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Immunohistochemical expression of plasminogen activator inhibitor-1 in subcutaneous versus omental adipose tissue in patients after elective abdominal surgery

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ABSTRACT

Plasminogen activator inhibitor-1 (PAI-1) is a biomarker of thrombosis. Adipose and vascular tissues are among the major sources of PAI-1 production. Previous studies indicated that fat deposits mediate increased cardiovascular risk among obese individuals. We investigated the immunohistochemical (IHC) expression of PAI-1 in adipose and vascular tissues from the omentum and the subcutaneous tissue. The pathology samples were selected from 37 random patients who underwent elective abdominal surgery between 2008-2009. PAI-1 expression was semi-quantitatively scored and compared between the groups. Significant differences were noted in the IHC expression of PAI-1 between the omental and the subcutaneous adipose tissues (1.1 ± 0.8 versus 0.8 ± 0.6 , respectively ($p=0.05$)). Adipose tissue displayed higher IHC expression of PAI-1 compared to vascular wall tissue in both omentum and subcutaneous sections (1.1 ± 0.8 versus 0.5 ± 0.9 ($p=0.004$), and 0.8 ± 0.6 versus 0.4 ± 0.6 ($p=0.003$), respectively). In conclusion, our study compared PAI-1 expression in the omentum versus the subcutaneous tissue and adipose versus vascular tissues. IHC expression of PAI-1 level was significantly higher in the omental adipose tissue compared to the subcutaneous adipose tissue. Adipose tissue displayed significantly higher PAI-1 expression than vascular tissue. The study elucidates the biological differences of adipose and vascular tissue from subcutaneous versus omental sections.

Keywords

Adipose Tissue; Immunohistochemistry; Plasminogen Activator Inhibitor-1

INTRODUCTION

Plasminogen activator inhibitor (PAI-1) is a member of the superfamily of serine-protease inhibitors and plays a crucial role in the inhibition of both tissue and urinary type of plasminogen activators.¹ PAI-1 is produced in various cells as the liver, brain,

muscle, and adipocytes. PAI-1 production is stimulated by various cytokines such as IL-6, TNF- α , and TGF- β .^{2,3} Basic and clinical science studies confirmed that obesity and metabolic syndrome are associated with alterations in the fibrinolytic system and supported the hypothesis

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that an increased PAI-1 expression by the adipose and vascular tissues might contribute to cardiovascular disease progress.^{1,4,5}

The volume of adipose tissue, but also the types of adipose tissue is associated with the development of cardiovascular risk.^{6,7} Adipocytes display biological differences based on their origin. The visceral adipose tissues were associated with increased risk of major cardiovascular events compared with the adipose tissue of the subcutaneous.^{6,8} In this study, we examined immunohistochemical (IHC) expression of PAI-1 in surgical pathology samples from patients who underwent elective abdominal surgery.

METHODS

Surgical Pathology Samples

The study was approved by the Marmara University Medical School Institutional Review Board. The pathological samples were selected retrospectively from the archives of Marmara University Pathology Department. Randomly 37 patients were selected who underwent elective abdominal surgery for various clinical indications between 2008 and 2009 (Table 1).

The types and indications for abdominal surgery included splenectomy for thalassemia and immune thrombocytopenia, lymph node resection for Non-Hodgkin’s lymphoma, total pancreatectomy and gastrectomy for cancer, and colon resection for ulcerative colitis. Nearly 20% of patients had the history of diabetes mellitus. Since the study samples were selected retrospectively, no informed consent was required.

Immunohistochemical Expression

IHC expression of PAI-1 staining (Rabbit anti-human PAI-1 antiserum, Molecular Innovations, Inc) was performed. Three to five fields were evaluated per section for PAI-1 expression. Adipose tissue from

the omentum and the subcutaneous tissue was removed immediately and cut in 2 mm thick slices. These were fixed in 10% formalin and embedded in paraffin followed by the IHC reaction. IHC expression of PAI-1 semi-quantitatively scored from the adipose and vascular wall tissues from the omentum and subcutaneous. Blinded pathologists selected at least three pathological slides per block at 10X (magnification) and analyzed on the cellularity and density of PAI-1 expression. Then, BX51 Olympus[®] microscopy was used to count cells that expressed PAI-1. A visual grading scale (0 to 3) was used for the assessment of the intensity IHC expression of PAI-1: Score “0” represented no expression, score “1” represented mild expression, score “2” represented moderate expression, and score “3” or more represented the most extensive PAI-1 expression.⁹ The average score was calculated for each pathological samples. Comparison between groups and semi-quantitative scores were performed for statistical evaluation. A value of p<0.05 was considered statistically significant.

RESULTS

Significant differences were noted in the IHC expression of PAI-1 between the omental and the subcutaneous adipose tissues. Mean ± standard deviation scores of IHC expression of PAI-1 for the omental versus the subcutaneous adipose tissue were 1.1 ± 0.8 versus 0.8 ± 0.6 (p=0.05). The omental adipose tissue also displayed higher IHC expression of PAI-1 compared to omental vascular wall (1.1 ± 0.8 versus 0.5 ± 0.9 (p=0.004)). Similarly, the subcutaneous adipose tissue displayed higher IHC expression of PAI-1 compared to subcutaneous vascular wall (0.8 ± 0.6 versus 0.4 ± 0.6 (p=0.003)), while the IHC expression of PAI-1 semi-quantitative scores were similar between the omental versus the subcutaneous vascular wall tissues (0.5 ± 0.9 versus 0.4 ± 0.6 (p=0.32)) (Figures 1-3).

DISCUSSION

Adipose tissue has a crucial role in the development of cardiovascular diseases. Adipose tissues secrete adipokines. Considerable interest remains in understanding the endocrine role of

Table 1. Characteristics of the study sample as median age and gender

	Age (years)	Females (%)
Mean ± SD	53 ± 14	43
Median (IR)	55 (26)	

IR = interquartile range; SD = standard deviation.

Omental adipose tissue
Omental vascular wall

Subcutaneous adipose tissue
Subcutaneous vascular wall

IHC expression of PAI-1

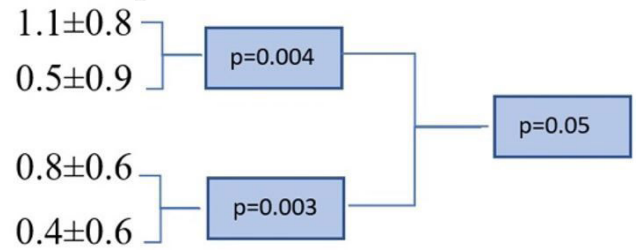


Figure 1. Comparison of IHC PAI-1 expression between omental and subcutaneous tissues. IHC = immunohistochemical; PAI-1 = plasminogen activator inhibitor-1.

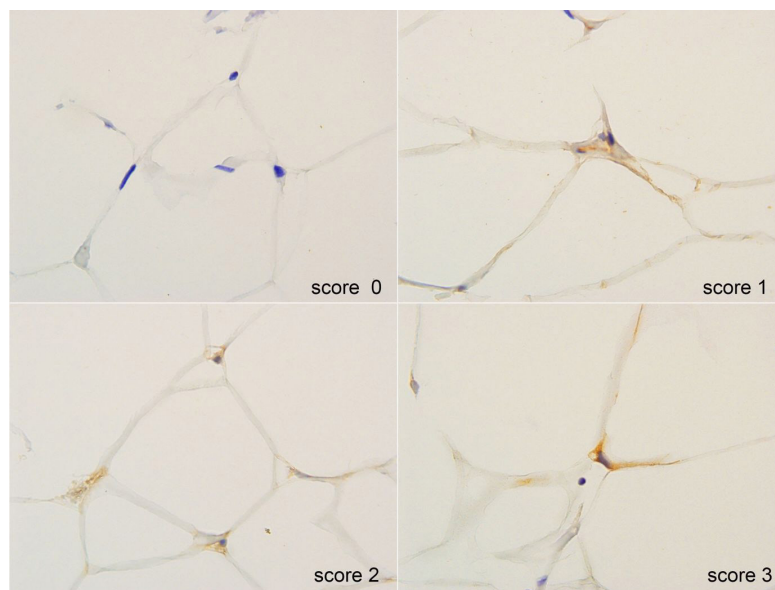


Figure 2. Scoring of IHC PAI-1 expression in adipose tissue.

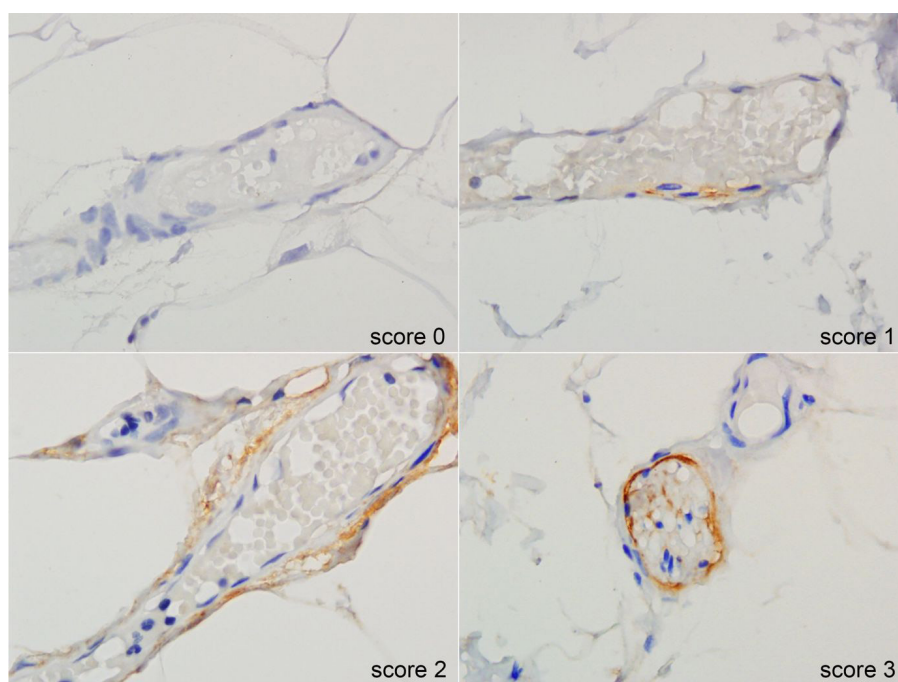


Figure 3. Scoring of IHC PAI-1 expression in vascular tissue.

adipokines. Adipocyte-derived PAI-1 can serve as a link between the increased body fat of the obese and the cardiovascular risk. The biological importance of the PAI-1 molecule is not limited to the coagulation-fibrinolysis cascade but is also demonstrated in many physiological and pathological processes, including obesity, inflammation, insulin resistance, and malignancy.^{4,10} PAI-1 is produced and released by adipose tissues; however, the PAI-1 production varies not only with the adipose tissue burden but also with the type of the adipose tissue.^{11,12} In this context; the biological differences of adipose tissues, subcutaneous versus omentum, have been demonstrated in favor of different gene expression, secretion of various inflammatory markers, growth factors, and fibrinolysis agents.¹³⁻¹⁶

Several ex-vivo human studies showed an increased production of PAI-1 by the visceral adipose tissues compared with the subcutaneous adipose tissues.¹⁷⁻¹⁹ However, conflicting data exist in the literature about the biological differences between the omental versus the subcutaneous adipose tissues. Van Harmelen et al.²⁰ reported higher PAI-1 mRNA expression and PAI-1 antigen secretion by the subcutaneous adipose tissue compared with the visceral adipose tissue. He et al.²¹ reported that no differences exist in PAI-1 expression between the omental and the subcutaneous adipose tissue; however, yet after incubation, a higher expression of PAI-1 was observed in the omental than the subcutaneous adipose tissue. Our study extends the evidence by using IHC and demonstrates the relation of increased PAI-1 production by the visceral origin adipose tissues (omentum). Our observations might be supportive for the prior findings by several other groups. Hardy et al.²² showed that inflammation in the omental adipose tissue is associated with insulin resistance. O'Connel et al.²³ indicated that omental adipocyte size was an indicator of liver fibrosis, metabolic disease, and possibly progression from hepatic steatosis to fibrosis. Yang et al.²⁴ reported that mesentery adipose depot played a pivotal role in obesity-related diabetes. Harman-Boehm et al.²⁵ reported that preferential macrophage infiltration into the omental adipose tissue compared to the subcutaneous adipose tissue, among the obese population, might be the link between with increased risk of coronary artery disease and central obesity

Accumulated fat and enhanced adipose tissue-derived PAI-1 might induce fibrosis and chronic inflammation. As a potential explanation, TGF- β is a strong inducer of PAI-1 expression.²⁶ A previous study reported that the molecular mechanism involves tissue-specific TGF- β response to Ang II infusion; hence the PAI-1 response to TGF- β can display tissue-specific characteristics.²⁷

Our study has several limitations. It was a retrospective surgical pathology sample analysis of PAI-1 expression in the tissues of patients who underwent elective intra-abdominal surgery. There was no blinding in the pathology assessment of IHC expression of PAI-1. Therefore, the PAI-1 expression in different tissues can vary based on patients' baseline vascular risk characteristics. We did not measure the plasma PAI-1 antigen and activity levels; therefore, we cannot assess the overall fibrinolytic activity in these patients. The sample size was relatively small, and this could be related to the restrictive eligibility criteria and availability of the tissue samples to assess PAI-1 expression. However, our study directly compares the IHC expression of PAI-1 in different tissues. We did find significant differences in IHC expression of PAI-1 in different tissue segments. We believe our data can provide clinicians with a rationale for a detailed assessment of the patients with cardiovascular risk.

In conclusion, IHC staining scores displayed higher levels of PAI-1 expression in the adipose tissues than the vascular wall and higher levels of PAI-1 expression in the omental adipose tissues than the subcutaneous adipose tissues. Future studies in large cohorts involving patients' characteristics, plasma PAI-1 levels, and follow-up data would be more explanatory for the role of PAI-1 in cardiovascular and metabolic diseases.

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