Review

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Hemorheology in thyroid abnormalities: old team player, new insights

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ABSTRACT

Thyroid dysfunctions significantly impact various physiological processes, extending their influence on hemorheological properties and microcirculation. This comprehensive review explores the intricate relationship between thyroid disorders and hemorheology, emphasizing the substantial effects on blood flow dynamics and tissue perfusion. Examining the alterations in blood viscosity, erythrocyte behavior, and microvascular circulation in both hypothyroidism and hyperthyroidism reveals crucial insights into the pathophysiology of these conditions. Furthermore, elucidating the hemorheological changes associated with thyroid dysfunctions offers potential avenues for improved clinical management strategies. This review synthesizes current research findings, highlighting the importance of considering hemorheological aspects in understanding the complexities of thyroid-related complications and advancing patient care paradigms.

Keywords: Hemorheology, thyroid dysfunction, hypothyroidism, hyperthyroidism, erythrocyte deformability, erythrocyte aggregation, blood viscosity, plasma viscosity

INTRODUCTION

The thyroid gland plays a crucial role in regulating various bodily functions by producing hormones that act as chemical messengers. The primary hormones produced by the thyroid gland are thyroxine (T4) and triiodothyronine (T3). These hormones are essential for maintaining metabolic rate, energy production, and body temperature. They also influence the growth and development of tissues and organs throughout the body, including the brain, heart, muscles, and bones. Moreover, thyroid hormones help regulate heart rate, digestion, and the body's response to other hormones, impacting overall health and well-being.

Hyperthyroidism refers to the excessive synthesis and secretion of thyroid hormones from the thyroid tissue due to its over-activity. Moreover, factors such as exogenous intake of thyroid hormones, release from an alternate source within the body, or the circulation of previously produced hormones owing to thyroid gland destruction may contribute to thyrotoxicosis, a condition where an excessive presence of thyroid hormones in circulation occurs without the presence of hyperthyroidism.[1-3]

Hypothyroidism is characterized by an underactive thyroid gland, which fails to produce an adequate amount of thyroid hormones essential for regulating various bodily functions. This deficiency in thyroid hormone production can lead to a slowdown in metabolism and affect numerous physiological processes in the body. Some common causes of hypothyroidism include autoimmune disorders (such as Hashimoto's thyroiditis), thyroid gland inflammation, surgical removal of the thyroid gland, or radiation therapy affecting the thyroid.[4]

Hemorheology is a scientific field that delves into the fluidic attributes of blood. It explores the fluidity features of blood plasma and the constituents within blood, including red blood cells, white blood cells, and platelets. Its focus encompasses the assessment of blood's fluidic properties within both microcirculation and macrocirculation. For optimal tissue perfusion, it is imperative for blood to possess suitable rheological characteristics. Failure to meet these criteria may lead to disruptions, particularly in microcirculatory function.[5,6]

Thyroid dysfunctions significantly influence blood-related parameters and contents of plasma, affecting the blood's flow characteristics. The involvement of thyroid hormones in the regulation of erythropoiesis, especially their interaction with specific receptors present on hematopoietic stem cells, plays a pivotal role.[7] This review underscores the pivotal interplay between thyroid dysfunctions and hemorheological alterations, highlighting

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the critical role of blood flow properties in understanding and managing thyroid-related complications.

FACTORS DETERMINING HEMORHEOLOGY

The factors influencing the fluidity characteristics of blood can be broadly categorized into two primary groups: those stemming from the endothelial lining of blood vessels and those originating from the inherent physical properties of blood itself. Parameters linked to the physical traits of blood encompass the hematocrit percentage, effects associated with the elasticity/deformability and aggregation tendencies of erythrocytes, as well as plasma and whole blood viscosity. These factors are subject to variation due to various pathogenic conditions and are also susceptible to alterations based on physiological circumstances, including ambient temperature, nutritional status, hydration levels, physical exertion, and other related physiological states.

Hematocrit signifies the proportion of erythrocytes within the total blood volume. With an elevation in hematocrit values, blood viscosity proportionally rises.[8] This augmentation becomes notably more significant when hematocrit surpasses 60%, manifesting as a logarithmic, rather than a linear, escalation. Studies reveal that at moderate and high shear rates, a single unit rise in hematocrit corresponds to a 4% upsurge in blood viscosity.[7] Consequently, an elevation in hematocrit directly influences the fluidic attributes of blood.

Red blood cells (erythrocytes)

Erythrocytes constitute the most abundant cellular elements in the blood plasma and are known for their flexible cellular structure. Typically measuring around 8 µm in diameter, 2 µm in thickness, and displaying a biconcave disc shape, these circulating erythrocytes demonstrate the capacity to flex and bend when traversing small-diameter capillaries. This flexibility (deformability of the erythrocytes) ensures the smooth continuity of blood flow within the capillary circulation.[9]

Erythrocyte deformability (ED)

The principal factors governing deformability include the cytoplasmic viscosity of the erythrocyte, membrane properties, and the geometric structural attributes of the erythrocyte.

Cytoplasmic viscosity of erythrocytes

Also referred to as internal viscosity, it is chiefly determined by the concentration of hemoglobin within erythrocytes, denoted as MCHC (mean corpuscular hemoglobin concentration). Increased MCHC levels, indicative of heightened internal viscosity of erythrocytes, are associated with decreased deformability characteristics of erythrocytes.[10]

Erythrocyte membrane characteristics

Erythrocytes must exhibit high flexibility combined with stable membrane properties for efficient microcirculation. The membrane's stability is equally vital as its flexibility. In instances where erythrocytes lack the necessary stability (as observed in erythrocyte membrane disorders like hereditary spherocytosis), they become susceptible to premature breakdown during circulation. The structural balance of proteins within the erythrocyte membrane, including spectrin, actin, ankyrin, tropomyosin, protein 4.1, and 4.9, and their interplay, is responsible for maintaining the optimal balance between stability and flexibility in the erythrocyte membrane. When defects exist in membrane proteins, both the flexibility and stability of erythrocytes are significantly reduced, leading to conditions marked by increased vulnerability to cell breakdown, often accompanied by hemolytic anemia.[10,11]

Erythrocyte geometry and structural features

Under static conditions, erythrocytes in healthy individuals maintain a biconcave shape. The typical erythrocyte diameter measures around ~8 µm, with a thickness of ~2 µm, a surface area of approximately ~135 µm², and a volume of ~90 fL. These geometric attributes have the capacity to alter within physiological thresholds in response to flow dynamics or osmotic pressure, contributing to erythrocyte flexibility. The biconcave shape dictates a specific surface area-to-volume ratio for erythrocytes, typically denoted as 1.5 for healthy cells. Pathological conditions like hereditary spherocytosis, hemolytic anemias, malaria, and certain disorders exhibit a diminished surface area-to-volume ratio, causing a decline in erythrocyte flexibility and deformability characteristics.[12]

The deformability characteristic of erythrocytes plays a crucial role not just in determining the oxygen delivery to tissues but also serves as an indicator of their lifespan. The loss of deformability implies that the erythrocytes might be older. As these older erythrocytes lose their ability to deform, they become unable to traverse narrow splenic sinuses, ultimately leading to their breakdown.

Furthermore, the deformability of erythrocytes holds considerable importance in sustaining microcirculation within peripheral tissues. Pathologies such as erythrocyte membrane disorders, infections, sepsis, metabolic syndromes, diabetes mellitus, and similar conditions known to impair deformability, also disrupt the transportation of oxygen to the tissues.[13]

Erythrocyte aggregation (EA)

Aggregation is a behavior displayed by erythrocytes when subjected to low shear stress conditions, typically occurring during stasis when blood flow moves slowly. Under low shear stress, they tend to form

clusters known as rouleaux formation. These clusters can be two-dimensional, formed by the gathering of multiple erythrocytes, or they can manifest in a three-dimensional structure when the rouleaux adhere to each other. Aggregation is a reversible behavior; when shear stress intensifies, erythrocytes revert to their individual states.[14]

Factors affecting aggregation include not only the cellular properties of erythrocytes but also plasma-derived elements.[15] Components such as fibrinogen and von Willebrand factor in the plasma content, along with the ratio of acute-phase reactants during inflammatory processes, influence erythrocyte aggregation. Additionally, changes in the behavior of erythrocyte aggregation are observed in various pathological conditions.[12,16]

Two distinct models have been proposed to describe erythrocyte aggregation behavior: 1) the bridging model and 2) the depletion model.

The Bridging model postulates that macromolecules such as albumin and fibrinogen, adhering to the surface of adjacent erythrocytes, establish bridges, thereby hindering the forces responsible for disaggregation and facilitating erythrocyte clustering.[14,17]

Conversely, the Depletion model suggests that macromolecules present on the erythrocyte surface exhibit a lower concentration compared to the surrounding environment, indicating a relative depletion at the cellular surface. The sparsity of these macromolecules on the erythrocyte surface leads to the creation of an osmotic gradient, inducing fluid movement within the intercellular space. Consequently, this fluid movement exerts forces that draw nearby erythrocytes towards each other.[14,17]

The two models proposed to elucidate the erythrocyte aggregation mechanism present contrasting views regarding the density of macromolecules on the erythrocyte surface. The Bridging model is based on the assumption of higher macromolecular concentration, while the Depletion model contends the opposite by suggesting a lower concentration on the erythrocyte surface.[18]

VISCOSITY

Plasma viscosity (PV)

Blood plasma serves as the matrix supporting the various cellular components within the bloodstream, encompassing dissolved minerals, plasma proteins, vitamins, and other solutes. The viscosity of plasma primarily relies on its protein content. Pathological conditions like multiple myeloma and macroglobulinemia, marked by increased plasma proteins, exhibit heightened plasma viscosity during inflammatory processes. Conversely, conditions characterized by reduced fibrinogen or immunoglobulins show a decrease in plasma viscosity.[9] Elevated plasma viscosity impedes the smooth flow of blood within the vascular system and can lead to microcirculatory blockages. With Newtonian fluid characteristics, normal plasma viscosity at 37°C is typically within the range of 1.10 - 1.35 cP.[8]

Whole blood viscosity (WBV)

Blood fluidity exhibits non-Newtonian characteristics, demonstrating an increase in viscosity at low shear rate levels. In other words, it displays a "shear-thinning" property. Changes in whole blood viscosity are directly related to alterations in plasma viscosity, either increasing or decreasing. Factors impacting plasma viscosity also influence whole blood viscosity yet changes in the latter can occur despite constant plasma viscosity, owing to the non-Newtonian traits of whole blood. Alterations in whole blood viscosity can be observed due to erythrocytes' deformability and aggregation properties, while the hematocrit value remains a contributing factor. Blood flow in the vascular system encounters diverse vessel sizes, resulting in varied shear rates—higher in capillary vessels than in larger diameter vessels. As shear rates rise, whole blood viscosity declines. Temperature serves as another influential factor, as an increase in temperature correlates with decreased whole blood and plasma viscosity.[19]

HYPERTHYROIDISM AND HEMORHEOLOGY

Thyroid hormones impact numerous systems, including the cardiovascular system. Apart from accelerating metabolic rate, they induce relaxation of arterial smooth muscles and lead to vasodilation in the peripheral vascular system.[20,21] These effects culminate in a lowered resistance within peripheral vasculature. As this resistance diminishes, renal perfusion also decreases, triggering activation of the Renin-Angiotensin-Aldosterone system. Consequently, sodium and fluid retention occur, resulting in hypervolemia.[20] These shifts in blood volume directly impact the rheological properties of blood through alterations in viscosity.

Apart from the hemodynamic effects, it is recognized that lipid profiles, plasma proteins, and electrolyte concentrations change in the hyperthyroid patient group.[22] These alterations also elevate plasma viscosity, consequently contributing to hemorheological irregularities. The direct influence of thyroid hormones on erythrocytes leads to structural changes, negatively impacting erythrocyte aggregation and deformability.

In hyperthyroid conditions, an upsurge in red blood cell count and hematocrit levels is observed due to the heightened activity of these hormones. Consequently, this escalation often translates into an elevation in whole blood viscosity, impacting the blood's flow properties. Moreover, these thyroid-induced alterations contribute to modifications in erythrocyte aggregation behavior, potentially influencing blood clotting tendencies and circulation dynamics within the body.

In hyperthyroidism, there is a notable rise in various coagulation factors, including fibrinogen and other clotting components, which collectively contribute to a hypercoagulable state. The heightened presence of these factors promotes increased blood clotting tendencies and raises the risk of thrombosis.[23,24] Additionally, the surplus of fibrinogen and coagulation factors influences plasma viscosity, amplifying the resistance to blood flow within the vessels. This escalation in plasma viscosity is further compounded by the rise in whole blood viscosity, primarily due to the augmented erythrocyte count and hematocrit levels typical in hyperthyroid conditions. Moreover, the heightened erythrocyte count and altered behavior of erythrocytes in hyperthyroidism foster an increased tendency for these blood cells to form aggregates. These combined effects on plasma and whole blood viscosity, as well as the tendency for erythrocyte aggregation, contribute to altered hemorheological properties, potentially impacting blood flow and predisposing individuals to thrombotic events.

In hyperthyroidism, dysregulation in hemodynamic mechanisms arises from the hypermetabolic state induced by excessive thyroid hormone production. This condition often leads to cardiac complications, notably cardiac arrhythmias such as atrial fibrillation. Atrial fibrillation, a common occurrence in hyperthyroid individuals, disrupts the regular rhythm of the heart's upper chambers, affecting blood flow patterns and potentially contributing to disturbances in microcirculation.[25,26] Furthermore, the hypermetabolic state characteristic of hyperthyroidism results in an escalated demand for oxygen by the body tissues. This increased demand prompts a rise in the production of erythrocytes, consequently elevating both erythrocyte mass and count in the bloodstream. These alterations significantly impact the hemorheological status by influencing blood viscosity and circulation dynamics, potentially affecting overall blood flow and hemodynamic stability.

In light of this information, it's conceivable to anticipate potential hemorheological disturbances in hyperthyroid patients, potentially affecting tissue perfusion adversely. Considering the coexistence of other conditions like diabetes and hypertension, which influence peripheral circulation, close monitoring of hemorheology in hyperthyroid patients becomes increasingly critical.

HYPOTHYROIDISM AND HEMORHEOLOGY

In hypothyroidism, hemorheological parameters are affected in various ways. Plasma viscosity may undergo changes attributed to alterations in blood composition and fluid dynamics. The condition, characterized by decreased metabolic function, can lead to elevated levels of certain proteins such as lipoproteins and globulins. These heightened protein concentrations in the bloodstream may contribute to increased plasma viscosity.[27] Additionally, reduced metabolic activity in hypothyroidism might lead to fluid retention or alterations in fluid balance in the body. Changes in hydration levels can influence plasma viscosity, with decreased fluid levels potentially contributing to an increase in viscosity. Furthermore, disturbances in lipid metabolism associated with hypothyroidism, leading to elevated lipid levels like cholesterol, may further influence plasma viscosity. The condition's effects on blood circulation and flow dynamics within vessels might also indirectly impact plasma viscosity due to variations in blood flow patterns, emphasizing the multifaceted nature of hypothyroidism's impact on plasma viscosity. The condition often leads to a decreased red blood cell count or erythrocytes, resulting in lowered hematocrit levels, which can contribute to reduced whole blood viscosity. Moreover, hypothyroidism may cause variations in plasma protein levels, including factors involved in blood clotting, potentially influencing the viscosity of the plasma component of blood and subsequently affecting whole blood viscosity. Additionally, the condition's effects on blood flow patterns within vessels can indirectly impact whole blood viscosity by altering shear stress and circulation dynamics. Changes in lipid metabolism associated with hypothyroidism, such as increased cholesterol levels, may further contribute to variations in whole blood viscosity. However, the precise impact of hypothyroidism on whole blood viscosity may vary among individuals based on the interplay of these factors within their physiological makeup.[28,29]

In hypothyroidism, modifications in erythrocyte deformability and aggregation behaviors often manifest due to changes in blood composition and rheological characteristics. The condition can result in reduced erythrocyte deformability, possibly attributed to alterations in lipid metabolism, particularly elevated cholesterol levels. These changes impact the flexibility and pliability of erythrocyte membranes, potentially hindering their capacity to alter shape and traverse through smaller blood vessels efficiently. Additionally, hypothyroidism might augment erythrocyte aggregation tendencies. Elevated plasma protein levels, variations in fibrinogen concentrations, and disrupted blood flow dynamics may collectively contribute to an increased inclination for erythrocytes to aggregate or adhere

together. These adjustments in plasma composition, along with modifications in erythrocyte deformability and aggregation, could influence overall blood rheology, potentially impeding blood flow and microcirculation, thereby playing a role in the condition's pathophysiology.[30]

CONCLUSION

Hemorheological status carries a great importance in thyroid dysfunctions, due to its influence on blood flow dynamics and tissue perfusion. Understanding these hemorheological changes and their impact on microcirculation is crucial. These alterations can affect tissue oxygenation, nutrient delivery, and waste removal, contributing to various complications associated with thyroid dysfunctions. Management strategies that address these hemorheological aspects could potentially help mitigate the adverse effects on microcirculation, thereby improving clinical outcomes in individuals with thyroid disorders.

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