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Degenerative diseases associated with macronutrient imbalance and dietary intervention: A comprehensive review

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Abstract
Degenerative diseases represent a significant and growing global public health challenge, characterized by the progressive deterioration of cellular, tissue, and organ function. Although aging and genetic predisposition are non-modifiable contributors, dietary factors—particularly macronutrient intake—constitute a critical and modifiable determinant of disease development and progression. Macronutrients, namely carbohydrates, proteins, and fats, are fundamental to metabolic homeostasis, energy provision, and structural maintenance. However, chronic excesses or deficiencies in these nutrients disrupt metabolic regulation and promote insulin resistance, oxidative stress, chronic inflammation, and mitochondrial dysfunction, thereby accelerating degenerative processes. This comprehensive review synthesizes current evidence on the physiological roles of macronutrients and elucidates the mechanisms through which macronutrient imbalance contributes to a wide spectrum of degenerative diseases, including metabolic, cardiovascular, neurodegenerative, and musculoskeletal disorders. In addition, the review presents extensive disease examples associated with imbalances in individual macronutrients and evaluates evidence-based dietary interventions aimed at restoring metabolic balance. By integrating pathophysiological insights with practical nutritional strategies, this review underscores the pivotal role of balanced macronutrient intake in the prevention and management of degenerative diseases and highlights nutrition as a cornerstone of healthy aging and chronic disease mitigation.

Keywords: Degenerative diseases, macronutrients, carbohydrates, proteins, dietary fats, macronutrient imbalance, metabolic homeostasis

Introduction

Degenerative diseases represent a major and escalating global public health challenge, characterized by the progressive deterioration of cellular, tissue, and organ function over time. These conditions, which include diabetes mellitus, cardiovascular disease, neurodegenerative disorders, musculoskeletal degeneration, and metabolic syndromes, contribute substantially to morbidity, mortality, and reduced quality of life worldwide. According to the World Health Organization (2020) [60], non-communicable degenerative diseases account for the majority of global deaths, underscoring the urgent need for effective preventive strategies.

Although aging and genetic predisposition are well-established non-modifiable risk factors, growing evidence highlights the critical role of lifestyle factors—particularly dietary patterns—in influencing the onset and progression of degenerative diseases. Macronutrients, namely carbohydrates, proteins, and fats, are fundamental to metabolic homeostasis, energy production, cellular repair, and structural integrity. However, chronic imbalances in macronutrient intake, whether through excess or deficiency, can disrupt metabolic regulation, promote insulin resistance, induce oxidative stress, and trigger chronic low-grade inflammation, all of which accelerate degenerative processes at the molecular and systemic levels.

Modern dietary trends, characterized by high consumption of refined carbohydrates, saturated and Tran's fats, and insufficient intake of high-quality protein, have been strongly associated with the rising prevalence of metabolic and degenerative disorders. These dietary patterns adversely affect glucose and lipid metabolism, impair mitochondrial function, and compromise tissue repair mechanisms. Consequently, nutrition has emerged as one of the most significant modifiable determinants of degenerative disease risk.

This review aims to critically examine the physiological roles of macronutrients, elucidate the mechanisms by which macronutrient imbalance contributes to degenerative disease development, and present extensive disease examples associated with each macronutrient category. Furthermore, evidence-based dietary interventions are discussed to highlight the role of targeted nutritional strategies in disease prevention and health promotion.

Physiological Roles of Macronutrients

Dietary intervention remains a cornerstone in the prevention and management of macronutrient-related degenerative diseases. Evidence indicates that dietary quality, rather than caloric intake alone, plays a decisive role in modulating metabolic pathways associated with inflammation, oxidative stress, and tissue degeneration. Low–glycemic index diets effectively reduce insulin resistance and microvascular complications, while adequate high-quality protein intake preserves lean body mass and immune competence, particularly in aging populations. Furthermore, dietary patterns emphasizing unsaturated fats—such as the Mediterranean diet—demonstrate significant cardioprotective, hepatoprotective, and neuroprotective effects.

An integrated dietary strategy that balances macronutrient quantity and quality, combined with lifestyle interventions such as regular physical activity, offers the most effective approach for mitigating degenerative disease risk and promoting healthy aging.

1. Carbohydrates

Carbohydrates constitute the primary source of metabolic energy in humans and are particularly indispensable for tissues with high glucose demand, including the brain, central nervous system, and erythrocytes. Glucose derived from dietary carbohydrates fuels cellular respiration and supports normal cognitive and neuromuscular function. Complex carbohydrates, such as whole grains, legumes, and vegetables, also provide dietary fiber, which plays a crucial role in maintaining gastrointestinal integrity, regulating postprandial glycemia, and modulating lipid metabolism (Ludwig, 2002) [40].

In contrast, excessive consumption of refined carbohydrates and added sugars disrupts glucose homeostasis, leading to chronic hyperglycemia and compensatory hyperinsulinemia. Over time, this metabolic burden contributes to insulin resistance, oxidative stress, and the formation of advanced glycation end products (AGEs), which accelerate cellular aging and tissue degeneration (Reaven, 1988; Brownlee, 2001) [9, 50]. Consequently, carbohydrate imbalance is strongly implicated in the pathogenesis of metabolic, cardiovascular, neurological, and microvascular degenerative diseases.

Carbohydrate Imbalance and Degenerative Diseases

Excessive consumption of refined carbohydrates disrupts glucose homeostasis and promotes insulin resistance, leading to multisystem degeneration.

Examples of carbohydrate-related degenerative diseases include

1. Type 2 diabetes mellitus (Reaven, 1988) [50]
2. Diabetic neuropathy (Brownlee, 2001) [9]
3. Diabetic retinopathy (Cheung *et al*., 2010) [14]
4. Diabetic nephropathy (Forbes & Cooper, 2013) [23]
5. Metabolic syndrome (Grundy, 2004) [26]
6. Obesity-related osteoarthritis (Felson, 2004) [21]
7. Alzheimer's disease ("type 3 diabetes") (de la Monte, 2014) [16]
8. Cognitive decline and dementia (Luchsinger *et al*., 2007) [39]
9. Cardiomyopathy (Boudina & Abel, 2007) [7]
10. Endothelial dysfunction (Ceriello, 2006) [13]
11. Accelerated aging via advanced glycation end products (Singh *et al*., 2001) [53]
12. Cataract formation (Kyselova, 2010) [37]
13. Stroke (Hu *et al*., 2012)
14. Erectile dysfunction (Kamenov, 2015) [35]
15. Polycystic ovary syndrome (Diamanti-Kandarakis *et al*., 2007) [19]
16. Periodontal disease (Taylor, 2001) [56]
17. Impaired wound healing (Falanga, 2005) [20]
18. Chronic low-grade inflammation (Hotamisligil, 2006) [30]
19. Non-alcoholic fatty pancreas disease (Smits & van Geenen, 2011) [54]
20. Immune dysfunction (Delamaire *et al*., 1997) [17]

Dietary Interventions for Carbohydrate-Related Degenerative Diseases

Carbohydrate-related degenerative diseases are primarily driven by chronic hyperglycemia, insulin resistance, and oxidative stress. Conditions such as type 2 diabetes mellitus, diabetic neuropathy, retinopathy, nephropathy, metabolic syndrome, Alzheimer's disease, cardiovascular complications, and obesity-related degeneration share common metabolic pathways. Nutritional strategies therefore focus on glycemic control, insulin sensitivity, and inflammation reduction.

Recommended Diet Plan (Applies to Examples in Section 3)

Dietary Goals

- Stabilize blood glucose levels
- Improve insulin sensitivity
- Reduce oxidative stress and advanced glycation end products

Macronutrient Distribution (Approximate)

- **Carbohydrates:** 40–45% (low glycemic index)
- **Protein:** 20–25%
- **Fat:** 30–35% (primarily unsaturated)

Key Dietary Components

- Whole grains (oats, barley, quinoa)
- Legumes (lentils, chickpeas, beans)
- Non-starchy vegetables (leafy greens, broccoli, peppers)
- Low-glycemic fruits (berries, apples)
- Lean proteins (fish, poultry, tofu)
- Healthy fats (olive oil, nuts, seeds)

Foods to Limit or Avoid

- Refined sugars and sweetened beverages
- White bread, pastries, and processed cereals
- Highly processed snack foods

Clinical Evidence

Low–glycemic index diets have been shown to improve glycemic control, reduce microvascular complications, and slow neurodegenerative progression in insulin-resistant states (Ludwig, 2002; Hu *et al*., 2012) [40].

2. Proteins

Proteins are fundamental structural and functional components of all living cells. They provide essential amino acids required for tissue growth, repair, enzymatic reactions, hormone synthesis, immune defense, and neurotransmitter production. Adequate protein intake is especially critical during periods of growth, illness, and aging, when anabolic demands are increased (Bauer *et al*., 2013) [3].

Insufficient protein intake or impaired protein utilization results in negative nitrogen balance, leading to progressive loss of skeletal muscle mass, reduced bone density, impaired immune competence, and delayed wound healing. In older adults, chronic protein deficiency is a major contributor to sarcopenia and frailty, conditions that significantly increase morbidity, disability, and mortality (Cruz-Jentoft *et al*., 2010) [15]. Thus, protein adequacy is a central determinant of functional capacity, resilience to disease, and healthy aging.

Protein Imbalance and Degenerative Diseases
Inadequate protein intake or poor protein quality accelerates tissue degeneration, particularly in aging populations.

Examples of protein-related degenerative diseases include
1. Sarcopenia (Cruz-Jentoft *et al*., 2010) [15]
2. Frailty syndrome (Morley *et al*., 2013) [3]
3. Osteoporosis (Bonjour, 2005) [6]
4. Muscle atrophy (Phillips & Van Loon, 2011) [46]
5. Impaired immune response (Calder, 2006) [10]
6. Delayed wound healing (Demling, 2009) [18]
7. Anemia (World Health Organization, 2001)
8. Kwashiorkor-related tissue degeneration (Golden, 2009) [25]
9. Cognitive decline in the elderly (Volkert *et al*., 2019)[59]
10. Hair loss disorders (Rushton, 2002)
11. Nail dystrophy (Cashman, 2007) [12]
12. Hormonal dysregulation (Wolfe, 2017)
13. Enzyme insufficiency (Berg *et al*., 2015) [5]
14. Neurotransmitter imbalance (Fernstrom, 2013) [22]
15. Reduced bone density (Heaney, 2003) [29]
16. Pressure ulcers (Langer & Fink, 2014) [38]
17. Poor recovery from illness (Paddon-Jones *et al*., 2008) [45]
18. Growth retardation (UNICEF, 2019)
19. Liver dysfunction (Plauth *et al*., 1997) [47]
20. Chronic fatigue syndromes (Benton & Donohoe, 1999) [4]

Dietary Interventions for Protein-Related Degenerative Diseases
Protein-related degenerative conditions such as sarcopenia, frailty syndrome, osteoporosis, and immune dysfunction, poor wound healing, and age-related cognitive decline are frequently associated with inadequate protein intake or impaired protein utilization. Nutritional interventions emphasize sufficient high-quality protein distributed evenly throughout the day.

Recommended Diet Plan (Applies to Examples in Section 4)
Dietary Goals
- Preserve lean muscle mass
- Support tissue repair and immune function
- Prevent age-related degeneration

Protein Intake Recommendation
- Older adults: 1.0–1.2 g/kg/day
- Clinical conditions: up to 1.5 g/kg/day (as tolerated)

Key Dietary Components
- Lean animal proteins (fish, poultry, eggs, low-fat dairy)
- Plant proteins (soy, legumes, quinoa)
- Protein-rich snacks (Greek yogurt, nuts)
- Adequate vitamin D and calcium intake

Meal Pattern
- Even protein distribution across meals (25–30 g per meal)
- Inclusion of resistance exercise for anabolic stimulation

Foods to Limit
- Highly processed meats
- Protein-deficient refined carbohydrate diets

Clinical Evidence
Adequate protein intake has been demonstrated to reduce sarcopenia, improve bone density, enhance immune competence, and support recovery from illness (Bauer *et al*., 2013; Cruz-Jentoft *et al*., 2010) [3, 15].

3. Fats
Dietary fats provide a concentrated source of energy and are essential for the absorption of fat-soluble vitamins (A, D, E, and K), synthesis of steroid hormones, and maintenance of cellular membrane integrity. Fatty acids also serve as key signaling molecules involved in inflammatory regulation and metabolic control. Unsaturated fats, particularly monounsaturated and omega-3 polyunsaturated fatty acids, exert cardioprotective, anti-inflammatory, and neuroprotective effects (Mozaffarian *et al*., 2011) [44].
Conversely, excessive intake of saturated and Trans fats promotes lipotoxicity, characterized by abnormal lipid accumulation in non-adipose tissues such as the liver, pancreas, heart, and skeletal muscle. This process induces mitochondrial dysfunction, oxidative stress, and chronic inflammation, thereby accelerating degenerative changes in cardiovascular, hepatic, renal, and neural tissues (Younossi *et al*., 2016) [61]. Fat quality, rather than total fat quantity alone, is therefore a critical determinant of long-term metabolic and degenerative outcomes.

Fat Imbalance and Degenerative Diseases
Excessive intake of unhealthy fats leads to lipid accumulation in non-adipose tissues, triggering inflammation and cellular dysfunction.

Examples of fat-related degenerative diseases include
1. Atherosclerosis (Ross, 1999) [51]
2. Coronary artery disease (Mozaffarian *et al*., 2011) [44]
3. Stroke (Iso *et al*., 2001) [33]
4. Non-alcoholic fatty liver disease (Younossi *et al*., 2016) [61]
5. Obesity (Bray *et al*., 2004) [8]
6. Hypertension (Hall *et al*., 2015) [28]
7. Dyslipidemia (Grundy, 2016) [27]
8. Insulin resistance (Unger & Scherer, 2010) [57]
9. Cardiomyopathy (Goldberg *et al*., 2012) [24]
10. β-cell dysfunction (Poitout & Robertson, 2008) [48]
11. Gallstone disease (Portincasa *et al*., 2006) [49]
12. Chronic kidney disease (Kovesdy *et al*., 2017) [36]
13. Osteoarthritis (Spector *et al*., 1994) [55]
14. Inflammatory bowel disease (Ananthakrishnan, 2015) [2]
15. Neurodegenerative disorders (Morris *et al*., 2015) [43]
16. Depression (Jacka *et al*., 2010) [34]
17. Hormonal imbalance (Messina *et al*., 2006) [41]
18. Immune suppression (Calder, 2010) [11]
19. Reduced fertility (Afeiche *et al*., 2014) [1]
20. Accelerated cellular aging (Salvadori *et al*., 2015) [52]

Dietary Interventions for Fat-Related Degenerative Diseases
Fat-related degenerative diseases—including atherosclerosis, coronary artery disease, non-alcoholic fatty liver disease, obesity, dyslipidemia, neurodegeneration, and chronic inflammation—are closely linked to excessive

intake of saturated and trans fats. Dietary strategies prioritize lipid quality over quantity.

Recommended Diet Plan (Applies to Examples in Section 5)

Dietary Goals

- Improve lipid profile
- Reduce systemic inflammation
- Prevent lipotoxicity

Macronutrient Distribution (Approximate)

- **Total fat:** 25–35%
- **Saturated fat:** <10% of total energy
- Emphasis on omega-3 and monounsaturated fats

Key Dietary Components

- Fatty fish (salmon, sardines)
- Olive oil as primary fat source
- Nuts and seeds
- Avocados
- Whole grains and vegetables (Mediterranean pattern)

Foods to Limit or Avoid

- Trans fats and fried foods
- Processed meats
- Excessive red meat and full-fat dairy

Clinical Evidence

Mediterranean-style diets are associated with reduced cardiovascular mortality, improved hepatic outcomes in NAFLD, and neuroprotective effects (Mozaffarian *et al*., 2011; Younossi *et al*., 2016) [44, 61].

Mechanisms Linking Macronutrient Imbalance to Degeneration

Macronutrient imbalance contributes to the development and progression of degenerative diseases through multiple interconnected molecular and physiological mechanisms. Chronic excess or deficiency of carbohydrates, proteins, and fats disrupts metabolic homeostasis, initiating a cascade of pathological processes that impair cellular integrity and accelerate tissue degeneration.

One of the primary mechanisms is insulin resistance, which arises predominantly from excessive intake of refined carbohydrates and saturated fats. Persistent hyperglycemia and hyperinsulinemia lead to impaired insulin signaling in peripheral tissues, resulting in reduced glucose uptake and increased lipolysis. This metabolic dysfunction promotes endothelial damage, microvascular complications, and progressive organ impairment, particularly in the liver, kidneys, nervous system, and cardiovascular tissues (Reaven, 1988; Brownlee, 2001) [9, 50].

Oxidative stress represents another central pathway linking macronutrient imbalance to degeneration. Excess nutrient availability overwhelms mitochondrial oxidative capacity, leading to the overproduction of reactive oxygen species (ROS). These reactive molecules damage cellular proteins, lipids, and nucleic acids, compromising structural integrity and accelerating cellular aging. Additionally, the formation of advanced glycation end products (AGEs) in states of chronic hyperglycemia further exacerbates oxidative damage and inflammatory signaling, contributing to vascular and neural degeneration (Brownlee, 2001) [9].

Mitochondrial dysfunction plays a critical role in degenerative processes associated with macronutrient imbalance. Lipid oversupply and impaired glucose metabolism disrupt mitochondrial energy production, reducing adenosine triphosphate (ATP) synthesis and promoting apoptotic pathways. Mitochondrial impairment has been strongly implicated in neurodegenerative disorders, sarcopenia, and cardiomyopathies, underscoring the importance of balanced substrate utilization for cellular longevity (Mozaffarian *et al*., 2011) [44].

Chronic low-grade inflammation further amplifies degenerative progression. Excessive intake of unhealthy fats and refined carbohydrates activates pro-inflammatory pathways, including nuclear factor-kappa B (NF-κB) signaling and increased secretion of inflammatory cytokines such as tumor necrosis factor-alpha and interleukin-6. This persistent inflammatory state disrupts tissue repair mechanisms, promotes fibrosis, and accelerates degeneration across multiple organ systems (Hotamisligil, 2006) [30].

Finally, hormonal dysregulation resulting from macronutrient imbalance alters appetite regulation, energy expenditure, and tissue metabolism. Disruptions in adipokines such as leptin and adiponectin, as well as insulin-like growth factor signaling, impair anabolic processes and exacerbate catabolic states. These hormonal alterations contribute to muscle wasting, bone loss, metabolic inflexibility, and increased susceptibility to degenerative diseases.

Prevention and Nutritional Strategies

Preventing degenerative diseases associated with macronutrient imbalance requires a comprehensive nutritional approach that emphasizes both macronutrient quality and appropriate distribution. Evidence consistently demonstrates that diets rich in complex carbohydrates, adequate high-quality protein, and unsaturated fats promote metabolic stability and reduce degenerative risk.

Complex carbohydrates derived from whole grains, legumes, fruits, and vegetables provide sustained energy while minimizing postprandial glycemic fluctuations. Their high fiber content supports gastrointestinal health, improves insulin sensitivity, and modulates lipid metabolism. In contrast, reducing intake of refined sugars and ultra-processed foods is essential for preventing metabolic overload and oxidative stress (Ludwig, 2002; Hu *et al*., 2012) [40].

Adequate protein intake plays a pivotal role in preserving lean body mass, supporting immune competence, and facilitating tissue repair. This is particularly important in aging populations, where anabolic resistance increases susceptibility to sarcopenia and frailty. Distributing protein intake evenly throughout the day and combining it with resistance-based physical activity enhances muscle protein synthesis and functional capacity (Bauer *et al*., 2013; Cruz-Jentoft *et al*., 2010) [3, 15].

Dietary fat quality is equally critical. Replacing saturated and Trans fats with monounsaturated and omega-3 polyunsaturated fatty acids improves lipid profiles, reduces systemic inflammation, and provides cardiovascular and neuroprotective benefits. Mediterranean-style dietary patterns, characterized by high intake of olive oil, fatty fish, nuts, and vegetables, have been consistently associated with

reduced incidence of degenerative diseases (Mozaffarian *et al*., 2011; Younossi *et al*., 2016) [44, 61].

Physical activity synergistically enhances the benefits of nutritional interventions by improving insulin sensitivity, mitochondrial function, and inflammatory balance. Thus, integrated lifestyle modification remains the most effective preventive strategy.

Integrated Preventive Dietary Model

An integrated preventive dietary model that balances macronutrient intake and prioritizes nutrient quality represents the most effective strategy for mitigating the risk of macronutrient-related degenerative diseases. This model emphasizes low–glycemic index carbohydrates, sufficient high-quality protein, and predominantly unsaturated fats, thereby supporting metabolic flexibility and cellular resilience.

Such dietary patterns align closely with globally recommended nutritional frameworks, including the Mediterranean and Dietary Approaches to Stop Hypertension (DASH) diets, which have demonstrated efficacy in reducing cardiovascular, metabolic, and neurodegenerative disease risk. By simultaneously addressing glycemic control, inflammatory regulation, and anabolic support, this integrated approach fosters long-term metabolic homeostasis and delays age-related functional decline.

Incorporating personalized nutrition strategies that account for age, metabolic status, and lifestyle factors may further enhance the effectiveness of this model. As research in precision nutrition advances, tailored macronutrient recommendations hold promise for optimizing disease prevention and promoting healthy aging across diverse populations.

Conclusion

Macronutrient imbalance plays a pivotal role in the initiation and progression of degenerative diseases affecting multiple organ systems. Excessive intake of refined carbohydrates and unhealthy fats, combined with inadequate consumption of high-quality protein, contributes to metabolic dysregulation, insulin resistance, chronic inflammation, oxidative stress, and impaired cellular repair mechanisms. These interconnected processes accelerate tissue degeneration and increase susceptibility to chronic non-communicable diseases.

Evidence presented in this review demonstrates that carbohydrate, protein, and fat imbalances are each associated with distinct yet overlapping degenerative disease pathways, underscoring the importance of dietary quality rather than caloric intake alone. Importantly, the findings highlight that evidence-based dietary interventions—such as low-glycemic carbohydrate consumption, adequate protein intake tailored to physiological needs, and prioritization of unsaturated fats—can significantly mitigate disease risk, slow degenerative progression, and improve functional outcomes.

In conclusion, nutrition remains one of the most powerful, accessible, and modifiable determinants of degenerative disease prevention. Integrating balanced macronutrient strategies into public health policies and clinical practice is essential for promoting healthy aging, reducing disease burden, and improving long-term population health outcomes. Future research should continue to explore personalized and precision-based nutritional approaches to optimize disease prevention and management.

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