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Adipose Tissue Hypoxia Correlates with Adipokine Hypomethylation and Vascular Dysfunction

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Abstract: Obesity is characterized by the accumulation of dysfunctional adipose tissues, which predisposes to cardiometabolic diseases. Our previous in vitro studies demonstrated a role of hypoxia in inducing adipokine hypomethylation in adipocytes. We sought to examine this mechanism in visceral adipose tissues (VATs) from obese individuals and its correlation with cardiometabolic risk factors. We propose an involvement of the hypoxia-inducible factor, HIF1α, and the DNA hydroxymethylase, TET1. Blood samples and VAT biopsies were obtained from obese and non-obese subjects ($n = 60$ each) having bariatric and elective surgeries, respectively. The analyses of VAT showed lower vascularity, and higher levels of HIF1α and TET1 proteins in the obese subjects than controls. Global hypomethylation and hydroxymethylation were observed in VAT from obese subjects along with promoter hypomethylation of several pro-inflammatory adipokines. TET1 protein was enriched near the promotor of the hypomethylated adipokines. The average levels of adipokine methylation correlated positively with vascularity and arteriolar vasoreactivity and negatively with protein levels of HIF1α and TET1 in corresponding VAT samples, serum and tissue inflammatory markers, and other cardiometabolic risk factors. These findings suggest a role for adipose tissue hypoxia in causing epigenetic alterations, which could explain the increased production of adipocytokines and ultimately, vascular dysfunction in obesity.

Keywords: visceral adipose tissue; obesity; hypoxia; DNA methylation; TET1; inflammation; adipokines; vascular dysfunction; nitric oxide; flow-induced dilation

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1. Introduction

Obesity is a considerable public health issue that affects more than one-third (36.5%) of the US population and over 600 million adults worldwide [1]. Obesity is associated with many life-threatening yet preventable comorbidities, such as cardiovascular (CVD), diabetes, and cancer [2]. Therefore, unlocking the complicated interplay between obesity and its comorbidities is critical. Obesity is characterized by a vast accumulation of dysfunctional adipose tissue, and currently, it is largely accepted that these fat depots represent key secretory organs that release multiple bioactive molecules, hormones, and inflammatory cytokines [3]. Obesity is also associated with hypoxia, especially in the expanding adipose tissues, as shown in previous clinical and preclinical studies [4]. It was postulated over a decade ago that adipose tissues could become hypoxic due to obesity-induced adipose accumulation. Several studies in obese mice have shown that severe adiposity can cause