Letter to the Editor

Increased Activity of the Oncogenic Fatty Acid Synthase and the Impaired Glucose Uptake in the Metabolic Syndrome

To the Editor: Ashbeck et al. (1) report that components of metabolic syndrome (MS) that capture impaired glucose uptake increase the odds of colorectal metachronous neoplasia. I would like to add the following comments to strengthen some issues of this theme. (*a*) Insulin resistance in obesity, specifically within adipose tissue, is thought to be caused by increased glucocorticoids (2). Furthermore, the metabolic consequences of visceral obesity, the hallmark of the MS, have been associated with amplification of glucocorticoids, due to increased activity of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) in adipose tissue. Indeed, inhibitors of 11β-HSD1 have shown considerable potential in rodents and primates as insulin sensitizers and as agents that may aid weight loss (3). Consistent with these studies, converging evidence has also shown that increased 5-α-reductase activity is associated with obesity and type 2 diabetes (2). In addition, treatment with insulin sensitizers decreases the expression of 5-α-reductase enzymes in the liver of rodents (2). Taken together, this evidence indicates that the activities of both 11β-HSD1 and 5-α-reductase increase in MS. (*b*) In the MS, the activities of both 5-α-reductase enzymes are activated. As a result, there is increased conversion rate of testosterone to dihydrotestosterone, a more potent androgen. A consequence of increased 5-α-reductase activity is activation of the sterol regulatory element binding protein pathway (4) and a downstream effect of sterol regulatory element binding protein pathway activation is abnormal activation of the oncogenic enzyme, fatty acidsynthase (FAS). The expression of FAS is markedly increased in several human malignancies, and its overxpression in tumor tissues from patients with colon, breast, and prostate carcinomas, as well as melanoma and gastrointestinal stromal tumors, is associated with poor prognosis (5).

In summary, impaired glucose uptake due to the MS is related to increased activities of both 11β-HSD1 and 5-α-reductase. These changes could lead to FAS activation and tumorigenesis. These data concur with the proposal of Ashbeck et al. (1), relating the impaired glucose uptake to the increased odds of metachronous neoplasia in colorectal tissue.

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

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