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The Endocrine-Modulating Potential of the Mediterranean Diet: Narrative Review

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Abstract

The Mediterranean diet (MedDiet) is a plant-centered nutritional model recognized for its profound anti-inflammatory and antioxidant properties. This narrative review evaluates evidence from clinical and epidemiological studies to synthesize the impact of MedDiet adherence on human hormonal regulation across the pancreatic, adipokine, stress, thyroid, and

gonadal axes. Current evidence indicates that adherence to the MedDiet, particularly in energy-restricted or polyphenol-enriched forms, significantly enhances insulin sensitivity and downregulates pro-inflammatory markers such as leptin and plasminogen activator inhibitor-1 (PAI-1). Furthermore, long-term adherence to a "Green-MedDiet" variant has been demonstrated to reduce fasting morning cortisol (FMC), suggesting a role in hypothalamic-pituitary-adrenal (HPA) axis modulation. While the MedDiet appears protective against thyroid autoimmunity and assists in correcting hormonal dysregulation in conditions such as Polycystic Ovary Syndrome (PCOS), its impact on circulating sex hormones in healthy, homeostatic populations is negligible. This review highlights the MedDiet as a therapeutic tool for managing endocrine disruptions associated with obesity and metabolic syndrome.

Key words:

Mediterranean diet; Endocrine system; Hormones; Reproduction

Background

The Mediterranean diet is a plant-centered nutritional model renowned for its anti-inflammatory and antioxidant properties. While its cardiovascular benefits are well-documented, its systemic impact on the human endocrine system—particularly in countering obesity-related "metainflammation" and hormonal disruptions—requires comprehensive synthesis.

Aim

This review aims to examine and synthesize the evidence regarding the influence of Mediterranean diet adherence on various human hormonal axes, including glucose homeostasis, adipose tissue secretion, stress response, thyroid function, reproductive health and intestinal barrier.

Material and methods

A narrative review was conducted by analyzing clinical and epidemiological data from the following databases: Google Scholar and PubMed using main keyword: Mediterranean Diet and other specific keywords such as; endocrine system; reproductive system; hormones; thyroid; adrenal glands; gonads; ovaries; testis; pituitary. Keywords was connected by advanced commands AND/OR. The search procedure was performed in both Polish and English. The inclusion criteria for eligible articles were as follows: observational studies, clinical studies, reviews, systematic reviews, meta-analyses, and randomized controlled trials. Studies had to be published between 2010 and 2026. Studies on unrelated topics, articles without sufficient methodological rigor, and study types different from those specified in the inclusion criteria were excluded.

When writing the review, we additionally used scientific literature and specialized websites regarding the Mediterranean diet and the human hormonal system.

Results

Adherence to the Mediterranean diet significantly enhances insulin sensitivity and reduces levels of insulin, leptin, and pro-inflammatory markers such as PAI-1. Long-term interventions, particularly polyphenol-rich "Green" variants, demonstrate a capacity to lower fasting morning cortisol, while clinical evidence supports its role in improving hormonal profiles in patients with PCOS and thyroid autoimmunity.

Conclusions

The Mediterranean diet acts as a multi-axial endocrine modulator that primarily corrects hormonal dysregulation associated with obesity and metabolic syndrome. While it is a potent therapeutic tool for clinical conditions, it appears to have a negligible impact on the endocrine baseline of healthy, homeostatic individuals.

1. Introduction

The Mediterranean diet

The Mediterranean diet (MedDiet) is defined as a traditional dietary model followed by populations in the olive-growing regions of the Mediterranean basin, characterized by a high intake of minimally processed plant-based foods, including vegetables, fruits, whole grains, legumes, and nuts [1,2,3]. The primary source of dietary lipids is extra-virgin olive oil (EVOO), while the consumption of red meat, processed meats, and refined sugars is kept low [2,4]. Moderate intake of fish, poultry, and fermented dairy products is encouraged, often accompanied by a moderate consumption of red wine during meals [3,5]. Beyond its nutritional profile, the MedDiet is a comprehensive lifestyle heritage recognized by UNESCO, involving regular physical activity, social conviviality, and adequate rest [2,6]. All elements of the Mediterranean diet can be presented using a pyramid or other graphics to facilitate understanding of its core values (Figure 1.).

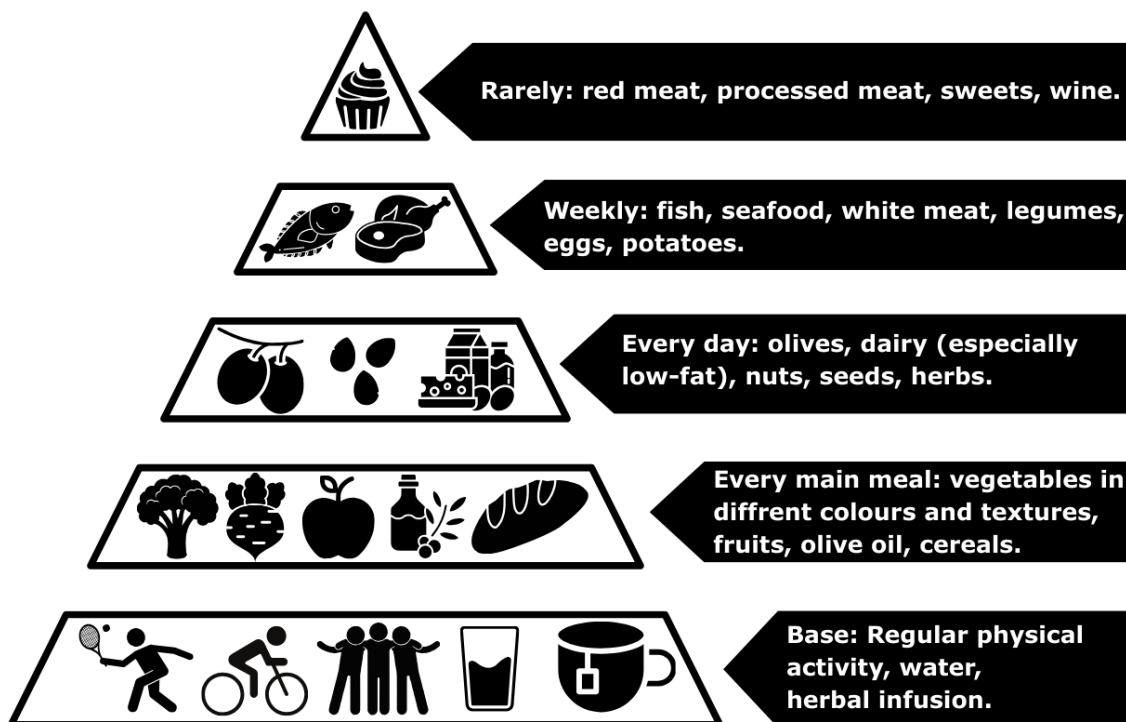


Figure 1. A pyramid presenting the most important assumptions of the Mediterranean diet.

The Endocrine System

The endocrine system regulates vital physiological functions, including appetite, nutrient storage, and reproduction, through a complex network of glands and hormones [7]. In the context of the global obesity pandemic, adipose tissue has been acknowledged as an active endocrine organ that contributes to "metainflammation" through the secretion of pro-inflammatory adipokines [7,8]. This low-grade chronic inflammation often disrupts systemic hormonal homeostasis, leading to insulin resistance and altered stress responses [8]. Identifying dietary patterns capable of modulating these hormonal axes is of paramount clinical importance. This review examines how MedDiet adherence influences human hormonal health based on clinical and epidemiological data from 20 specialized sources.

2. Material and methods

A narrative review was conducted by analyzing clinical and epidemiological data from the following databases: Google Scholar and PubMed using main keyword: Mediterranean Diet and other specific keywords such as; endocrine system; reproductive system; hormones; thyroid; adrenal glands; gonads; ovaries; testis; pituitary. Keywords was connected by advanced commands AND/OR. The search procedure was performed in both Polish and English. The inclusion criteria for eligible articles were as follows: observational studies, clinical studies, reviews, systematic reviews, meta-analyses, and randomized controlled trials. Studies had to be published between 2010 and 2026. Studies on unrelated topics, articles without sufficient methodological rigor, and study types different from those specified in the inclusion criteria were excluded.

When writing the review, we additionally used scientific literature and specialized websites regarding the Mediterranean diet and the human hormonal system.

3. Results - Influencing potential of Mediterranean diet

3.1. Glucose Homeostasis and Pancreatic Hormones

Adherence to the MedDiet is robustly associated with improvements in carbohydrate metabolism. Clinical interventions, such as the PREDIMED-PLUS trial, show that an energy-reduced Mediterranean diet (erMedDiet) significantly decreases fasting insulin and C-peptide

levels over 6 to 12 months in subjects with metabolic syndrome [8]. These hormonal reductions are associated with a decrease in the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) index [8]. Furthermore, gender-specific responses have been observed; in a controlled 4-week trial, men experienced an 8.1% increase in peripheral insulin sensitivity and a 17.8% reduction in insulin iAUC, while these benefits were less pronounced in premenopausal women [9]. The diet also appears to lower glucagon levels, particularly as a result of weight loss [8]. In specialized clinical populations, such as those with Celiac disease (CD), transitioning to a Mediterranean-style gluten-free diet is hypothesized to reduce the prevalence of insulin resistance and metabolic syndrome [10].

3.2. Adipose Tissue Secretion and Satiety Hormones

Adipose tissue acts as a metabolic active organ, and the MedDiet serves as a potent modulator of its endocrine output [8].

- **Leptin:** High-level evidence indicates that erMedDiet interventions lead to significant reductions in circulating leptin levels, which correlate with decreases in body weight and waist circumference [7,8].
- **Resistin and Visfatin:** These adipokines, typically upregulated in obesity and linked to insulin resistance, show steady decreases over 12 months in subjects following Mediterranean lifestyle interventions [8].
- **Ghrelin and GLP-1:** Findings for the orexigenic hormone ghrelin and the anorexigenic glucagon-like peptide-1 (GLP-1) are less conclusive, with some studies reporting no statistically significant fasting changes over 12 months [8].
- **Adiponectin:** Ongoing research is investigating whether the MedDiet can specifically elevate adiponectin to improve anti-inflammatory status in populations with autoimmune conditions like Celiac disease [7,10].

3.3. The Hypothalamic-Pituitary-Adrenal (HPA) Axis and Cortisol Regulation

The stress hormone cortisol is a critical marker of HPA axis dysregulation. The DIRECT-PLUS clinical trial demonstrated that long-term adherence to the "Green-MedDiet" - a variation further enriched with polyphenols (via green tea and *Wolffia globosa* Mankai) and reduced in red/processed meat—significantly lowers fasting morning cortisol (FMC) levels over 18

months [11]. This reduction in FMC was statistically significant compared to standard healthy dietary guidelines and was associated with favorable changes in glycemic control and TSH levels [7,11]. Interestingly, these improvements in the cortisol response appear to be largely independent of the total amount of weight lost [11].

3.4. Thyroid Function and Immunomodulation

The MedDiet supports thyroid health through the provision of essential trace elements such as iodine, selenium, and zinc [6,12]. Adherence to this pattern is associated with a lower risk of thyroid nodular disease and high-risk thyroid malignancy [6]. Furthermore, higher MedDiet adherence is an independent predictor of lower levels of thyroid peroxidase antibodies (TPOAbs) and thyroglobulin antibodies (TgAbs), suggesting an immunomodulatory effect that may slow the progression of Hashimoto's thyroiditis [4,12]. However, a survey of obese subjects in Southern Italy noted that higher adherence was inversely related to serum levels of free T3 (fT3) and free T4 (fT4), although these remained within the normal reference range, potentially reflecting increased peripheral sensitivity [13].

3.5. Reproductive and Gonadal Hormonal Axes

The impact of the MedDiet on reproductive hormones is context-dependent, showing different effects in healthy versus clinical cohorts:

In Healthy Populations: Observational data from the Nurses' Health Study II showed that the alternate Mediterranean diet (aMED) score was not significantly associated with estrogens, androgens, prolactin, or SHBG levels in premenopausal women [14]. Similarly, in healthy young men, adherence to the relative MedDiet score (rMED) was unrelated to serum levels of FSH, LH, SHBG, testosterone, or estradiol [15].

In Clinical Populations: In contrast, the MedDiet is clinically beneficial for women with PCOS, where it is associated with reduced clinical severity, improved insulin sensitivity, and decreased testosterone levels [6,7]. For male fertility, the diet's bioactive compounds, such as omega-3 polyunsaturated fatty acids and flavonoids like resveratrol, protect Leydig cell function and sperm mitochondria from oxidative stress [6,7].

3.6. Intestinal barrier and Microbiota Modulation

The MedDiet is a primary determinant of intestinal eubiosis, characterized by enhanced alpha-diversity and a favorable shift in microbial composition [16]. Adherence to this pattern promotes the proliferation of fiber-degrading and short-chain fatty acid (SCFA)-producing taxa, such as *Faecalibacterium prausnitzii*, *Roseburia*, *Eubacterium rectale*, and *Bifidobacterium* [17,18]. These microbes utilize dietary fibers to synthesize metabolites—primarily butyrate, acetate, and propionate—that strengthen the gut mucosal barrier, regulate the gut-brain axis, and exert systemic anti-inflammatory effects by inhibiting pro-inflammatory cytokines [17,18]. In clinical cohorts with inflammatory bowel disease (IBD), the MedDiet significantly reshapes the bacteriome, increasing protective species like *Alistipes finegoldii* and *Flavonifractor plautii* while reducing fecal calprotectin levels and clinical disease activity [19,20]. Furthermore, by suppressing metabolic endotoxemia through the reduction of circulating lipopolysaccharides (LPS), the MedDiet assists in maintaining the integrity of the gut-liver axis, which is frequently compromised in obesity and non-alcoholic fatty liver disease (NAFLD) [16,17,20]. However, human interventional data regarding the direct modulation of intestinal permeability remain complex; while the diet improves metabolic markers and liver steatosis, some crossover trials report no significant changes in ⁵¹Cr-EDTA excretion over 16 weeks, suggesting that physiological restoration of the gut barrier may require longer-term adherence [19].

3.7. Other Hormonal Regulators and Phytochemical Factors

The MedDiet provides significant amounts of plant-derived melatonin, found in tomatoes, wine, and olive oil [5]. This plant-based melatonin has high bioavailability and contributes to the total antioxidant status of the serum [5]. Additionally, the diet significantly reduces levels of plasminogen activator inhibitor-1 (PAI-1), a marker of a pro-thrombotic and pro-inflammatory endocrine state [8]. In the management of neuroendocrine tumors (NETs), the MedDiet may also help modulate growth-related pathways such as IGF-1 [6,7].

4. Conclusions

The synthesis of these articles reveals a clear dichotomy: the MedDiet is highly effective at correcting hormonal dysregulation in diseased or overweight states, but it does not significantly

alter the endocrine baseline of healthy, homeostatic individuals. There is strong consensus that the diet lowers insulin, leptin, and cortisol, with polyphenol-rich variants showing enhanced efficacy in HPA axis modulation.

A notable inconsistency exists regarding thyroid function; while most evidence points to immunomodulatory protection, some articles report an inverse association with fT3/fT4 levels. This may be an adaptive response specific to obese populations. Furthermore, some researches highlighted that the metabolic benefits of the MedDiet may be more pronounced in men, suggesting a need for sex-stratified nutritional research. A shared limitation across many studies is the reliance on self-reported dietary data, which may introduce bias.

Adherence to the Mediterranean diet exerts a multi-axial impact on human hormonal regulation. Its primary endocrine benefits include the enhancement of insulin sensitivity, the downregulation of leptin and cortisol, and a protective effect against thyroid autoimmunity. While the MedDiet acts as a potent therapeutic tool for correcting hormonal imbalances in conditions like obesity, metabolic syndrome, and PCOS, it does not alter reproductive hormone concentrations in healthy adults. Future research should prioritize randomized trials to explore the long-term effects of this pattern on hormone-related cancers and sex-specific hormonal sensitivity.

5. Limitations of studies

A shared limitation across many evaluated studies is the reliance on self-reported dietary data, such as food frequency questionnaires, which are inherently susceptible to recall bias and under- or over-reporting by participants. Furthermore, a significant portion of the current literature consists of observational or cross-sectional designs, which limits the ability to establish definitive causality between Mediterranean diet adherence and specific endocrine shifts. Many randomized controlled trials (RCTs) focusing on metabolic and hormonal outcomes present a relatively short follow-up duration, often failing to demonstrate long-term physiological restoration of complex endpoints, such as intestinal barrier permeability or permanent thyroid autoantibody suppression. Additionally, there is a notable lack of standardization regarding the exact composition of the Mediterranean diet across different clinical cohorts, with variations ranging from energy-restricted models to polyphenol-enriched "Green" variants, which complicates the direct comparison of hormonal efficacy.

6. Direction of future research

Future research should prioritize long-term, large-scale randomized controlled trials with standardized dietary intervention protocols to further elucidate the exact molecular mechanisms underlying multi-axial endocrine modulation. Special emphasis should be placed on sex-stratified nutritional research, given the emerging evidence that metabolic and peripheral insulin sensitivity responses to the Mediterranean diet may be significantly more pronounced in men than in premenopausal women. Moreover, prospective investigations are needed to explore the potential protective effects of this dietary pattern against hormone-related malignancies, such as advanced thyroid and reproductive cancers. Finally, integrating advanced multi-omics approaches—combining metagenomic gut microbiota tracking with deep serum metabolomics—will be crucial to understanding how short-chain fatty acids (SCFAs) and phytochemical factors directly interact with human homeostatic and stress axes over extended periods.

Author Contribution

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methodology, A.P., M.Š., K.Ž., P.C., M.S., M.S., K.C., M.K., I.G., A.A

validation, A.P., K.C., M.S., A.A.;

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writing—review and editing, A.P., K.Ž., P.C., M.Š., M.S., M.S., K.C., M.K., I.G., A.A.;

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The data presented in this study are available on request from the corresponding author.

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