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Effects of weight loss induced by bariatric surgery on hepatic adipocytokine expression☆

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***Background/Aims*: Adipocytokines play a key role in the pathophysiology of non-alcoholic fatty liver diseases (NAFLD). Whereas adiponectin has mainly anti-inflammatory functions, leptin, resistin and pre-B cell enhancing factor (PBEF)/Nampt/visfatin are considered as mainly pro-inflammatory mediators regulating metabolic and immune processes.**

***Methods*: We prospectively examined the effect of weight loss on systemic levels and/or hepatic expression of adiponectin/adiponectin receptors, leptin/leptin receptors, resistin and PBEF/Nampt/visfatin. Severely obese patients underwent laparoscopic adjustable gastric banding (LABG) and serum samples ($n = 30$) were collected before, and after 6 and 12 months. Paired liver biopsies (before and 6 months after LABG) were obtained from 18 patients.**

***Results*: Bariatric surgery improved insulin resistance, abnormal liver function tests and liver histology. Pronounced weight loss after 6 and 12 months was accompanied by a significant increase in serum adiponectin levels whereas both leptin and PBEF/Nampt/visfatin levels decreased. Resistin serum levels increased after 6 months but fell below baseline values after 12 months. Liver mRNA expression of adiponectin increased slightly after 6 months whereas leptin mRNA expression did not change. Interestingly, weight loss resulted in a significant decrease of hepatic mRNA expression of resistin, PBEF/Nampt/visfatin and both leptin receptor isoforms while expression of type 1 and 2 adiponectin receptor was not affected. Liver immunohistochemistry performed on index and follow-up liver biopsies revealed an increase in adiponectin staining, showed no effect on resistin/leptin positivity, and demonstrated a decrease in PBEF/Nampt/visfatin immunoreactivity.**

***Conclusions*: Weight loss after LABG surgery drives the adipocytokine milieu towards a more anti-inflammatory direction both systemically and in the liver.**

***Keywords*: Adipocytokine; NAFLD; NASH; Weight loss; Bariatric surgery**

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Abbreviations: NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; LAGB, laparoscopic adjustable gastric banding; IR, insulin resistance; adipoR, adiponectin receptor; IL, interleukin; TNF, tumor necrosis factor; CRP, C-reactive protein; RT-PCR, reverse-transcription polymerase chain reaction; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; LEPR, leptin receptor; TIIDM, type II diabetes mellitus.

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1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is increasingly recognized as a major cause of liver disease worldwide [1,2]. There is now convincing evidence that NAFLD is part of the metabolic syndrome and insulin resistance (IR) has been identified as a crucial pathophysiologic factor in this disease [3]. Obesity and associated IR are pro-inflammatory states with increased adipose tissue expression of various pro-inflammatory mediators such as tumor necrosis factor-alpha (TNFα) and systemic signs of inflammation [4].

On the basis that NAFLD is part of the metabolic syndrome, weight loss seems to represent a logical treatment modality for NAFLD patients who are overweight or obese [5]. Weight loss, induced by bariatric surgery, improves liver biochemistries and steatosis [6–8], although some controversy exists from earlier studies about the histologic outcome of such procedures [7,9]. Among bariatric surgery procedures laparoscopic adjustable gastric banding (LAGB) allows for controlled weight loss without major alterations to the structure and function of the gastrointestinal tract. Compared to alternative surgical procedures, such as biliopancreatic diversion and long limb Roux-en-Y gastric bypass, LAGB has proved to be effective with less perioperative morbidity and mortality [10].

Adipose tissue secretes a variety of bioactive proteins or adipocytokines that have recently gained great interest [11]. This heterogenous group of mediators includes adipocytokines such as adiponectin, leptin, resistin, pre-B-cell enhancing factor (PBEF)/Nampt/visfatin and others [11]. Adiponectin, a major anti-steatotic and anti-inflammatory adipocyte-derived mediator [12,13] binds to two receptors (ADIPOR1/2) with ADIPOR1 being widely expressed and ADIPOR2 being predominantly confined to the liver [14]. Adiponectin$^{-/-}$ mice show evidence of increased local and systemic TNFα activity [15]. Moreover, adiponectin suppresses inflammation via induction of anti-inflammatory mediators such as IL-10 and IL-1 receptor antagonist (IL-1Ra) [16]. Leptin, the second major adipocytokine, has very diverse immune and metabolic functions. Obesity is associated with high circulating leptin levels and leptin resistance in the central nervous system as leptin fails to correct hyperglycemia in patients with obesity, supporting the idea of "leptin resistance" in these patients [17]. Leptin is in many instances considered the counterpart of adiponectin having mainly pro-inflammatory functions [18]. The leptin receptor (LEPR) exists in at least 6 alternatively spliced forms. The short isoforms of the LEPR (LEPR^{short}) are expressed by several non-immune tissues and believed to mediate transport and degradation of leptin. The long isoform, known as LEPRb (LEPR^{long}) is expressed by the hypothalamus, by endothelial cells, macrophages, B and T cells and others [18]. Resistin, initially correlated with IR at least in mice, has been described as a more pro-inflammatory mediator mainly produced by leukocytes [19]. However, even though the pro-inflammatory properties of resistin indicate its role as an inflammatory mediator [20], such a role in humans has not yet been convincingly demonstrated. PBEF/Nampt/visfatin has been recently characterized as a novel adipocytokine [21]. We demonstrated potent pro-inflammatory effects of this adipocytokine in human leukocytes [22]. Elevated serum levels have also been described in states of active inflammation such as sepsis, acute lung injury, rheumatoid arthritis, and inflammatory bowel disease [22–25]. The aim of the present study was to evaluate liver expression and systemic levels of various adipocytokines before and after weight loss induced by LAGB.

2. Materials and methods

2.1. Subjects and preoperative assessment

Selection and preoperative assessment of patients considered for the placement of an adjustable gastric banding device was performed at the Department for General Internal Medicine. Severely obese patients with a body mass index (BMI) of more than 35 kg/m^2 who had no significant medical, physical, or psychosocial disabilities were considered to be enrolled into the study. In all patients current and past alcohol intake was less than 20 g per week. Hepatitis B and C serological analyses were negative in all study subjects. Additional investigations were performed to exclude the following disorders: autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, hemochromatosis, Wilson's disease, and α1-antitrypsin deficiency.

During a period from March 2003 until June 2006, 30 patients were included in our study. In all 30 patients index liver biopsies were performed percutaneously under laparoscopic view at the time of laparoscopic surgery. Eighteen of these patients agreed to have an ultrasound-guided follow-up biopsy after 6 months. All study patients gave their informed written consent before participating in this study. The study was performed in accordance with the ethical guidelines of the Helsinki Declaration and was approved by the local Ethical Studies Committee of Medical University Innsbruck, Austria.

2.2. LAGB surgery

LAGB surgery involves the placement of an adjustable silicone gastric band containing an inflatable inner balloon that can be adjusted by adding or removing saline via a small subcutaneous access port. All patients were operated at the Department of General and Transplant Surgery using the Swedish adjustable gastric band (Johnson & Johnson, Obtech, Vienna, Austria) according to the pars-flaccida technique described elsewhere [26]. During a 6-month follow-up weight losses between 6.5 and 49.5 kg were achieved without complications. The mean postoperative hospital stay was 3 days. A contrast swallow was performed 2 days after operation to confirm correct band placement.

2.3. Clinical and laboratory analysis

A complete physical examination was performed on each study participant including anthropometric data such as body height and weight whereof BMI was calculated as weight (kg) divided by height (m) squared. On the morning of index and follow-up liver biopsies venous blood samples were drawn after an overnight fast and serum was obtained by centrifugation at 1200 RCF for 15 min at 4 °C and stored at −80 °C. Serum samples were also collected 6 and 12 months after LABG. Serum insulin and serum adiponectin were both deter-