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Tumor Discovery

PERSPECTIVE ARTICLE

Vasculoendothelial dysfunction and bone health in obese children: A connection with cancers

Simmi Kharb[†]* and Gurpreet Singh Gill[†]

Department of Biochemistry, Pt. B.D. Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India

Abstract

Obesity in children, a growing global epidemic, is not merely characterized by excessive body fat but also by a cascade of metabolic and functional derangements with significant musculoskeletal consequences. One of the key underpinnings of these detrimental effects is vasculoendothelial dysfunction (VED), a multifaceted pathological process characterized by impaired endothelial cell function. The endothelium, lining the vasculature, plays a pivotal role in regulating vascular tone, inflammation, and coagulation, and its dysfunction in obese children leads to a plethora of downstream complications with profound implications for musculoskeletal and bone health. Diagnosing VED in obese children remains a challenge. Traditional cardiovascular risk factors such as hypertension and dyslipidemia are often detected long after the occurrence of endothelial dysfunction. In the context of bone sarcoma, the interaction between cancer cells and vascular endothelium in the bone microenvironment is critical. The bone is a highly vascularized tissue, and the vascular endothelium plays a role in regulating bone homeostasis. In the presence of cancer cells, altered bone microenvironment provides a milieu favorable to tumor growth and invasion. The relationship between the vascular endothelium and cancer is complex and can vary depending on the type of cancer and its microenvironment. Understanding the interactions between vascular endothelium and bone sarcoma is crucial for developing targeted therapies. New molecular and cellular mechanisms involved in these interactions are awaiting to be uncovered, shedding light on potential therapeutic strategies for cancer treatment. On a relevant note, emerging vasculoendothelial markers hold promise for early detection and intervention. Early identification of VED, through the detection of vasculoendothelial markers, opens doors for timely interventions aimed at preventing its detrimental effects on musculoskeletal and bone health in obese children.

Keywords: Childhood obesity; Vasculoendothelial; Vascular dysfunction; Inflammatory markers; Cancer; Bone

1. Introduction

Obesity in children, a growing global epidemic, is not merely characterized by excessive body fat but also by a cascade of metabolic and functional derangements with significant musculoskeletal and bone health consequences. One of the key underpinnings of these detrimental effects is vasculoendothelial dysfunction (VED), a multifaceted

[†]These authors contributed equally to this work.

***Corresponding author:**
Simmi Kharb
(drsimmikharab@uhrs.ac.in)

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pathological process characterized by impaired endothelial cell function.[1]

The endothelium, lining the vasculature, plays a pivotal role in regulating vascular tone, inflammation, and coagulation. Emerging evidence suggests a dynamic interplay between obesity and endothelial dysfunction.[2] A recent study has reported impaired endothelial function in obese children, emphasizing the importance of vascular health assessment. Obesity influences endothelial function through obesity-related complications such as hypertension, dyslipidemia, diabetes, metabolic syndrome, and obstructive sleep apnea syndrome. An association between obesity and endothelial function has been demonstrated by means of anthropometric indices and imaging modalities.[3] In the context of obesity, metabolic complications (e.g., diabetes) and cardiovascular complications (e.g., atherosclerosis) are resulted from dysfunctional adipose tissue that generates a pro-inflammatory, hyperlipidemic, and insulin-resistant environment.[4]

Understanding the intricate relationship between obesity and vascular health is crucial for early intervention and prevention. Although a few studies have explored the relationships between VED and obesity, information regarding various vasculoendothelial and inflammatory markers in obese children is still lacking.

After critically examining the literature regarding various experimental methodologies and verification in children, we realize that there are no studies thus far regarding the correlation between vasculoendothelial and inflammatory markers in obese children and the implications of obesity for bone health and cancers. Thus, the present paper intends to offer a perspective of childhood obesity, focusing on vasculoendothelial and inflammatory markers in the context of obesity, as well as bone growth and cancers in children.

2. VED and bone health in obese children

2.1. Vascular endothelium

The vascular endothelium serves as a physical barrier between blood and tissues. It is also an endocrine structure that helps maintain cardiovascular homeostasis. Endothelial dysfunction occurs at an early stage in the development of atherosclerosis, leading to an increased risk of cardiovascular events. Vascular homeostasis is maintained by a balance between endothelium-derived relaxing and contracting factors. However, the disruption of this balance, mediated by inflammatory and traditional cardiovascular risk factors, renders the vasculature susceptible to atheroma formation.

2.2. VED

Fundamental and translational studies have led to a significant understanding of cellular and molecular alterations responsible for endothelial dysfunction. Unfortunately, progression of atherosclerosis in obese adults, who have been chronically affected by endothelial dysfunction, is still the dominant topic in literature. Despite technical difficulties and ethical concerns, the investigation of endothelial function in obese children stands as a necessary step to deepen our understanding of the initiation and progression of endothelial dysfunction, which is crucial to the development of treatment strategies.

2.2.1. VED and obesity

Emerging evidence suggests a dynamic interplay between obesity and endothelial dysfunction.[2] Accumulating evidence indicates that endothelial dysfunction is an independent predictor of cardiovascular events and may serve as an early indicator of cardiovascular risk in obese children.[5] Childhood obesity has also been associated with endothelial dysfunction although there has been relatively little research into the relationship between biomarkers of endothelial activation and either insulin resistance or inflammation in obese children.

Reactive oxygen species (ROS), which is generated during oxidative stress, contributes to endothelial dysfunction. ROS and ox-low-density lipoprotein (ox-LDL), a modified form of low-density lipoprotein (LDL), have been implicated in the pathogenesis of atherosclerosis. Oxidative modification of LDL renders it more atherogenic, promoting endothelial dysfunction and recruitment of inflammatory cells to the arterial wall, which might be the mechanisms underlying atherosclerotic processes in the context of excess adiposity.[5] Oxidative damage of LDL produces ox-LDL, which is implicated in endothelial dysfunction and atherosclerosis that are often observed in obese children; therefore, exploring the mechanistic relationship between ox-LDL and endothelial dysfunction would help with identifying potential therapeutic targets. It has been demonstrated that the impairment of endothelial nitric oxide synthase (eNOS) and the loss of nitric oxide (NO), a major vasodilator and anti-inflammatory agent, are hallmarks of obesity-induced endothelial dysfunction.

Although various studies have independently explored the impact of vasculoendothelial and inflammatory markers in the context of childhood obesity, a comprehensive understanding of their association is still lacking.

2.3. Vasculoendothelium and bone health

The endothelium is an integral part of bone tissue, performing physiological paracrine functions through

growth factors and chemokines release, and interacting with different cell types. Endothelial cells in bone have several functions, namely maintenance of vascular integrity, bone formation, and direct stimulation of osteoblasts/osteoclasts crosstalk.[6]

Alterations of the complex biochemical interactions between vasculature and bone cells dramatically affect bone metabolism and health and may lead to various clinical manifestations. Changes to the blood supply in the vascular networks surrounding bone cells very often could lead to inhibition of bone metabolism, resulting in decreased bone formation.

Obesity influences bone metabolism by stimulating pre-osteoblasts to differentiate into adipocytes rather than osteoblasts, thus filling the cavities of bone marrow with adipocytes rather than trabecular bone, consequently increasing bone fragility. The RANKL/RANK/OPG pathway is a signaling pathway that regulates the formation and activity of osteoclasts, which are cells responsible for breaking down bone tissue. Increased levels of pro-inflammatory cytokines due to obesity would dysregulate this pathway, leading to an increase in osteoclast formation and activity. Ultimately, this results in a decrease in bone density and an increased risk of fractures. Therefore, it is crucial to maintain a healthy weight through proper dietary intake and exercise, especially for obese children, to ensure good bone health.[7]

Obesity is related to inflammatory musculoskeletal diseases (i.e., osteoarthritis).[8] VED in obese children manifests in several ways, impacting various aspects of musculoskeletal function. Endothelial NO bioavailability is significantly reduced in obesity, leading to impaired vasodilation and decreased blood flow to muscles and causing diminished exercise capacity, muscle fatigue, and reduced exercise tolerance, which poses a hindrance to physical activity participation, thereby perpetuating the obesity cycle. Furthermore, VED promotes chronic low-grade inflammation, contributing to muscle weakness, pain, and impaired bone health, all of which increase the risk of musculoskeletal injuries and fractures. VED also promotes pro-thrombotic changes, increasing the risk of deep vein thrombosis and other musculoskeletal complications.[9]

Spatiotemporal interaction between endothelial cells and neighboring skeletal cells plays critical roles in development, homeostasis, and pathological bone destruction. The altered relationship between endothelium, vasculature, and bone tissue can result in pathologies such as avascular necrosis, osteopetrosis, rickets, osteoporosis, inflammatory bone loss, multiple myeloma, Paget's disease, and metastatic bone disease. Thus, a greater understanding of the role of bone vasculature in both normal development and pathological condition may lead to new therapeutic approaches for a range of bone conditions.

2.3.1. VED and its implications in cancer

VED is characterized by an imbalance in the production and release of various substances by endothelial cells, leading to altered vascular tone, increased inflammation, and impaired blood vessel function. While VED is commonly associated with cardiovascular diseases, emerging research has also highlighted its implications for cancer development and progression. VED can contribute to increased angiogenesis, which is a critical process for supplying tumors with nutrients and oxygen in cancer patients, facilitating their growth and progression. Endothelial dysfunction is often associated with chronic inflammation. Inflammation in the tumor microenvironment can promote cancer development and contribute to the evasion of immune surveillance. The dysfunctional endothelium may facilitate the recruitment of immune cells that support tumor growth. Dysfunction of the vascular endothelium can lead to increased permeability of blood vessels that might contribute to the intravasation and extravasation of cancer cells, facilitating their spread to distant sites and promoting metastasis.

Endothelial dysfunction can induce a procoagulant state and may contribute to cancer-associated thrombosis, a common complication in cancer patients. Cancer cells can influence the endothelium through the release of various factors that may further exacerbate VED and create a microenvironment conducive to tumor growth.

Markers of VED, such as elevated levels of circulating endothelial cells, von Willebrand factor (vWF), and adhesion molecules, have been investigated for their diagnostic and prognostic value in cancer. These markers may serve as indicators of the vascular changes associated with tumor development.

Targeting VED has become an area of interest in cancer therapeutics. Anti-angiogenic therapies are conceptualized to disrupt the formation of new blood vessels so as to impede tumor growth. In addition, drugs targeting inflammation and endothelial function are being explored in cancer treatment.

Understanding the intricate relationship between VED and cancer is essential for developing targeted therapeutic strategies and improving patient outcomes. The molecular and cellular mechanisms underlying this relationship are currently under exploration in ongoing research.

2.3.2. Vascular endothelium and bone sarcomas

In the context of bone sarcoma, the interaction between cancer cells and the vascular endothelium in the bone microenvironment plays a critical role.[10] Osteosarcoma is the

most common tumor in children and adolescents, followed by chondrosarcoma. The bone is a highly vascularized tissue, and the vascular endothelium plays a role in regulating bone homeostasis. In the presence of cancer cells, changes in the bone microenvironment can favor tumor growth and invasion. Angiogenesis is essential for tumor growth and metastasis, and vascular endothelium is involved in angiogenesis by releasing growth factors and signaling molecules that promote the formation of new blood vessels.

The immune response plays a complex role in cancer, with immune cells potentially either suppressing or promoting tumor growth. The vascular endothelium is involved in the recruitment of immune cells to the tumor site. Furthermore, vascular endothelium influences the migration of immune cells to the tumor microenvironment, affecting the balance between anti-tumor and pro-tumor immune responses.

The relationship between the vascular endothelium and cancer is complex and can vary depending on the type of cancer and its microenvironment. The molecular and cellular mechanisms underlying the interactions between the vascular endothelium and cancer are currently under exploration in ongoing research, with a view to uncovering potential new therapeutic strategies for cancer treatment.

2.4. Markers of endothelial function

Various biomarkers of endothelial function and integrity include C-reactive protein, endothelial adhesion molecules, E-selectin, cytokines, CD62+, ox-LDL, asymmetric dimethylarginine, and endocan. Novel biomarkers of endothelial dysfunction include endoglin, annexin V+, matrix metalloproteinases, ANGPTL2, serum homocysteine, hepatokines, cellular adhesion molecules (CAMs; including E-selectin, intercellular adhesion molecule 1 [ICAM-1, pentraxin-3, vascular cell adhesion molecule 1 [VCAM-1), and various sonographic parameters (liver ultrasound and carotid intima-media thickness parameters).[11-14]

2.4.1. Markers of endothelial dysfunction

Elevated levels of sICAM-1 have been implicated in obesity-related inflammation and could be a potential indicator of endothelial dysfunction and cardiovascular risk.[14] VCAM and E-selectin, which are endothelial adhesion molecules, contribute to the inflammatory cascade by facilitating the recruitment of immune cells to adipose tissue, thereby exacerbating chronic low-grade inflammation associated with obesity.[15]

Advances in spatial omics such as spatial transcriptomics, epigenomics, proteomics, and metabolomics, and their integrations at various biological scales, may help decipher the previously unappreciated pathophysiological mechanisms in bone and refine classifications of certain diseases, facilitating precise and individualized medical treatment for patients.[15]

Exploration of the dynamics of these adhesion molecules in the context of obesity and the musculoskeletal would provide valuable insights into the pathophysiological mechanisms underlying obesity-related vascular complications. Emerging evidence underscores the importance of unveiling further skeletal-vascular interactions, which are instrumental to enhancing treatment for patients suffering from cancer as well as other bone-destructive diseases.

2.4.2. Markers of vasculoendothelial and bone growth

Several markers are associated with vasculoendothelial and bone growth that reflect the dynamic processes involved in angiogenesis, bone formation, and remodeling. These markers are often used in research and clinical settings to assess the status of blood vessels and bone tissue. Common markers for vasculoendothelium and bone growth include vasculoendothelial growth factor, endothelial cell markers (CD31 [PECAM-1, vWF), bone formation markers (osteocalcin, bone alkaline phosphatase), bone resorption markers (tartrate-resistant acid phosphatase, C-terminal telopeptide of type I collagen), transforming growth factor-beta, fibroblast growth factor, platelet-derived growth factor, and angiopoietins.[16]

These markers can be measured from blood or tissue samples to assess the activity of endothelial cells, osteoblasts, and osteoclasts. Changes in the levels of these markers can provide insights into the status of vasculoendothelium, bone growth, angiogenesis, bone formation, and remodeling in cancer and may have implications for cancer diagnosis, prognosis, and/or response to therapeutic interventions.

3. Conclusion

At present, there are no specific studies addressing the possible link between VED and bone health in obese children, as well as investigating the diagnostic utility of vasculoendothelial and bone growth markers in the context of cancer. However, it is known that the seemingly disparate research domains of obesity, cardiovascular health, bone health, and cancer often intersect, offering a distinct direction to advance research progress. Early identification of VED, through measurement of vasculoendothelial markers, opens doors for timely interventions aimed at preventing its detrimental effects on musculoskeletal health in obese children. Lifestyle modifications, including dietary changes and increased physical activity, are crucial first-line interventions, promoting NO bioavailability and reducing inflammation.[16] In addition, specific therapeutic strategies targeting endothelial function, such as anti-inflammatory medications and antioxidants, might hold

promise in the future. Understanding the interactions between the vascular endothelium and bone sarcoma is crucial for developing targeted therapies. At present, anti-angiogenic therapies are being conceptualized and designed, with the aim of disrupting blood supply to tumors by targeting vascular endothelium, to inhibit tumor growth and metastasis. By proactively addressing VED and its musculoskeletal consequences, we can empower obese children to lead healthier, more active lives.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

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