Serum Bilirubin in Obese Individuals

Subjects: Others
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Bilirubin, the end product of heme metabolism, is a potent endogenous antioxidant with anti-inflammatory, immunomodulatory, antithrombotic, and endocrine properties. Serum bilirubin concentrations depend on the complex interactions between bilirubin production, consumption (depending on oxidative stress and inflammation), metabolism, and elimination. Importantly, numerous studies have shown that serum bilirubin levels are inversely associated with obesity, metabolic syndrome (MetS), type 2 diabetes mellitus (T2DM), and other oxidative-stress-mediated diseases, including atherosclerosis. Moreover, serum bilirubin levels were recently proposed as a potential pre-disease biomarker for developing metabolic syndrome in asymptomatic middle-aged individuals.

Keywords: adipokines ; antioxidant ; anti-inflammatory ; bilirubin ; obesity ; overweight

1. Overview

Obesity is a chronic condition involving low-grade inflammation and increased oxidative stress; thus, obese and overweight people have lower values of serum bilirubin. Essentially, bilirubin is a potent endogenous antioxidant molecule with anti-inflammatory, immunomodulatory, antithrombotic, and endocrine properties.

Bilirubin, the end product of heme metabolism, is a potent endogenous antioxidant with anti-inflammatory, immunomodulatory, antithrombotic, and endocrine properties [1][2][3]. Serum bilirubin concentrations depend on the complex interactions between bilirubin production, consumption (depending on oxidative stress and inflammation), metabolism, and elimination. Importantly, numerous studies have shown that serum bilirubin levels are inversely associated with obesity, metabolic syndrome (MetS), type 2 diabetes mellitus (T2DM), and other oxidative-stress-mediated diseases, including atherosclerosis [2][4][5]. Moreover, serum bilirubin levels were recently proposed as a potential pre-disease biomarker for developing metabolic syndrome in asymptomatic middle-aged individuals [6].

Obesity and overweight are considered pathological states of chronic low-grade inflammation with increased oxidative stress and altered endocrine signaling; therefore, these conditions result in lowered serum bilirubin levels [6]; on the other hand, reducing body weight leads to increased serum bilirubin levels [7][8]. Importantly, mild hyperbilirubinemia is associated with health benefits in overweight and obese individuals, as well as with lower adiposity [9][10]. This review addresses the current knowledge on how overweight and obesity affect bilirubin levels, along with the potential intervention strategies to modulate systemic bilirubin levels to alleviate the obesity-related negative effects on health.

2. Obesity

Obesity is the accumulation of excessive fat that harms health. Indeed, obesity and overweight are associated with several dysmetabolic conditions, including T2DM, non-alcoholic fatty liver diseases, cardiovascular diseases (CVDs), cancer, and neurodegenerative disorders, among others. Recently, the understanding of adipose tissue has undergone radical changes. Adipose tissue has been recognized as a heterogeneous tissue; indeed, it is composed of several cell types, including preadipocytes, mature adipocytes, fibroblasts, dendritic cells, mast cells, T-cells, endothelial cells, and macrophages [11]. Importantly, obesity is linked to a state of chronic low-grade inflammation, mainly due to proinflammatory cytokine secretion, macrophage infiltration, and disrupted function of tissue involved in glucose homeostasis [12]. Additionally, obesity is also associated with a significant increase in macrophage number [13][14], which also contributes to the maintenance of the low-grade chronic inflammation state linked to obesity [15]. Macrophages are increased in adipose tissue during obesity due to several factors, free fatty acids, cholesterol, and lipopolysaccharide [16]. Macrophages can be classified, based on their surface expression or their cytokine or chemokine expression, into two main populations. M1 macrophages are associated with a proinflammatory profile and secrete proinflammatory cytokines (tumor necrosis factor α (TNF-α), interleukin 1ß (IL-1ß), and interleukin 6 (IL-6)), whereas M2 macrophages are associated with tissue remodeling and inflammation resolution and secrete anti-inflammatory cytokines (IL-10, IL-1) [17][18]. Moreover, treating macrophages with a mix of glucose, palmitate, and insulin generates a unique macrophage

proinflammatory phenotype that is different from M1 and secretes proinflammatory cytokines (TNF-α, IL-1ß), while the secretion depends on peroxisome-proliferator-activated receptor gamma (PPAR-γ) and p62 expression [19]. The mechanisms by which inflammation increases during obesity are still not fully understood. First, increased proinflammatory cytokine secretion contributes to insulin resistance and other complications related to obesity. Second, obesity not only promotes the infiltration of macrophages but also induces a shift in macrophage balance toward the M1 phenotype [17]; however, the adipose tissue is not the sole site of inflammation. In contrast, obesity-related inflammation occurs in many other tissues, such as the liver, muscle, hypothalamus, pancreatic islets, and the gut [20].

Adipose tissue was considered as an inert tissue having a primary role in controlling energy homeostasis. Additionally, it is now recognized that adipose tissue exhibits endocrine-regulatory properties and releases a cluster of bioactive substances, among them hormones and adipokines with pleiotropic functions [11][21][22][23]. Adipokines comprise, among others, classical cytokines (TNFα, IL-6) and chemokines (IL-8, monocyte chemoattractant protein 1 (MCP-1), macrophage-inflammatory protein-1α, macrophage-inflammatory protein-2α, stromal-cell-derived factor-1), vasoactive and coagulation factors, regulators of lipoprotein metabolism, and proteins more specifically secreted by the adipocytes, such as leptin and adiponectin [24]. Adipocytes have been recognized as important sources of MCP-1, which was the first discovered human ß-chemokine and is a recognized marker of adipose tissue dysfunction in obesity and T2DM [25]. An early study determined a link between obesity and inflammation and showed that adipose tissue synthesizes and releases the proinflammatory cytokine TNF-α [26]. Based on these findings, it was suggested that adipose tissue plays an important immune role and might be a major source of proinflammatory mediators, which initiate the development of low-grade chronic inflammation. Indeed, excess adipose tissue leads to high levels of proinflammatory cytokines TNF-α and IL-6 and a sensitive marker of inflammation C-reactive protein (CRP) in circulating blood. TNF-α is synthesized as a 26 kDa transmembrane protein. It has been shown that macrophages from the stromal vascular fraction are also the source of adipose-derived TNF-α and that its increased levels in obesity are due to the increased infiltration of adipose tissue with M1 macrophages [13]. Several studies have demonstrated that TNF-α impairs insulin signaling in hepatocytes and adipose tissue [27][28]. Moreover, IL-6 is a cytokine produced by many different cells. Approximately one-third of the IL-6 detected in plasma is attributed to the production from white adipose tissue [29]. In adipocytes and hepatocytes, IL-6 has been demonstrated to impair insulin-induced insulin receptor and insulin receptor substrate 1 phosphorylation [30][31]. Furthermore, it has been shown that IL-6 stimulates hepatocytes to produce and secrete CRP, indicating a state of inflammation [32]. CRP is a sensitive marker of inflammation, which is synthesized and secreted mainly by the liver [32], the serum concentrations of which are higher among obese subjects [33][34]. Adiponectin is one of the most abundant adipokines produced by adipocytes and is involved in glucose and lipid metabolism [35]. In adipose tissue, adiponectin exerts an anti-inflammatory function by reducing macrophage infiltration and inhibiting the local production of numerous proinflammatory cytokines [36]. Leptin, which is almost exclusively secreted from adipocytes, controls food intake and energy expenditure and has atherogenic and growth properties [37]. Since the discovery of leptin, the number of adipokines has notably increased in the last years with new molecules such as omentin-1, chemerin, resistin, visfatin, apelin, adipocyte fatty acid-binding protein (A-FABP), retinol-binding protein 4 (RBP4), among others [38]. Visfatin, originally identified as a pre-B-cell colony-enhancing factor (PBEF), is expressed in many cells and tissues act as a cytokine with immune regulatory action and as nicotinamide phosphoribosyltransferase (Nampt), an enzyme involved in the NAD^+ salvage pathway [39].

3. Anti-Inflammatory Activity of Bilirubin

Bilirubin has evident anti-inflammatory activity, and indeed several studies have shown an inverse relationship between serum bilirubin levels and CRP in overweight or diabetic subjects [5][8][40][41]. Since low-grade chronic inflammation plays an important role in adipose tissue, the liver, the aorta, the kidneys, and pancreatic cells, the anti-inflammatory and antioxidative effects of bilirubin may likely contribute to the protective effect on vascular damage [1]. Recently, adipokines were studied along with serum bilirubin levels in normal and overweight asymptomatic adults. Importantly, there was an inverse relationship between serum bilirubin levels and proinflammatory cytokines (TNF-α, IL-6, visfatin, and CRP) and a positive relationship between serum bilirubin levels and adiponectin [5][42].

Moreover, recently biliverdin treatment reduced the expression levels of M1 macrophage markers in adipose tissues induced by high-fat diet feeding mice. This indicates that bilirubin may improve high-fat-diet-induced insulin resistance by reducing chronic inflammation in adipose tissue [10].

Additionally, adiponectin exerts anti-inflammatory and antiatherogenic properties via its ability to stimulate vascular endothelial nitric oxide (NO) production [43]. Equivalently, more recent studies have shown the role of bilirubin in the activation of Akt and endothelial nitric oxide synthase leading to the synthesis of NO, which can also improve endothelial cell function and insulin resistance [44].

To address the potency of bilirubin responses, in several animal models of endotoxemia, septicemia, and ischemia–reperfusion injury, bilirubin exhibited significant anti-inflammatory activity via mechanisms such as inhibiting the expression of adhesion molecules, suppressing the infiltration of inflammatory cells and reducing the levels of proinflammatory cytokines [45]. In another study, bilirubin also suppressed T cell proliferation and activation [46]. Overall, bilirubin has complex immunosuppressive effects [47]. A recent study also identified the neutrophil-to-lymphocyte ratio in blood as a variable that is negatively associated with total bilirubin levels [48].

4. Conclusions

Overweight and obese adults have lower serum bilirubin values compared to normal-weight individuals. Since bilirubin is an endogenous molecule with antioxidant, anti-inflammatory, antithrombogenic, endocrine, and many other activities, the modulation of serum bilirubin levels represents a novel therapeutic approach. Mildly increased serum bilirubin levels will protect other organs and directly affect the adipose tissue and its adipokine secretion pattern. In our opinion, the modulation of serum bilirubin levels will be an effective adjunctive therapy for obesity that can improve several obesity-induced pathological conditions.

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