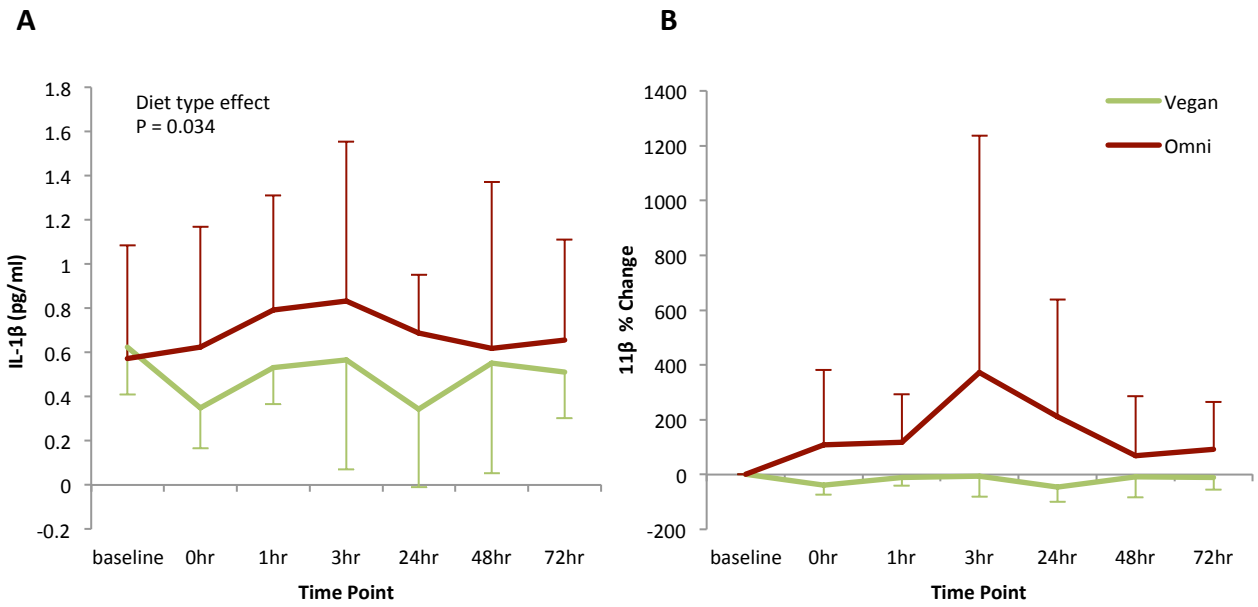

Figure 8. Plasma IL-1β values over the time course of muscle damage-inducing exercise. Panel A: Absolute Values: Diet type effect: F = 1.010, P = 0.034; Time effect: F = 0.580, P = 0.741; Interaction between diet and time: F = 0.550, P = 0.766. Panel B: % change from baseline: Diet type effect: F = 1.040, P = 0.337; Time effect: F = 0.650, P = 0.687; Interaction between diet and time: F = 0.730, P = 0.628. STATS method: two way within-subjects ANOVA, repeated measures. Values presented as mean ± SD. Vegan N = 4; Omnivore N = 6. Results from two vegan participants were excluded as they were below the ELISA kit detection threshold.

3.5 Discussion

The results obtained from CK analysis indicated that the exercise protocol was sufficient enough to induce muscle damage for both vegan and omnivore groups, with a gradual incline in CK levels observed immediately following the exercise protocol and a clear peak at around 24h for both groups. CK levels subsided by 48h post-exercise, which could indicate a transition from the degradation phase toward muscle regeneration by the 48h time point. These findings suggest that while a validated protocol was adopted (Howatson et al. 2009) and shown to induce some muscle damage, the protocol used in this study may not have been of sufficient intensity to elicit a strong CK release and inflammatory reaction. This was supported by low TNF-α and CRP responses to the protocol, minimal variations in inflammatory changes and IL-10 and IL-6 concentrations that were below the levels required for detection by ELISA kits (< 2 pg/ml). However, given that a post-protocol increase in CK levels was observed, with an increasing trajectory in CRP and IL-1β levels and accompanying delayed onset muscle soreness (DOMS) for both omnivores and vegans (Appendix C), some muscle damage with a mild inflammatory response was evident.

Creatine Kinase (CK) is an enzyme released from damaged muscle cells and elevated levels can be used as a measure of muscle injury. In healthy individuals, baseline levels of CK plasma typically average between 35-175 U/L (Gagliano et al., 2009), but can range between 20 U/L to 16,000 U/L (Prelle et al., 2002). Conflicting results have been found in previous studies that have engaged male participants in a single bout of high-intensity exercise, some of which show similar initial CK values to what was found in this study (ranging from 150-850 U/L) with around 100% increases from baseline levels (Kindermann, 2016; Laufs et al., 2015), while others have shown a much stronger CK response with increases of around 380% from baseline (Bessa et al., 2016; Liu et al., 2017).

Although no significant percentage change in serum CK levels from baseline was observed between vegans and omnivores in this study, absolute CK levels among omnivores were significantly higher (P=0.036). This was consistent with other studies showing that individuals with creatine-poor vegetarian and vegan diets display lower estimated muscle and serum creatine levels than meat-eaters (Brosnan & Brosnan, 2016; Delanghe et al., 1989; Yazigi Solis et al., 2014). Alternatively, the elevated CK baseline levels for omnivores may be indicative of pre-existing muscle damage in this group, although physiological variations in muscle mass and physical activity levels have also been shown to affect serum CK concentrations in healthy individuals (Baird et al., 2012). Participants with higher muscle mass will invariably release higher levels of CK as injured muscle is degraded (Hedayati et al., 2020). Although body composition parameters were not directly measured in this study, the omnivorous group were found to have higher total body mass than vegans (Appendix B1), which may have translated to higher muscle mass among the omnivores and account for the higher CK levels observed by this group. While individuals engaging in elite athletics were excluded from the study, sustained exercise such as long-distance running have also been shown to display increased CK levels in skeletal muscle (Belonje et al., 2007).

Further, non-modifiable factors such as ethnicity and age are known to drastically affect enzyme tissue activity and therefore, serum CK levels (Heled et al., 2007).

CRP is a protein released from the liver in response to generalised inflammation and is a useful diagnostic biomarker to support results suggesting elevated inflammation (Kasapis & Thompson, 2005). CRP responses are also associated with high CK levels in individuals unaccustomed to exercise (Isaacs et al., 2019), making it a useful measure to support findings of muscle damage and inflammation. Post-exercise CRP concentrations in this study were comparable with similar studies involving untrained male subjects in a bout of eccentric exercise, in which increases of around 50% from baseline levels have been reported (Nosaka & Clarkson, 1996; Phillips et al., 2003). However, no significant variation in CRP levels over time, or between groups was observed in this study, despite extensive research showing a correlation between vegan diets and lower generalised CRP levels compared to non-vegans (Barnard et al., 2019; Menzel et al., 2020). This may be in part due to the fact that while previous studies have linked lower CRP levels in vegan individuals with higher antioxidant and fibre intake, differences in the intake of these nutrients in this study were not found to be significantly different between groups (Appendix B2).

Dietary fatty acids have been extensively reviewed in the literature for their influence on inflammation and are thought to have an impact on muscle recovery. Fatty acids such as omega-3 are known to have anti-inflammatory properties, while LDL cholesterol and saturated fatty acids are associated with pro-inflammatory processes and increased CRP levels (Calder, 2010; Haversen et al., 2009). Saturated fat is typically higher in omnivorous diets since it is found predominantly in animal foods, although plant-based foods such as coconut cream and vegetable oils are also high in saturated fat and are often used as dairy replacements in vegan diets (Coulston, 1999; Davey et al., 2003; Fresán & Rippin, 2021). Interestingly, the current study found saturated fat intake among the vegans was similar to that of the omnivores, with no significant difference found between groups (Appendix B2). Cholesterol is another lipid-based compound found primarily in animal-derived foods such as eggs, meat and dairy. Consistent with the literature, the omnivorous group reported significantly higher cholesterol intake to that of the vegan group (Appendix B2), although this did not translate into higher CRP levels among the omnivores.

Similarly, TNF-α responses between vegans and omnivores were not found to be significant across time points or between diet types. This may be attributed to the fact that high intensity exercise is required to significantly elevate exercise-induced TNF-α levels (Hirose et al., 2004; Smith et al., 2000; Suzuki et al., 2000). Baseline values were in agreement with other studies at around 2.0 pg/ml (Hirose et al., 2004; Smith et al., 2000). However, absolute TNF-α levels among vegans were consistently higher than omnivores across the time course, despite not being statistically significant.

Some research has shown that TNF-α is affected by iodine intake due to its ROS-reducing properties (Venturi & Venturi, 2009). Iodine is typically acquired from iodised salt, but also from

foods such as seaweed, seafood, eggs and dairy and is a common deficiency in vegan diets (Murai et al., 2021). Consistent with the literature, iodine intake among the vegan group was below the recommended daily intake (Nutrient Reference Values, 2006) (Appendix B2). While there is currently no research exploring the direct effects of iodine intake in muscle inflammation and recovery specifically, studies suggest iodine has an important influence on biomarkers of inflammation. However, the difference in iodine intake between diet groups in this study did not translate to significant differences in inflammation markers, despite previous research showing high doses of iodine enhances its action as an electron donor to neutralise ROS (Venturi & Venturi, 2009) which influences TNF-α levels through an inextricable link between ROS, TNF-α and NF-κB (Blaser et al., 2016; Moore et al., 1997; Pangestuti & Kim, 2011). While studies using high doses of iodine through supplementation have reported suppression in the levels of pro-inflammatory messengers such as nitric oxide, prostaglandin E2, and macrophage-generated TNF-α in animals with pre-existing inflammation (Moore et al., 1997; Pangestuti & Kim, 2011), the results of this study may suggest that iodine intake at very low levels may not affect inflammatory responses following exercise in the same way.

A significant difference in IL-1β levels was observed between groups (P=0.034), with omnivores demonstrating consistently higher levels to that of the vegans. While the vegan group demonstrated little change in plasma IL-1β concentration across time points, the omnivores showed a clear peak at around 3h post-exercise, followed by a sharp decline, although absolute IL-1β concentrations did not change significantly across time points. Conflicting results have been reported in previous studies using similar protocols. One study demonstrated similar IL-1β peaks at 1-2h following an eccentric downhill treadmill running protocol in sedentary middle-aged men (Peake et al., 2005), while another study using isokinetic eccentric contraction of elbow flexors showed no significant change from baseline levels (Chen & Hsieh, 2001). Baseline levels in this study were also slightly above values found in the literature (0.6 pg/ml vs 0.21 pg/ml) (Hirose et al., 2004).

Several micronutrients have been shown to influence IL-1β levels. Zinc is an important nutrient in the pathogenesis of inflammation and immune systems as it is required for the production of pro-inflammatory cytokines including IL-1β and IL-6 (Bonaventura et al., 2015). Zinc also functions as a key structural or catalytic component in hundreds of enzymes and promotes monocyte adhesion to endothelial cells that facilitate inflammatory responses (Chavakis et al., 1999). While zinc intake among vegans in this study was found to be similar to that of the omnivores (Appendix B2), plant-derived zinc has poor bioavailability (Hunt, 2003). Given that zinc deficiency is common among vegans (Foster et al., 2013; Menzel et al., 2021; Yeliosof & Silverman, 2018), it is feasible that the disparity in IL-1β levels between diet groups may be related to differences in bioavailable zinc intake. Future studies may consider more extensive dietary and blood analysis to accurately evaluate zinc status in this cohort.

Differences in magnesium intake between groups may have further contributed to observed differences in IL-1β levels. Plant-based diets are typically higher in magnesium since it is found

abundantly in green leafy vegetables, whole grains, legumes and nuts (Grober et al., 2015). Unsurprisingly, the vegan group reported magnesium intake met recommendations, while omnivores reported intakes were below recommended amounts (*Nutrient Reference Values*, 2006) (Appendix B2). While magnesium may not be considered a primary nutrient linked specifically with muscle recovery, it has been implicated as playing a crucial role in regulating inflammation and is correlated with lower IL-1β levels, even at normal dietary concentrations (Nakagawa et al., 2001; Nielsen, 2018). This was found to be the case among the vegans in this study, with high magnesium intake corresponding to a lower IL-1β response. Proposed mechanisms include magnesium-activated suppression of IL-1β through extracellular signal-regulated kinases 1 and 2 (ERK1/2) and peroxisome proliferator-activated receptor gamma (PPARγ) signalling pathways (Wang et al., 2017).

3.6 Conclusion

This cross-sectional study in a sample of healthy vegan and omnivorous men found some variations in inflammation responses between groups. However, variations were largely inconsistent. Omnivores demonstrated significantly higher levels of CK across all time points, even though the proportional increase of CK from exercise was similar between groups. Therefore, there is no evidence to support either group experienced a higher degree of muscle damage from the eccentric exercise protocol used in this study. An initial increase in TNF-α concentrations was also detected following the exercise protocol, with levels consistently higher among vegans, although no clear TNF-α peak or significant difference between groups was observed. On the other hand, serum IL-1β levels were significantly higher among omnivores, with a clear peak at 3h post-exercise, while little change was observed among vegans. Serum CRP concentrations were not significantly different between diet types and remained relatively unchanged over the time course.

While some variability in biomarkers between groups was detected, neither vegans nor omnivores demonstrated a strong inflammatory response to the exercise protocol and no marked accentuations were found across time points for any biomarker. IL-6 and IL-10 levels were also below detection levels, suggesting the inflammatory response was mild. However, the post-exercise increases in CK levels were indicative of some muscle damage in both groups and the observed fluctuations in serum TNF-α, CRP and IL-1β concentrations showed an overall increasing trend that suggests an inflammatory response. Dietary analysis also revealed notable differences in nutrient intake between vegans and omnivores, particularly cholesterol, iodine and magnesium, which may have contributed to variations in biomarker responses between groups. The small changes in biomarkers over the time course of muscle recovery were found to be similar between groups, which provides evidence that no significant difference in inflammatory biomarkers in muscle recovery between those following a vegan diet compared to those following an omnivorous diet was found in this study.

CHAPTER 4. CONCLUSIONS AND RECOMMENDATIONS

4.1 Overview and Conclusions

This study aimed to test whether individuals following a vegan diet presented differences in muscle inflammation biomarkers after a bout of muscle damage-inducing exercise compared to individuals following an omnivorous diet. The specific objectives were: 1) To measure levels of CK as a biomarker of muscle damage and IL-6, IL-10, IL-1β, TNF-α CRP as biomarkers of inflammation from blood samples acquired at baseline, 0h, 1h, 3h, 24h and 72h following a muscle damage-inducing protocol of the lower body. 2) To investigate differences in biomarkers of muscle inflammation and nutrient intake between groups of vegans and omnivores.

Muscle damage was confirmed through serum CK analysis which showed a clear post-protocol increase in CK concentrations from both groups, with simultaneous peaks at around the 24h time point before subsiding. While the CK response was mild, concentrations were at levels akin to what has been seen in other studies using similar protocols and reports of DOMS further supported the presence of muscle damage as a result of the protocol (Appendix C). Generalised and specific indicators of inflammation were measured through serum CRP, TNF-α and IL-1β analysis. A clear post-exercise peak in IL-1β levels was observed from the omnivorous group at levels similar to other studies, while vegans demonstrated little change from baseline levels in either biomarker. CRP was not significantly affected in this study. These findings may be attributed to reported differences in dietary intake of cholesterol and magnesium between groups, which have previously been found to influence these biomarkers. While no clear peak in TNF-α was observed from either group, observed differences may be attributed to corresponding variations in iodine intake between groups.

Overall, while biomarker concentrations fluctuated, no dramatic peaks were observed in this study and statistical analyses found no significant differences across time points for any marker. These findings suggest that the inflammatory response to the protocol was mild. This was further supported by the fact that post-protocol anti-inflammatory biomarkers IL-6 and IL-10 levels were extremely low. Both groups also responded similarly to the protocol, with CK levels peaking to around 100% of baseline level by the 24h time point. In conclusion, considering a single bout of eccentric exercise at mild intensity, no significant difference in inflammatory biomarkers in muscle recovery was found between those following a vegan diet compared to those following an omnivorous diet.

4.2 Contribution to Knowledge

Muscle recovery may be the single most important consideration of a training or exercise programme because it enables improved performance, allows time for the body to heal in preparation for the next training load, and decreases the risk of injury (Laumonier & Menetrey,

2016). Inflammation is integral to muscle recovery, as it functions to remove damaged muscle and initiates the repair process (Peake et al., 2017). Frequent participation in sport or exercise also creates unique nutritional requirements. However, despite the rise in veganism among athletes, little is known about how vegan diets impact inflammatory responses and the ability of muscle to recover. Hence it is becoming more important for athletes and practitioners to understand the nutritional profile of vegan diets and their implications for recovery.

Investigations of muscle recovery among vegans also have applications beyond athletic ability. Muscle plays an important role in chronic disease, as it serves as the principal reservoir for proteins to maintain function of vital organs and the immune system (Kadar et al., 2000). Chronic disease, including cancer, is often associated with rapid and extensive loss of muscle mass, strength, and metabolic function (Kadar et al., 2000) and replenishing and maintaining muscle mass is an important determinant of recovery and survival from disease states (Anker et al., 2004). Maintaining muscle mass is also important for effective glycemic control for patients with diabetes, since muscle tissue is a major regulator of systemic glucose homeostasis and poor glycemic control is associated with low muscle mass (Buczkowska & Dworzecki, 2003; Sugimoto et al., 2019). Muscle also functions as an endocrine organ, releasing a multitude of myokines that regulate the function of other organs, including tissue regeneration and repair, immunomodulation and cell signaling (Pedersen et al., 2007; Pedersen & Febbraio, 2008). Nonetheless, muscle recovery is seldom targeted as a relevant endpoint of dietary recommendations and there is currently a significant knowledge gap regarding the consequences of vegan diets on skeletal muscle mass, strength and recovery.

Investigating the relationships and differences in metabolic biomarkers of muscle recovery between vegans and omnivores advances our understanding of the impact of diet on recovery. The findings of this study may help guide approaches to sports training and clinical practice through understanding whether differences in the reparative ability of muscle exists between vegans and non-vegans and how variations in habitual diets can impact muscle recovery. New knowledge in this area may help guide future studies and inform dietetic strategies to facilitate enhanced and complete recovery from exercise or disease.

4.3 Strengths

Strengths of this research include the investigation of habitual diets without nutritional intervention, reflecting real-life dietary habits and patterns. An extensive variety of inflammatory biomarkers were also tested, with inclusion of both general and specific measures of inflammation and indicators of muscle damage. This enabled confirmation of muscle damage following the exercise protocol, as well as exploration of different aspects of inflammation and its associations with muscle damage and recovery. Another strength was appropriate identification of time points at which to conduct testing. This ensured high retention rate of participants while allowing for accurate evaluation of the trajectory of inflammatory responses within groups.

4.4 Limitations

A limitation inherent to a cross sectional design is that it is conducted at one point in time so that only associations can be made and causality cannot be inferred. Limitations were also found in making comparisons between individuals, as load was not normalised to the fitness level of each participant in the exercise protocol. While the counter movement jump height was adjusted to be maximal for each participant, the box height was standardised. Another limitation was that all participants performed the same number of drop jumps at the same intensity, which may have contributed to variability in individual responses. The small number of participants may also have contributed to reducing the power of the study, potentially skewing results and preventing application to the wider population. The results presented from this study may also not be representative of the entire population of men living in NZ, as participants were recruited only from the Auckland region. Further, results cannot be extrapolated to female populations since only males were included in the study and it is not clear whether females would respond similarly under the same conditions.

There were also limitations in biomarker analysis with elevated CK levels among the omnivores at baseline. This potentially indicated some muscle damage or training in this group prior to the protocol, which may have skewed results. Ethnic differences between participants may also have affected CK readings through differences in tissue enzyme activity. Further, the protocol used may have been of insufficient intensity to induce a strong inflammatory response. Variations in fitness levels and body composition between participants may also have impacted the extent of muscle damage, and variations in the age of participants may have affected recovery rate. There were also limitations in other biomarkers, with only one vegan participant providing usable data for IL-10 values, as concentrations were too low to detect in other participants. Consequently, IL-10 responses could not be accurately investigated. IL-6 concentrations were also too low to be detected and were not able to be accurately analysed.

Other limitations were presented by allowing for habitual diets in that macro- and micro-nutrient intake was not controlled for, inhibiting the evaluation of causal affects from diet. Further, participants could elect days to complete food records, which may not have truly reflected long-term habitual diets. The lack of distinction between ‘food’ and ‘supplements’ may also have led to participants consuming enriched or fortified foods during the experimental period, which may have elevated specific nutrients in blood and impacted on inflammatory responses to the protocol.

4.5 Recommendations for Future Research

Future studies should consider adaptations to the protocol such as adjusting the box height to be maximal for each participant, thus correcting for individual variations in physical ability. Future studies assessing exercise-induced inflammation may benefit from the use of an isokinetic dynamometer (IKD) to target specific leg muscles, and precisely adjust the load of the exercise to

each participant, potentially inducing a stronger inflammatory response and providing a more accurate evaluation of the progression of recovery. The inclusion of body composition and muscle mass measures in future studies would also be useful for isolating responses directly associated with the protocol. Recruiting a larger sample size that includes females, different ethnicities and regions, would also help identify patterns of responses and allow results to be extrapolated to a wider population. Future studies should specify days for participants to complete their diet records to be distanced from the study period, along with providing a clear definition of what constitutes supplements that must be avoided during the protocol period. This would likely provide a more accurate representation of habitual diets. Longitudinal research would be useful for investigating the long-term associations between veganism and biomarkers of muscle damage.

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APPENDICES

APPENDIX A. QUESTIONNAIRES AND MATERIALS

Document 1. Participant Information Sheet

VEGAN VS OMNIVOROUS DIETS - IMPACT ON MUSCLE RECOVERY

Researchers: Anastasia Woolsey; Tam Leach

Introduction

We are Massey University students studying toward a MSc Nutrition and Dietetics, supervised by Associate Professor Andy Foskett and Dr Kaio Vitzel and we are recruiting men to participate in a project investigating recovery of muscle after exercise, in those consuming a vegan diet (diets absent of any animal product) or an omnivorous diet (diets that include animal-based foods).

This participant Information sheet will help you decide if you'd like to take part in the study. Before you decide, you may want to talk about the study with other people, such as family, whānau, friends, or healthcare providers. Feel free to do this. Participation in this study is entirely voluntary and you are free to decline to participate, ask any questions about the study, or to withdraw from the research at any time.

If you agree to take part in this study, you will be asked to sign the Consent Form on the last page of this document. You will be given a copy of both the Participant Information Sheet and the Consent Form to keep.

Project Description

Vegan diets are becoming increasingly popular, as people move towards lifestyles deemed to be healthier and more environmentally friendly. Plant-based and vegan diets may support good health and prolong life expectancy, and may impact on sports performance. Recovery is an important consideration for anyone engaged in regular sports or exercise, since a speedy recovery prevents injury and gets you ready for the next training session as soon as possible. However, little is known about how vegan diets affect muscle recovery after exercise, compared to diets that include animal-based foods. Therefore, the main aim of the project is to investigate the impact of vegan diet vs omnivorous diet on muscle recovery after exercise.

Who can take part? We are looking for men who:

- Have adhered to either a vegan or an omnivore diet for at least the past 2 years.
- Recreationally active
- 18-45 years of age
- Non-smoker
- No chronic health conditions

The study is not suitable for Individuals who are advanced/elite athletes (someone who trains four or more times per week for their sport and competes at a high level), or performs lower limb strength/resistance training or has any conditions identified on the "Health Screening Questionnaire".

Project Procedures

The study requires you to attend five sessions at the School of Sport, Exercise and Nutrition at Massey University (Auckland campus)

The first session is a Familiarisation session. This involves a health-screening questionnaire, consent form and familiarisation with the exercise protocols/tests and other study procedures.

This will take around 45-60 minutes to complete.

Before you start the other tests, you will be asked to record the food that you eat for 3 days.

The following 4 visits will comprise the Research Trials.

Day 1:

Baseline tests

We will measure your body mass and stature.

Participants will first perform baseline measures where we will ask you to perform 3 vertical jumps on a floor mat to measure how high you can jump. We will also ask you to tell us how sore your leg feels at various times, using a scale system and a piece of equipment that presses gently on your leg, called an algometer. We will then take some blood samples to measure blood markers associated with muscle inflammation.

These initial tests will take about 30-40min to complete.

Exercise regimen

Next, you will be asked to do an exercise regimen. For this we will ask you to perform 100 drop jumps, which involves jumping off a 0.6m high box and landing with both feet on the ground, followed by an immediate vertical jump from the ground. There will be a 10 second interval between jumps and 2 min rest between each set of 20 jumps and we will direct you to do this activity safely. This will take about 30 mins.

You will then repeat the baseline tests as previously outlined, which will also be done again after 1 hour and 3 hours and will take about 30 min each time.

Between tests you can rest, have lunch, watch television etc.

We will also ask you to complete a one-day food diary for the day of the study, and another 3-day food diary on days where you are eating normally.

Day 2, 3 and 4:

At 24 hours (day 2), 48 hours (day 3) and 72 hours (day 4) after the exercise regimen, you will return to the lab and repeat the baseline tests as above.

This will take about 30 min each time.

That is the end of the tests.

Things you will need to avoid during the study

You will need to abstain from alcohol, caffeine and taking supplements for 24 hours before the test and for the duration of the tests You will also need to avoid doing any exercise for 48 h hours before the start of the study, until after the study has finished.

What are the possible benefits of this study?

You will be involved in an exciting project looking at how vegan and omnivorous diets affect muscle recovery from exercise. You will gain insight into how research is done, you will receive valuable information about how your body responds to exercise, and you will be contributing to finding answers to unanswered questions about diet and muscle function.

What are the possible risks of this study?

You may experience some minor discomfort, such as muscle cramps, delayed muscle soreness, or fatigue, during or after the exercise regimen. There is also a chance of soreness, bruising or infection at the injection site when blood samples are taken. We will guide you through how to use the exercise equipment correctly to avoid injury and all practicable steps will be taken to minimize risks. Staff will be fully trained in the procedure they are carrying out and only fully qualified phlebotomists will be taking blood samples. We will also have support staff available in case you do experience any adverse affects.

Will any costs be reimbursed?

Participants will be offered a $50 MTA voucher to contribute to any transport and food costs incurred on the participation days.

What if something goes wrong?

If you were to be injured in this study, you would be eligible to apply for compensation from ACC just as you would be if you were injured in an accident at work or at home. If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won’t affect your cover.

What will happen to my information?

During this study the researchers will record information about you and your study participation. This includes the results of any study assessments and information collected from you before the study. You cannot take part in this study if you do not consent to the collection of this information.

Identifiable Information

Only researchers will have access to your identifiable information (your name, date of birth).

De-identified (Coded) Information

To make sure your personal information is kept confidential, information that identifies you will not be included in any report from the study. Instead, you will be identified by a code. The results of the study may be published or presented, but not in a form that would reasonably be expected to identify you.

Security and storage of your information

Your identifiable information is held at Massy University (Auckland campus) during the study and stored for no longer than five (5) years, then destroyed. All storage will comply with local and/or international data security guidelines.

Who has approved the study?

This project has been reviewed and approved by the Massey University Human Ethics Committee: Southern A, Application 22/10. If you have any concerns about the conduct of this research, please contact Chair, Massey University Human Ethics Committee: Southern A, telephone 04 801 5799 x 63363, email humanethicsoutha@massey.ac.nz.

Compensation for Injury

If physical injury results from your participation in this study, you should visit a treatment provider to make a claim to ACC as soon as possible. ACC cover and entitlements are not automatic, and your claim will be assessed by ACC in accordance with the Accident Compensation Act 2001. If your claim is accepted, ACC must inform you of your entitlements, and must help you access those entitlements. Entitlements may include, but not be limited to, treatment costs, travel costs for rehabilitation, loss of earnings, and/or lump sum for permanent impairment. Compensation for mental trauma may also be included, but only if this is incurred as a result of physical injury.

If your ACC claim is not accepted, you should immediately contact the researcher. The researcher will initiate processes to ensure you receive compensation equivalent to that to which you would have been entitled had ACC accepted your claim.

Who do I contact for more information or if I have any concerns?

If you have any questions, concerns or complaints about the study at any stage, you can contact:

Dr Kaio Vitzel
Senior Lecturer
School of Health Sciences
k.vitzel@massey.ac.nz
office: (09) 212 7050

Project Contacts

If you have any questions regarding this study, please do not hesitate to contact either of the following people for assistance:

Research coordinators

Tam Leach
[redacted]
MSc Nutrition and Dietetics Student
t.leach@massey.ac.nz

Anastasia Woolsey
[redacted]
MSc Nutrition and Dietetics Student
a.vulsi@massey.ac.nz

Good Practice and Cultural Safety for Massey University Research

This study has been discussed with Dr Bevan Erueti (Associate Dean Māori, Te Kura Hauora Tangata)
We have considered the inclusion of Māori and indigenous values and concepts, allowing for the use of whānau support and appropriate Māori protocols. We acknowledge the concept of manaakitanga, respecting the participant`s inherent dignity and acting in a caring manner towards them by way of:

- Taking full responsibility to perform research in a safe and ethical manner (aroha)
- Providing the participant with all of the critical information regarding the study in a clear way, so they can make informed decisions (tūmanako and whakapono)
- An awareness of the cultural significance and sensitivity for a culturally safe implementation of the study (māhaki)
- Respect for the privacy and confidentiality of Māori participants
- Acknowledging the tapu (sacred) nature of blood by offering remaining blood samples (if appropriate) back to the participant

All research activities will adhere to the Covid Protection Framework and guidelines from MoE and MoH.

This project has been reviewed and approved by the Massey University Human Ethics Committee: Southern A, Application 22/10. If you have any concerns about the conduct of this research, please contact Dr Negar Partow, Chair, Massey University Human Ethics Committee: Southern A, telephone 04 801 5799 x 63363, email humanethicsoutha@massey.ac.nz*.*

Participant's Rights

You are under no obligation to accept this invitation, but completion and return of the required forms implies consent. If you decide to participate, you have the right to:

- Decline to answer any particular question;
- Ask any questions or withdraw from the study at any time during participation;
-
- Provide information on the understanding that your name will not be used unless you give permission to the researcher;
- Be given access to a summary of the project findings when it is concluded.

Document 2. Health Screening Questionnaire

VEGAN VS OMNIVOROUS DIETS - IMPACT ON MUSCLE RECOVERY

Massey University Albany
Health Screening Questionnaire

Name:_____

Phone: _____

Age: _____

Gender:_____

Please read the following questions carefully. If you have any difficulty, please advise the medical practitioner, nurse or exercise specialist who is conducting the exercise test.

Please answer all of the following questions by ticking only one box for each question:

The questions are based upon the Physical Activity Readiness Questionnaire (PAR-Q), originally devised by the British Columbia Dept of Health (Canada), as revised by [1]Thomas *et al.* (1992) and [2]Cardinal *et al.* (1996), and with added requirements of the Massey University Human Ethics Committee. The information provided by you on this form will be treated with the strictest confidentiality.

Qu 1. Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?

Yes ☐ No ☐

Qu 2. Do you feel a pain in your chest when you do physical activity?

Yes ☐ No ☐

Qu 3. In the past month have you had chest pain when you were not doing physical activity?

Yes ☐ No ☐

Qu 4. Do you lose your balance because of dizziness or do you ever lose consciousness?

Yes ☐ No ☐

Qu 5. Have you ever been told that you have high blood pressure?

Yes ☐ No ☐

Qu 6. Do you experience shortness of breath during only mild exertion?

Yes ☐ No ☐

Qu 7. Do you have epilepsy or have you ever had a seizure of any sort? Explain?

Yes ☐ No ☐

Qu 8. Are you currently taking any prescribed medication? If so, what?

Yes ☐ No ☐

Qu 9. Do you ever get pains in your calves, buttocks or at the back of your legs during exercise which are not due to soreness or stiffness?

Yes ☐ No ☐

Qu 10. Do you have a bone or joint problem (for example, back, knee or hip) that could be made worse by a change in your physical activity?

Yes ☐ No ☐

Qu 11. Have you recently undergone surgery or are you carrying an injury? Explain.

Yes ☐ No ☐

Qu 12. Do you smoke?

Yes ☐ No ☐

Qu 13. Do you perform regular leg resistance/strength exercise?

Yes ☐ No ☐

Qu 14. Are you currently ill in any way? Please explain.

Yes ☐ No ☐

Qu 15. Are you aware of any other reason why you should not participate in physical exercise without medical supervision? If so, what?

Yes ☐ No ☐

Qu 16. Do you have any issues with having your blood taken?

Yes ☐ No ☐

Qu 17. Do you have any bleeding or healing disorders?

Yes ☐ ☐ No

Qu 18. Are there any issues that may prevent you from completing an approximately 45 min of single-leg exercise comprised of intense contractions of the thigh muscles? If yes, please explain.

Yes ☐ ☐ No

_____

_____

_____

Qu 19. Has your diet in the past 2 years included foods of animal origin (meat, chicken, fish, eggs, milk, dairy products)

Yes ☐ ☐ **No**

If YES, how many times per week do you consume animal-derived foods?

3 or more times per week ☐

Less than 3 times per week ☐

I have read, understood and completed this questionnaire.

Signature ***(Participant):*** _____ Date: _____

References

1. Thomas S, Reading J and Shephard RJ. Revision of the Physical Activity Readiness Questionnaire (PAR-Q). *Can J Sport Sci* 17(4): 338-345.
2. Cardinal BJ, Esters J and Cardinal MK. Evaluation of the revised physical activity readiness questionnaire in older adults. *Med Sci Sports Exerc* 28(4): 468-472

Document 3. Consent Form for Study Volunteers

Vegan diet vs Omnivorous diet: Impact on recovery of muscle function

CONSENT FORM FOR STUDY VOLUNTEERS

This consent form will be held for a minimum period of five (5) years

I have read the Participant Information Sheet and have had the details of the study explained to me. My questions have been answered to my satisfaction, and I understand that I may ask further questions at any time.

I understand that I have the right to withdraw from the study at any time and to decline to answer any particular questions (if I choose to withdraw, I cannot withdraw my data from the analysis after the data collection has been completed).

I agree to provide information to the researcher on the understanding that my name will not be used without my permission. (The information will be used only for this research and publications arising from this research project.)

I agree to participate in this study under the conditions set out in the Participant Information Sheet.

Signature: _____

Date_____

Full Name (printed)

_____

Phone Number_____ Age _____Date of Birth _____

Document 4. Diet Record Instruction Sheet

How to complete a 3-day food diary:

- Eat normally. You will not be assessed on the content of your diet
- Write down everything you eat and drink for **3 consecutive days.** Try and chose days that you are eating as you normally would
- Include water and any other drinks in your food record.
- Record cuts and **types** of meat, type of milk, type of bread, fruit varieties, brand names, etc. (eg Anchor dark blue top milk, vogels wholegrain bread)
- Include **how the food is cooked** (for example: fried, baked, boiled, barbecued)
- Record food and drink **in the form it will be eaten** (eg 1 cup cooked white rice - boiled)

Several methods can be used to indicate how much you have consumed:

- Measure **serving sizes** using household measures – for example, cups, teaspoons and tablespoons. E.g. 1 cup frozen peas, 1 heaped teaspoon of sugar.
- OR record the **amounts** of food you eat by weight marked on the packages – eg. a 425g tin of baked beans, a 32g cereal bar, 300ml Coke
- OR **weigh** the food with home kitchen scales. This is the ideal way to get an accurate idea of the quantity of food eaten, in particular for foods such as meat, fruits, vegetables and cheese (eg 125g chicken breast)
- Many purchased foods and drinks state the weight or volume on the labels, these can be used directly

Other information:

- Include anything you **add to food** during or after cooking. Eg: cream, sugar, oil, butter, jam, syrup, tomato sauce, salad dressings or condiments.
- **Subtract any food not consumed**. Don't worry about non-edible portions of food, e.g. apple cores and chicken bones. These are taken into account in the food composition data base
- Attach **recipes** for home prepared dishes where possible, and record the proportion of the dish you consumed (total serves; number serves you eat)
- If foods are **fortified** include a copy of the nutrition label with your record (check breakfast cereals)
- **Dining out**? Estimate portions using the hand model below

Handful (30g) Palm (90g) Fist (1 cup)

- If you're not sure, just ask. We are happy to provde more information.
- Return the completed food diary to the research team by the last day of the trial (by email or hard copy)

Thank you for your partcipation in our study

Document 5. Food Diary Example and Template

Meal and time food was eaten	**Complete description of food** (preparation, variety, brand) If possible attach the recipe or the nutrition label (fortified foods).	**Amount consumed (units, measures, weight)**
Example: Breakfast 7:55 AM	*Kellogs All Bran (original)*	*1 cup*
	Raw sugar	*1 tsp*
	Milk - dark blue top (Anchor)	*½ cup*
Snack 10 AM	*Carrot muffin (home made. Recipe attached)*	*1 muffin*
	Chai Tea	*200 ml*
	Milk - dark blue top (Anchor)	*¼ cup*
Lunch 1 PM	*Egg, fried in olive oil*	*1 egg*
	Wholegrain toast (vogel's thin slice)	*1 slice*
	Butter (Mainland buttersoft)	*15g*
	Banana smoothie	*1 small banana, ¼ cup frozen blueberries, ¼ cup unsweetened almond milk*

Diet Record Template (3-day record) - To complete on days considered as usual eating

Day _____ : Date & Day of week _____

Meal and time food was eaten	*Complete description of food (preparation, variety, brand) If possible attach the recipe or the nutrition label (fortified foods).*	*Amount consumed (units, measures, weight)*

Diet Record Template (1-day record) to complete on day of study protocol

Date & Day of week _____

Meal and time food was eaten	**Complete description of food** (preparation, variety, brand) If possible attach the recipe or the nutrition label (fortified	**Amount consumed (units, measures,**

APPENDIX B. SUPPLEMENTARY RESULTS

Table 1. Participant Anthropometry and Age

	Weight (kg) Mean ± SD	Height (m) Mean ± SD	BMI (kg/m^2) Mean ± SD	Age (years) Mean ± SD
Vegan (n=6)	74.59 ± 13.22	1.79 ± 0.06	23.10 ± 2.82	32.83 ± 5.95
Omnivore (n=6)	84.23 ± 12.30	1.77 ± 0.07	27.04 ± 4.82	28.14 ± 6.77

Table 2. Diet Record Nutrient Analysis Summary

Dietary data assessed using Foodworks Professional (Xyris software package 2007)

Nutrient	Recommended Daily Intake (RDI)*	Vegan Mean ± SD (n = 5)	Omni Mean ± SD (n = 6)	$p-value^d$
Energy (kJ)		12584.27 ± 2713.16	10081.36 ± 1669.37	0.3819
Protein (g)	15-25% EER	102.47 ± 30.46	108.28 ± 48.05	0.8298
Total Fat (g)	20-35% EER	134.20 ± 35.34	84.33 ± 11.00	0.1352
Sat fat (g)	<10% EER	33.33 ± 20.37	25.33 ± 6.41	0.4453
Trans fat (g)		0.40 ± 0.28	1.11 ± 0.40	**0.0463**
Poly fat (g)		32.80 ± 8.78	16.67 ± 3.96	0.1874
Mono fat (g)		48.67 ± 11.43	31.17 ± 4.74	0.2236
Cholesterol (mg)		5.27 ± 2.71	289.00 ± 162.66	**0.0104**
Carbohydrate (g)	45-65% EER	321.07 ± 65.14	287.75 ± 91.12	0.7168
Sugars total (g)		111.07 ± 28.50	85.67 ± 64.31	0.4818
Starch (g)		204.47 ± 38.33	192.83 ± 70.85	0.8706
Fibre (g)	30 g/d	56.73 ± 22.36	29.25 ± 6.81	0.0752
Thiamin (mg)	1.2 mg/day	1.95 ± 0.48	1.52 ± 0.87	0.3609
Riboflavin (mg)	1.3 mg/day	1.99 ± 0.29	1.36 ± 0.52	**0.0476**
Niacin (mg)		17.26 ± 5.23	22.40 ± 11.86	0.3842
Niacin equivalents (mg)	16 mg/day	36.65 ± 1.19	43.05 ± 20.67	0.5562
Vit C (mg)	45 mg/day	127.17 ± 63.89	137.58 ± 83.92	0.8506
Vit E (mg)	10 mg/day	43.67 ± 13.92	15.40 ± 6.39	0.2577
Tocopherol, alpha (mg)		24.17 ± 5.29	12.56 ± 2.82	0.2019
Vit B6 (mg)	1.3 mg/day	1.73 ± 0.51	1.36 ± 0.64	0.3959
Vit B12 (ug)	2.4 µg/day	2.07 ± 0.87	112.70 ± 263.23	0.3593
Folate total (ug)	400 µg/day	623.96 ± 267.65	575.49 ± 496.47	0.8478
Folic acid (ug)		81.51 ± 86.36	90.92 ± 63.83	0.8598
Food folate (ug)		542.63 ± 195.55	479.66 ± 430.39	0.7761
Vit A equivalents (ug)	900 µg/day (UL 3,000 µg/day)	1070.53 ± 387.04	730.63 ± 387.30	0.2202
Retinol (ug)		171.58 ± 68.27	187.84 ± 85.88	0.7933
Beta Carotene equivalents (ug)		5389.70 ± 2125.68	3256.91 ± 2270.16	0.1864
Beta Carotene (ug)		4200.26 ± 1084.19	2700.05 ± 1922.97	0.2621
Sodium (mg)	2,000 mg/day	3461.87 ± 761.23	2168.68 ± 876.01	0.0677
Potassium (mg)	3,800 mg/day	4104.62 ± 1133.92	3139.45 ± 1196.88	0.3172
Magnesium (mg)	420 mg/day	707.15 ± 190.72	361.71 ± 147.92	0.0963
Calcium (mg)	1,000 mg/day	1135.95 ± 344.90	625.68 ± 305.22	0.1169
Phosphorus (mg)	1,000 mg/day (UL 4,000 mg/day)	1820.60 ± 449.70	1498.91 ± 697.35	0.5208

Iron (mg)	8 mg/day	19.24 ± 5.57	13.08 ± 5.34	0.1681
Zinc (mg)	14 mg/day (UL 40 mg/day)	13.24 ± 3.47	10.50 ± 4.27	0.4729
Selenium (ug)	70 µg/day (UL 400 µg/day)	177.13 ± 60.56	92.11 ± 32.45	0.5608
Iodine (ug)	150 µg/day	128.78 ± 49.16	366.97 ± 614.30	0.3946

One missing vegan diet record, hence only 5 vegan participants were valid for analysis
d = *p* value tested using a dependent paired sampled t-test
* *Nutrient reference values for Australia and New Zealand: Including recommended dietary intakes*. (2006). National Health and Medical Research Council ; Ministry of Health.

APPENDIX C. MUSCLE FUNCTION SUPPLEMENTARY RESULTS

Results from Vegan Diet vs. Omnivorous Diet: Impact on recovery of muscle function. A thesis presented in partial fulfilment of the requirements for the degree of Master of Science in Nutrition and Dietetics at Massey University, Albany, New Zealand, by Anastasya Woolsey, 2023.

Results obtained from the same participants during the same experimental protocol as the present study. Consent obtained from A. Woolsey and supervisors to refer and attach results as appendix.

Counter-movement jumps (CMJ)

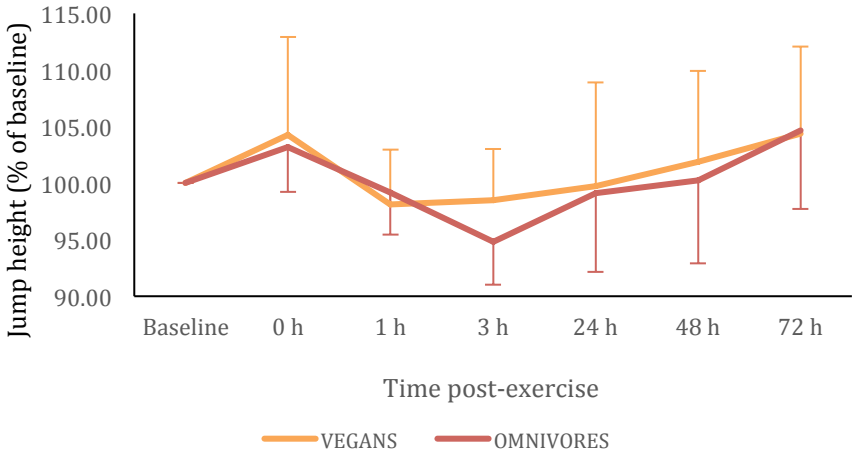

Figure 1 Change in CMJ height before and after the damaging exercise (% of baseline). Baseline values: Vegans 0.44±0.08m, Omnivores 0.42±0.06m. Values are mean ± SD. CMJ: counter-movement jump.

Pain

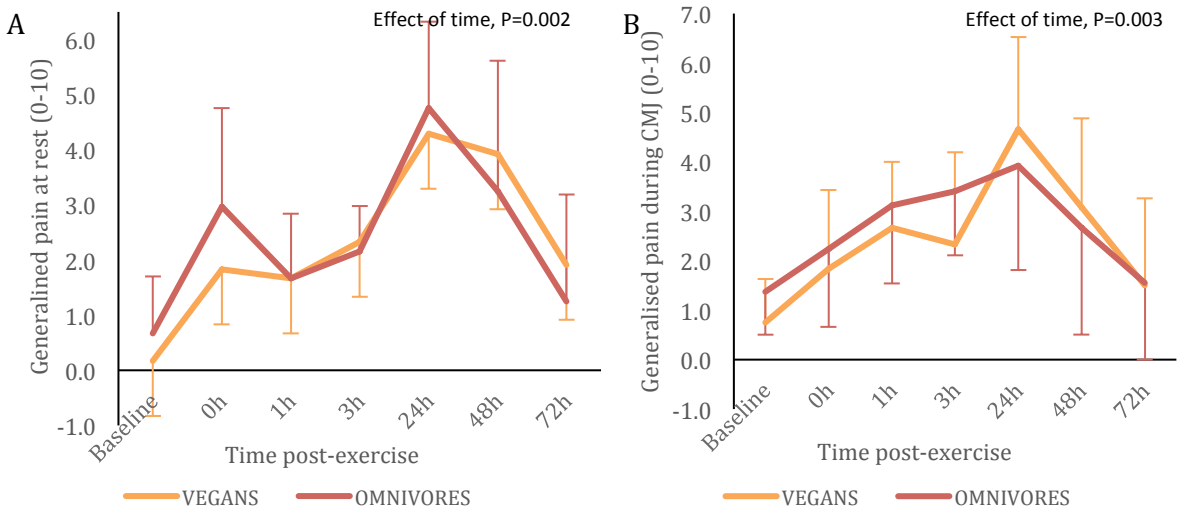

Figure 2 Subjective generalised pain scale (0-10), no pain (score 0) and worst pain (score 10). (A) at rest (F=10.868, P=0.002 for an effect of time using two-way repeated-measures ANOVA). (B) during CMJ (F=8.428, P=0.003 for an effect of time using two-way repeated-measures ANOVA). Values are mean ± SD. CMJ: counter-movement jump.

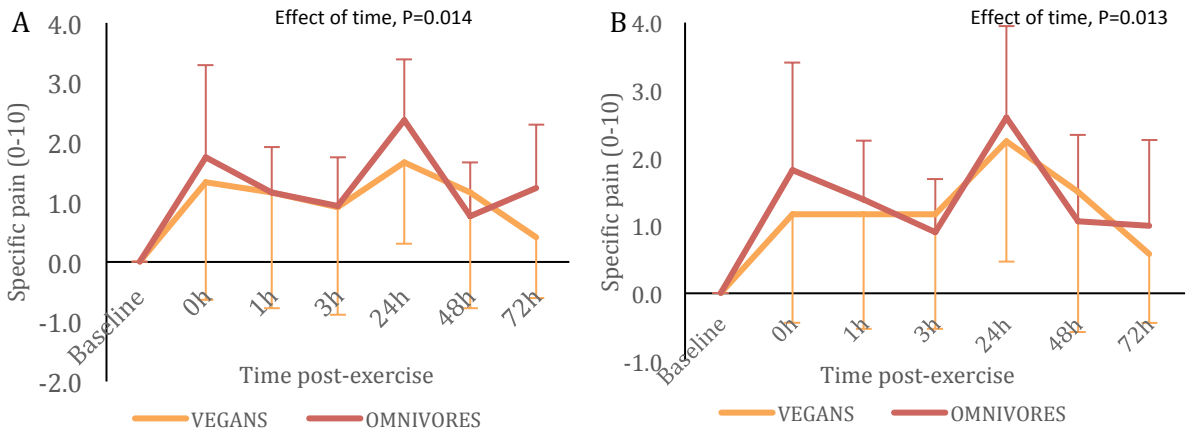

Figure 3 Subjective pain scale of the gastrocnemius muscle at rest (0-10), no pain (score 0) and worst pain (score 10). (A) left leg (F=4.510, P=0.014 for an effect of time using two-way repeated-measures ANOVA). (B) right leg (F=4.883, P=0.013 for an effect of time using two-way repeated-measures ANOVA). Values are mean ± SD

Figure 4 Subjective pain scale of the gluteus maximus muscle at rest (0-10), no pain (score 0) and worst pain (score 10). (A) left leg (F=12.377, P=0.017 for an effect of diet using two-way repeated-measures ANOVA). (B) right leg (F=5.285, P=0.02 for an effect of time using two-way repeated-measures ANOVA). Values are mean ± SD

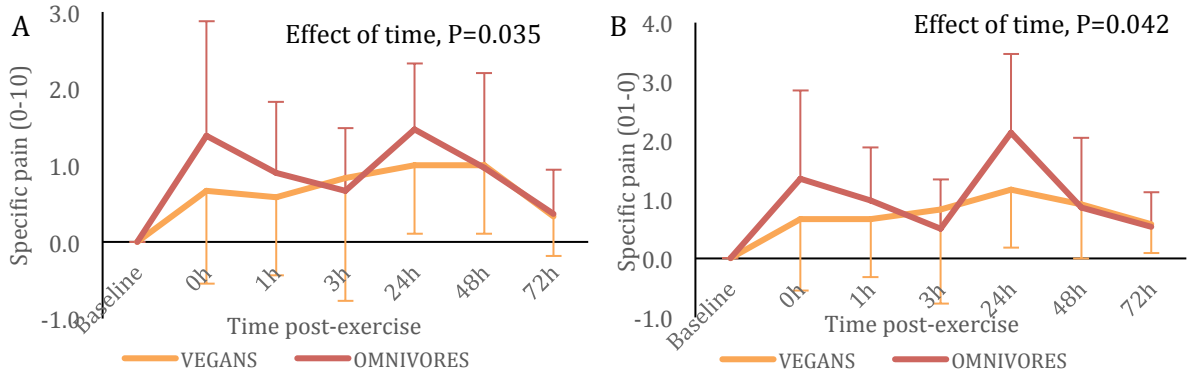

Figure 5 Subjective pain scale of the hamstrings muscle at rest (0-10), no pain (score 0) and worst pain (score 10). (A) left leg (F=3.947, P=0.035 for an effect of time using two-way repeated-measures ANOVA). (B) right leg (F=3.828, P=0.042 for an effect of time using two-way repeated-measures ANOVA). Values are mean ± SD

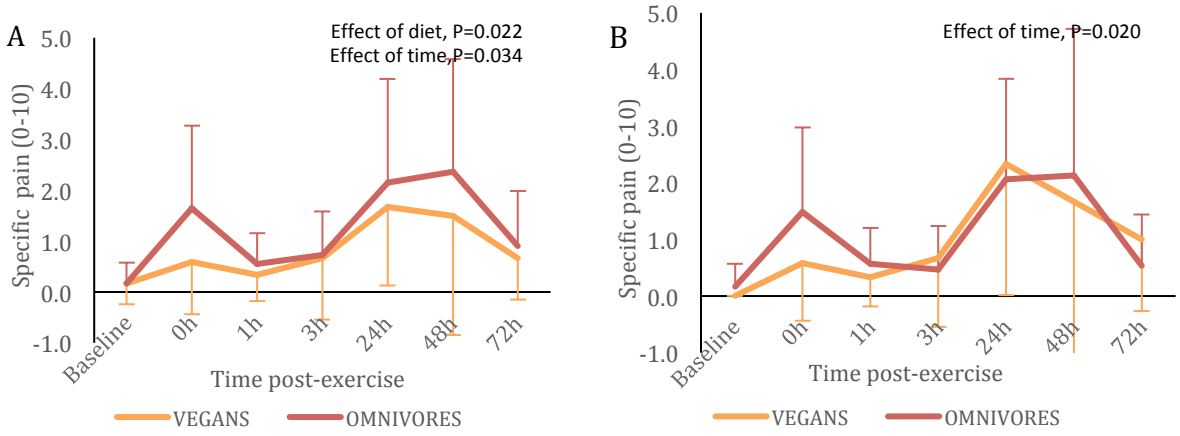

Figure 6 Subjective pain scale of the inner thigh muscle at rest (0-10), no pain (score 0) and worst pain (score 10). (A) left leg (F=4.252, P=0.034 for an effect of time using two-way repeated-measures ANOVA). (B) right leg (F=5.110, P=0.02 for an effect of time using two-way repeated-measures ANOVA). Values are mean ± SD

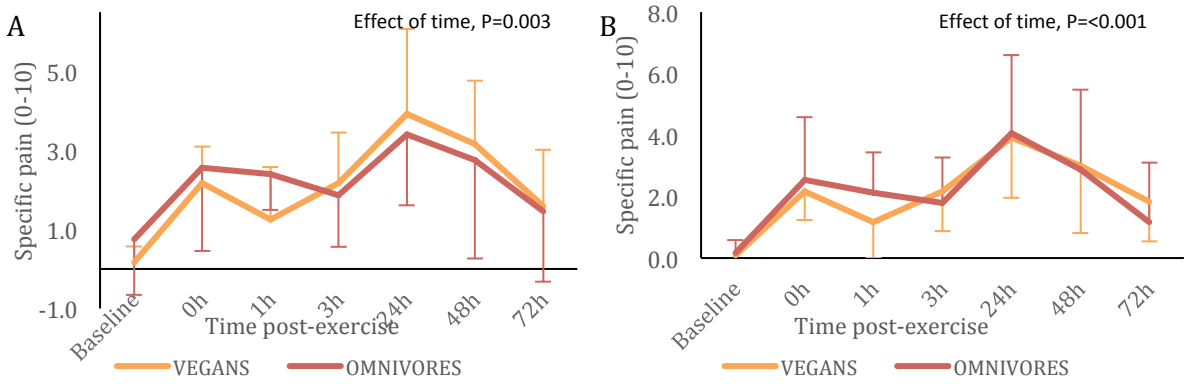

Figure 7 Subjective pain scale of the outer thigh muscle at rest (0-10), no pain (score 0) and worst pain (score 10). (A) left leg (F=7.452, P=0.003 for an effect of time using two-way repeated-measures ANOVA). (B) right leg (F=10.279, P<0.001 for an effect of time using two-way repeated-measures ANOVA). Values are mean ± SD

Pain Pressure Threshold (PPT)

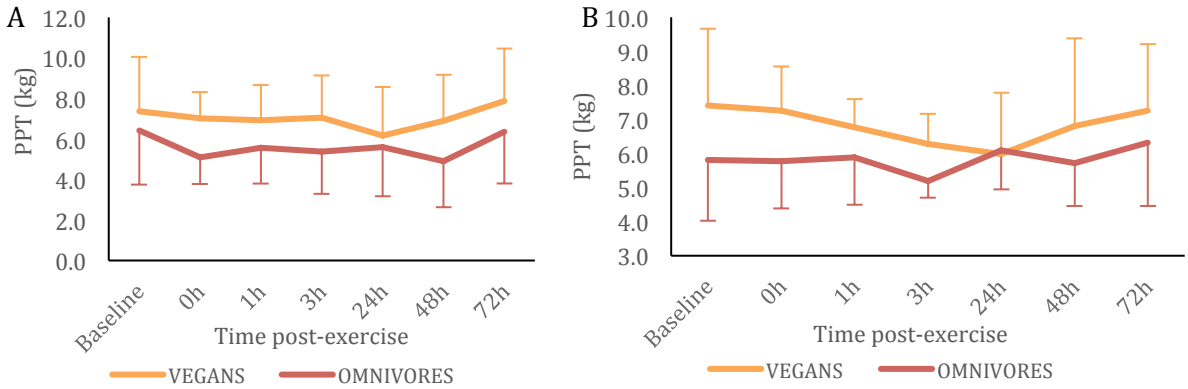

Figure 8 Pain Pressure Threshold (PPT) (kg) of the vastus lateralis muscle at rest. (A) left leg. (B) right leg. Values are mean ± SD

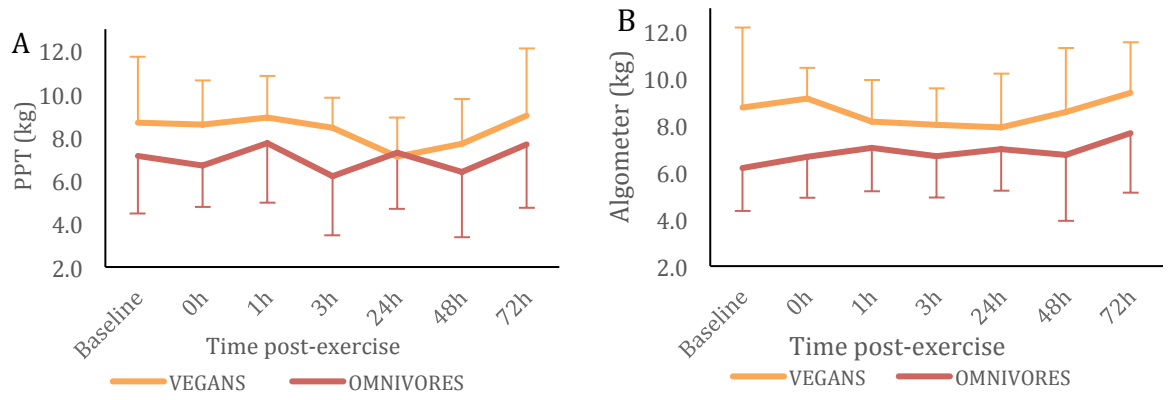

Figure 9 Pain Pressure Threshold (PPT) (kg) of the rectus femoris muscle at rest. (A) left leg. (B) right leg. Values are mean ± SD

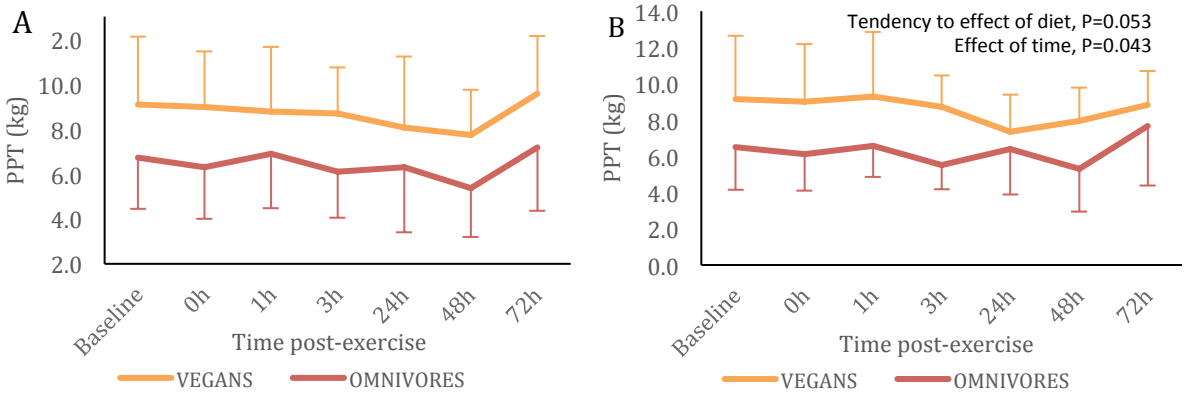

Figure 10 Pain Pressure Threshold (PPT) (kg) of the vastus medialis muscle at rest. (A) left leg. (B) right leg (F=3.455, P=0.043 for an effect of time using two-way repeated-measures ANOVA), (F=6.387, P=0.053 for an effect of diet using two-way repeated-measures ANOVA). Values are mean ± SD

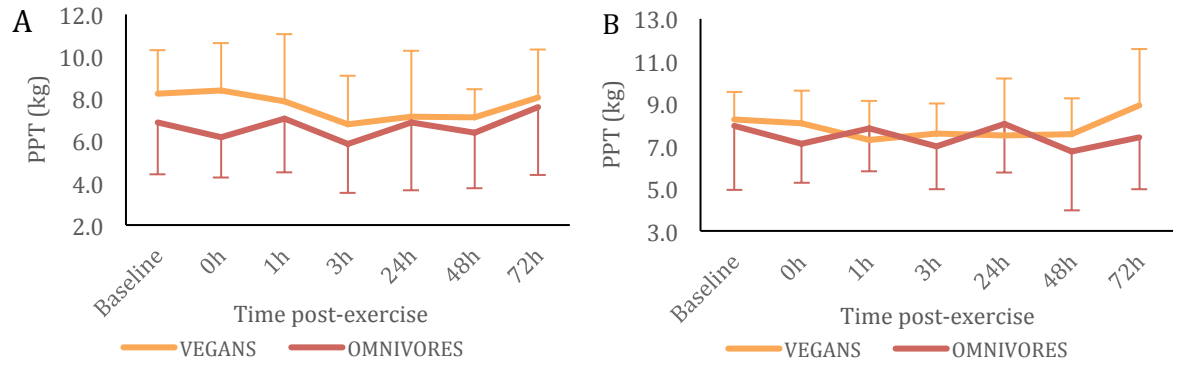

Figure 11 Pain Pressure Threshold (PPT) (kg) of the bicep femoris muscle at rest. (A) left leg. (B) right leg. Values are mean ± SD

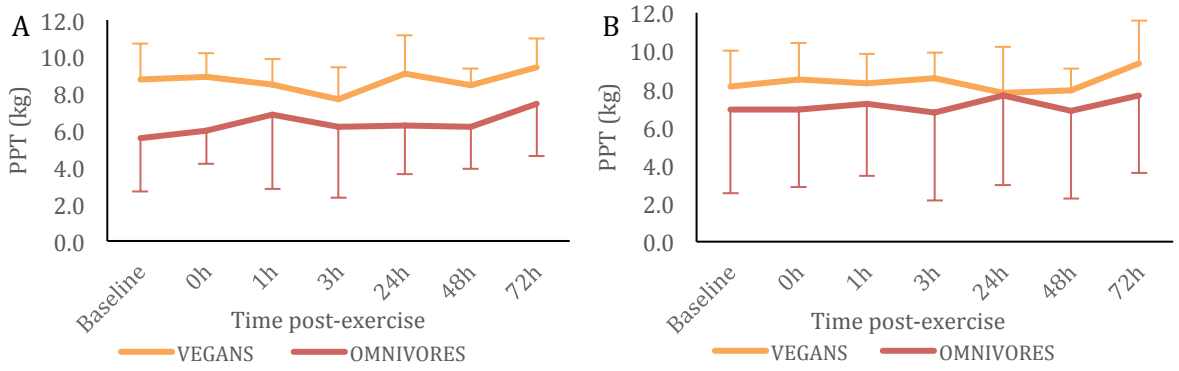

Figure 12 Pain Pressure Threshold (PPT) (kg) of the semi-tendinosis muscle at rest. (A) left leg. (B) right leg. Values are mean ± SD

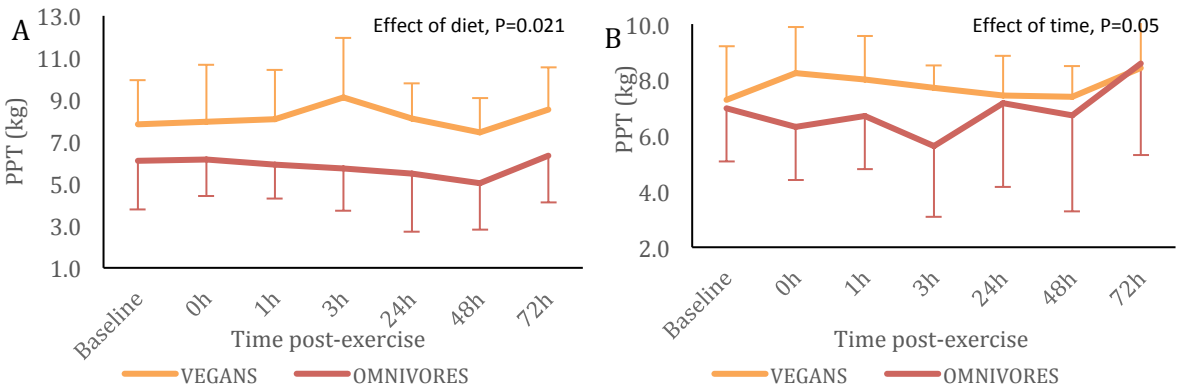

Figure 13 Pain Pressure Threshold (PPT) (kg) of the calf lateral head muscle at rest. (A) left leg (F=10.988, P=0.021 for an effect of diet using two-way repeated-measures ANOVA). (B) right leg (F=3.480, P=0.05 for an effect of time using two-way repeated-measures ANOVA). Values are mean ± SD

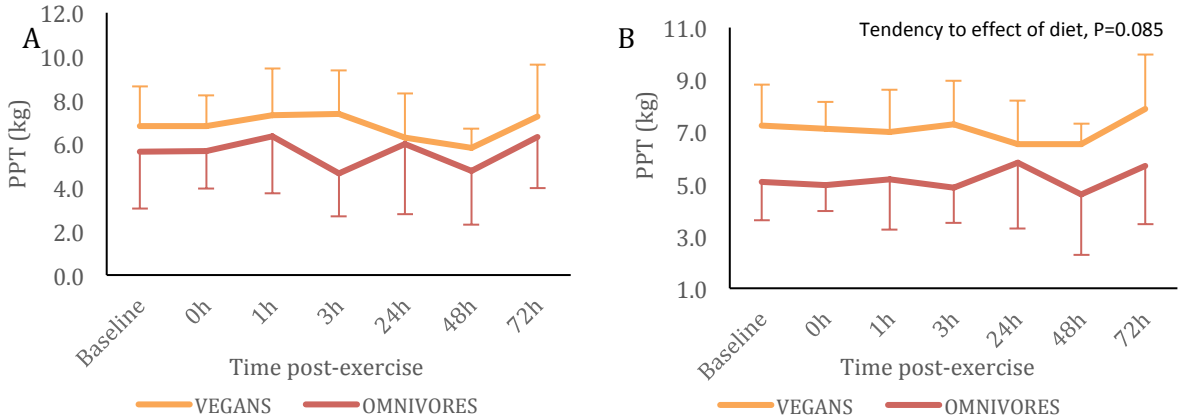

Figure 14 Pain Pressure Threshold (PPT) (kg) of the calf medial head muscle at rest. (A) left leg. (B) right leg (F=4.572, P=0.085 for an effect of diet using two-way repeated-measures ANOVA). Values are mean ± SD