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REVIEW

Obesity and Cardiovascular Risk in Rheumatology: Mechanisms and Clinical Implications

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Abstract
Obesity is a major public health issue with significant implications for the cardiovascular system and rheumatologic diseases. This paper analyzes the pathophysiological mechanisms by which obesity contributes to increased cardiovascular risk in rheumatologic contexts, highlighting the complex interaction between inflammation, adipokines, and endothelial dysfunction. Concepts such as metabolically healthy obesity and the obesity paradox are discussed, along with their clinical implications. Current therapeutic strategies for managing obese patients with rheumatologic conditions are also presented. The paper includes global and Romanian epidemiological data on obesity and cardiovascular diseases.

Keywords: obesity, cardiovascular risk, rheumatology, inflammation, adipokines, endothelial dysfunction, metabolically healthy obesity, obesity paradox, epidemiology.

Introduction

Obesity has become a global epidemic with a continuously increasing prevalence. According to the World Health Organization (WHO), over 650 million adults worldwide were obese in 2016, representing approximately 13% of the adult population [1]. In Europe, the prevalence of obesity has risen significantly in recent decades, with estimates indicating that over 20% of the adult population is obese [2].

In Romania, epidemiological data show a worrying trend. The PREDATORR study conducted in 2016 revealed that the prevalence of obesity in the Romanian adult population is approximately 21.3% [3]. Additionally, the prevalence of overweight individuals is 31.4%, meaning that over half of the adult population is above normal weight.

Cardiovascular diseases are the leading cause of mortality globally, responsible for approximately 17.9 million deaths in 2019 [4]. In Romania, cardiovascular diseases account for over 57% of total deaths, placing the country among the top in Europe for cardiovascular mortality [5].

Obesity is a major modifiable risk factor for cardiovascular diseases, type II diabetes mellitus, rheumatologic conditions, and certain types of cancer. In the rheumatologic context, obesity not only aggravates the evolution of existing diseases but can also contribute to the onset of new pathologies. The chronic low-grade systemic inflammation induced by obesity plays a crucial role in the pathogenesis of these conditions. Understanding the mechanisms by which obesity influences cardiovascular risk in rheumatologic diseases is essential for developing effective and personalized therapeutic strategies.

Pathophysiological Mechanisms of Cardiovascular Risk in Obesity

Obesity as a Pro-Inflammatory Factor

Adipose Tissue as an Active Endocrine Organ

Adipose tissue is recognized as an active endocrine and immunologic organ that secretes a variety of adipokines and cytokines with multiple roles in regulating energy metabolism, insulin sensitivity, and immune response [6]. Adipocytes, along with macrophages infiltrated in adipose tissue, produce bioactive substances such as leptin, adiponectin, resistin, visfatin, TNF-α, and IL-6.

Leptin is involved in regulating appetite and energy expenditure through its action on the hypothalamus. In obesity, plasma leptin levels are elevated, indicating leptin resistance, which

contributes to the disruption of energy homeostasis [7]. Leptin also has pro-inflammatory effects, stimulating the proliferation of helper T lymphocytes and the production of inflammatory cytokines.

Adiponectin has anti-inflammatory and insulin-sensitizing effects. Paradoxically, adiponectin levels are decreased in obesity, favoring inflammation and insulin resistance [8].

Resistin and visfatin are adipokines with pro-inflammatory roles and are associated with insulin resistance and atherogenesis [9].

Chronic Low-Grade Systemic Inflammation

Obesity is characterized by chronic low-grade inflammation, evidenced by increased plasma levels of C-reactive protein (CRP), IL-6, TNF-α, and other inflammatory markers [10]. The inflammation results from the activation of the immune system in adipose tissue, where macrophages and other immune cells release pro-inflammatory cytokines.

This systemic inflammation contributes to the development and progression of atherosclerosis, endothelial dysfunction, and insulin resistance. Additionally, inflammation can exacerbate rheumatologic diseases by stimulating immune responses and inflammatory processes at the articular level.

Endothelial Dysfunction

Endothelial dysfunction is an early pathogenic event in atherosclerosis and is characterized by decreased bioavailability of nitric oxide (NO) and altered balance between vasodilators and vasoconstrictors [11]. In obesity, pro-inflammatory cytokines and adipokines interfere with the synthesis and bioavailability of NO, promoting vasoconstriction, cellular proliferation, and leukocyte adhesion.

Oxidative stress is also increased in obesity, contributing to LDL cholesterol oxidation and endothelial dysfunction. Free radicals generate lipid peroxidation and alter endothelial protein function.

Accelerated Atherogenesis

Atherogenesis is a complex, multifactorial process involving lipid accumulation in the arterial wall, chronic inflammation, and vascular remodeling [12]. In obesity, elevated levels of LDL cholesterol and triglycerides, associated with low HDL cholesterol, favor subendothelial lipid deposition.

Pro-inflammatory cytokines stimulate the expression of vascular adhesion molecules (VCAM-1, ICAM-1), facilitating monocyte recruitment and their transformation into foam macrophages. These macrophages accumulate lipids and form the lipid core of the atherosclerotic plaque. Chronic inflammation and oxidative stress contribute to plaque instability and rupture risk, leading to acute cardiovascular events.

Metabolic Syndrome and Insulin Resistance

Visceral obesity is a central component of metabolic syndrome, which also includes hypertension, hyperglycemia, hypertriglyceridemia, and low HDL cholesterol [13]. Insulin resistance is a key mechanism resulting from the interference of pro-inflammatory cytokines and free fatty acids with insulin signaling.

Insulin resistance leads to hyperglycemia, compensatory hyperinsulinemia, and atherogenic dyslipidemia. These metabolic changes increase the risk of atherosclerosis and cardiovascular diseases. Additionally, hyperinsulinemia stimulates the proliferation of smooth muscle cells and the increase of extracellular matrix in the arterial wall.

Rheumatologic Implications of Obesity

Rheumatoid Arthritis (RA)

RA is a systemic autoimmune disease characterized by inflammatory synovitis and progressive articular destruction. Obesity negatively influences RA evolution through several mechanisms:

- **Systemic Inflammation**: Increased pro-inflammatory cytokines exacerbate synovial inflammation and tissue damage.
- **Adipokines**: Leptin and resistin can stimulate cytokine production and matrix metalloproteinases in synovial cells [14].
- **Diminished Therapeutic Response**: Obese patients exhibit a weaker response to biologic therapies, such as TNF-α inhibitors, possibly due to altered drug distribution and modified clearance [15].

Obesity is associated with an increased risk of cardiovascular comorbidities in RA patients, complicating disease management.

Osteoarthritis

Osteoarthritis is a degenerative joint disease characterized by cartilage degradation, bone remodeling, and mild synovial inflammation. Obesity is a major risk factor for osteoarthritis through:

- **Mechanical Mechanisms**: Excess weight increases mechanical load on weight-bearing joints, accelerating cartilage wear [16].
- **Metabolic Mechanisms**: Pro-inflammatory adipokines can affect cartilage homeostasis by stimulating extracellular matrix degradation and inhibiting proteoglycan synthesis.
- **Systemic Inflammation**: Chronic inflammation may contribute to mild synovitis observed in osteoarthritis.

Weight loss has been shown to reduce symptoms and slow osteoarthritis progression, emphasizing the importance of weight management in these cases.

Systemic Lupus Erythematosus (SLE)

SLE is a multisystem autoimmune disease involving cutaneous, articular, renal, and cardiovascular manifestations. Obesity can worsen SLE evolution through:

- **Immune Response Modulation**: Adipokines may influence T and B cell activity, increasing

autoimmunity [17].

- **Increased Inflammation**: Systemic inflammation exacerbates tissue damage and organ involvement.
- **Cardiovascular Risk**: SLE patients have an elevated cardiovascular risk, and obesity amplifies this risk through the mechanisms described earlier.

Interaction Between Adipokines and the Immune System

Leptin

Leptin plays a crucial role in the interaction between metabolism and the immune system [19]. It stimulates:

- **Proliferation and Activation of Helper T Cells Type 1 (Th1)**: Increases production of IFN-γ and IL-2, favoring a pro-inflammatory immune response.
- **Inhibition of Regulatory T Cells (Treg)**: Reduces immunological tolerance and may facilitate autoimmunity.
- **Activation of Monocytes and Macrophages**: Promotes production of pro-inflammatory cytokines.

In rheumatologic diseases, elevated leptin levels may contribute to articular inflammation and tissue destruction.

Adiponectin

Adiponectin has anti-inflammatory effects by:

- **Inhibiting Production of TNF-α and IL-6**: In macrophages and endothelial cells.
- **Stimulating Production of IL-10**: A cytokine with anti-inflammatory roles.
- **Promoting Insulin Sensitivity**: Through activation of AMPK and PPAR-α signaling pathways [20].

Low adiponectin levels in obesity may favor inflammation and metabolic dysfunction, contributing to the pathogenesis of cardiovascular and rheumatologic diseases.

Other Adipokines

Resistin and visfatin are involved in inflammatory and metabolic processes:

- **Resistin**: Associated with insulin resistance and production of pro-inflammatory cytokines [21].
- **Visfatin**: Involved in NAD synthesis and may have pro-inflammatory and pro-atherogenic effects.

These adipokines can modulate immune cell activity and influence the evolution of rheumatologic and cardiovascular diseases.

Therapeutic Strategies in Managing Obese Patients with Rheumatologic Conditions

Lifestyle Modifications

Lifestyle interventions are essential in obesity management and include:

- **Balanced Hypocaloric Diet**: Reducing caloric intake while maintaining a balance of macronutrients and micronutrients.
- **Regular Physical Activity**: Aerobic and resistance exercises adapted to the patient's functional capacity [22].
- **Nutritional and Psychological Counseling**: To support long-term behavioral changes.

A weight loss of 5-10% of initial body weight can significantly impact systemic inflammation, endothelial function, and rheumatologic symptoms.

Pharmacological Treatment

Medications can be used to facilitate weight loss and control rheumatologic symptoms:

- **Anti-Obesity Pharmacological Agents**: Orlistat, liraglutide, which may be considered when lifestyle changes are insufficient.
- **Antirheumatic Drugs**: NSAIDs, DMARDs, biologic agents (TNF-α inhibitors, IL-6, IL-1 inhibitors) [15].
- **Metformin**: May improve insulin sensitivity and has anti-inflammatory effects.

It is important to adjust doses and monitor drug pharmacokinetics in obese patients due to changes in distribution volume and hepatic and renal clearance.

Bariatric Surgery

Bariatric surgery is indicated in patients with morbid obesity (BMI ≥40 kg/m² or ≥35 kg/m² with associated comorbidities) and includes procedures such as gastric bypass, sleeve gastrectomy, and adjustable gastric banding [23].

Benefits of Bariatric Surgery:

- **Significant and Sustained Weight Loss**: Reduction of visceral adipose mass.
- **Improvement of Metabolic Profile**: Amelioration of hyperglycemia, dyslipidemia, and hypertension.
- **Reduction of Systemic Inflammation**: Decreased levels of pro-inflammatory cytokines and increased adiponectin.
- **Improvement of Rheumatologic Symptoms**: Some studies have shown amelioration of disease activity in RA and osteoarthritis after post-surgical weight loss.

Risks and benefits must be individually evaluated, and patients require multidisciplinary monitoring pre- and post-operatively.

Multidisciplinary Approach

Managing obese patients with rheumatologic conditions requires a multidisciplinary team:

- **Rheumatologists**: For diagnosis and treatment of rheumatologic disease.
- **Cardiologists**: Evaluation and management of cardiovascular risk.
- **Nutritionists**: Dietary counseling and personalized meal plans.
- **Internal Medicine Specialists and**

Endocrinologists: For metabolic comorbidities.
- **Physiotherapists**: Development of adapted exercise programs.
- **Psychologists**: Support for behavioral changes and treatment adherence [24].

Clinical Implications and Recommendations

Cardiovascular Risk Assessment

Periodic evaluation of cardiovascular risk in patients with rheumatologic diseases and obesity is essential:
- **Risk Scores**: Use of validated scores such as SCORE, Framingham, adapted for populations with inflammatory diseases [25].
- **Monitoring Inflammatory Markers**: CRP, ESR, fibrinogen.
- **Assessment of Endothelial Function**: Measurement of flow-mediated dilation or serum markers.

Personalized Treatment

Treatment should be individualized:
- **Dose Adjustments of Medications**: Based on body weight and pharmacokinetics.
- **Selection of Therapeutic Agents**: Choosing medications with favorable metabolic profiles.
- **Considering Comorbidities**: Diabetes mellitus, hypertension, dyslipidemia.

Patient Education

Education and active patient involvement are crucial:
- **Informing About Risks Associated with Obesity**: Impact on rheumatologic disease and cardiovascular risk.
- **Promoting a Healthy Lifestyle**: Balanced nutrition, physical activity.
- **Psychological Support**: Managing emotional and motivational factors [26].

Metabolically Healthy Obesity and the Obesity Paradox

Metabolically Healthy Obesity (MHO)

A subgroup of obese individuals presents a favorable metabolic profile without dyslipidemia, hypertension, or insulin resistance, known as metabolically healthy obese (MHO) [7]. Characteristics of these individuals include:
- **Peripheral Distribution of Adipose Tissue**: Predominance of subcutaneous fat over visceral fat.
- **Normal Adiponectin Levels**: Contributing to anti-inflammatory effects and insulin sensitivity.
- **Increased Physical Activity**: More active lifestyle.

Although MHO have a lower cardiovascular risk compared to obese individuals with altered metabolic profiles, some studies suggest that this state is not entirely benign. In the long term, MHO may develop metabolic and cardiovascular complications, and chronic low-grade inflammation may be present [8].

Obesity Paradox

The obesity paradox refers to the observation that in certain chronic diseases, including congestive heart failure and some rheumatologic conditions, patients with moderate obesity have a better prognosis than those with normal weight or underweight [9].

Possible explanations for this paradox include:
- **Greater Energy Reserves**: Obesity may provide an energetic advantage under metabolic stress or chronic illness.
- **Protective Effects of Adipokines**: Certain adipokines may have anti-inflammatory or cardioprotective roles.
- **Methodological Biases**: Some studies may have limitations related to design or confounding factors.

It is important to emphasize that the obesity paradox does not negate the long-term risks associated with obesity and does not change weight management recommendations [18].

Future Research

Future research directions include:
- **Identification of Specific Biomarkers**: For predicting cardiovascular risk and therapeutic response.
- **Clinical Studies on Therapeutic Interventions**: Efficacy of new pharmacological agents and biologic therapies in the context of obesity.
- **Exploration of Molecular Mechanisms**: Deeper understanding of the interaction between obesity, inflammation, and autoimmunity [27].

Conclusions

Obesity has a significant impact on cardiovascular risk and the evolution of rheumatologic diseases through complex inflammatory and metabolic mechanisms. The concepts of metabolically healthy obesity and the obesity paradox add complexity to understanding the relationship between obesity and health. Nonetheless, obesity remains a major risk factor that requires intervention.

Effective management of obese patients with rheumatologic conditions requires an integrated and multidisciplinary approach targeting both rheumatologic disease control and cardiovascular risk reduction. Lifestyle interventions, alongside appropriate pharmacological therapies and patient education, can significantly improve prognosis and quality of life.

Conflicts of Interest: The authors declare no conflicts of interest.

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