LETTERS
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Brown adipose tissue is associated with cardiometabolic health

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White fat stores excess energy, whereas brown and beige fat are thermogenic and dissipate energy as heat. Thermogenic adipose tissues markedly improve glucose and lipid homeostasis in mouse models, although the extent to which brown adipose tissue (BAT) influences metabolic and cardiovascular disease in humans is unclear[1,2]. Here we retrospectively categorized 134,529 ^{18}F-fluorodeoxyglucose positron emission tomography–computed tomography scans from 52,487 patients, by presence or absence of BAT, and used propensity score matching to assemble a study cohort. Scans in the study population were initially conducted for indications related to cancer diagnosis, treatment or surveillance, without previous stimulation. We report that individuals with BAT had lower prevalences of cardiometabolic diseases, and the presence of BAT was independently correlated with lower odds of type 2 diabetes, dyslipidemia, coronary artery disease, cerebrovascular disease, congestive heart failure and hypertension. These findings were supported by improved blood glucose, triglyceride and high-density lipoprotein values. The beneficial effects of BAT were more pronounced in individuals with overweight or obesity, indicating that BAT might play a role in mitigating the deleterious effects of obesity. Taken together, our findings highlight a potential role for BAT in promoting cardiometabolic health.

As early as 2003, reports[3] described increased uptake of the glucose analog ^{18}F-fluorodeoxyglucose (^{18}F-FDG) on positron emission tomography (PET) scans in areas corresponding to supraclavicular fat on computed tomography (CT) images, suggesting the presence of metabolically active BAT in adult humans. In 2009, a series of papers confirmed the presence of active BAT in adults, which correlated with lower body mass index (BMI), decreased age, colder outdoor temperature, female sex and decreased glucose levels[4–6]. Since then, small prospective studies in healthy humans have demonstrated that cold-activated BAT is associated with increased energy expenditure and enhanced disposal of glucose and free fatty acids[7,8]. Although these effects have generated enthusiasm for BAT as a therapeutic target for obesity and associated diseases, these studies have been too small to definitively address whether BAT is a clinically meaningful modulator of metabolic and cardiovascular disease in humans.

To address the relationship of BAT with metabolic and cardiovascular diseases, we reviewed 134,529 ^{18}F-FDG positron emission tomography–computed tomography (PET/CT) reports from 52,487 patients generated between 1 June 2009 and 31 March 2018 at Memorial Sloan Kettering Cancer Center (MSKCC) (Fig. 1a). ^{18}F-FDG PET/CT was conducted for cancer diagnosis, staging, monitoring of treatment response and surveillance, and it is MSKCC protocol to record BAT status in each scan. BAT was reported in 7,923 (5.9%) ^{18}F-FDG PET/CT scans (Fig. 1b and Supplementary Table 1) in 5,070 (9.7%) patients (Fig. 1c and Supplementary Table 2), with reporting consistent from 2009 to 2018 (Extended Data Fig. 1). BAT was more prevalent among women (13.8 versus 4.9%, $P<0.0001$), decreased with age ($r=-0.9850$, $P<0.0001$) and was inversely correlated with ambient temperature ($r=-0.6993$, $P<0.0001$) and BMI ($r=-0.9032$, $P<0.0001$), in accord with earlier, smaller retrospective studies (Fig. 1c–f and Extended Data Fig. 2a,b)[9,10].

To assess accuracy of reporting, all scans conducted in 2016 with reported BAT were manually reviewed (Methods), and BAT activity was measured in six depots (cervical, supraclavicular, axillary, mediastinal, paraspinal and abdominal) (Fig. 1g). Of the 1,139 scans with brown fat identified in 2016, 1,136 (99.7%) showed increased ^{18}F-FDG uptake in regions identified as fat on CT, while 3 (0.3%) were false-positive and reported resolution of previously detected BAT. In total, 1,091 (95.8%) scans met Brown Adipose Reporting Criteria in Imaging STudies (BARCIST 1.0) criteria in terms of ^{18}F-FDG uptake above the recommended threshold of standardized uptake value (SUV) normalized to body mass, $\geq 1.5\,g\,ml^{-1}$ (ref. [11]). As previously reported[12], detected BAT activity was more prevalent in the cervical (81.5%) and supraclavicular depots (87.9%) compared with paraspinal (58.2%), mediastinal (50.1%), axillary (31.4%) and abdominal depots (21.1%) (Fig. 1h). Maximum BAT activity was higher in the supraclavicular depot ($5.4\,g\,ml^{-1}$, interquartile range (IQR) 3.6–8.0) compared with paraspinal ($4.7\,g\,ml^{-1}$, IQR 3.3–6.7, $P<0.0001$), mediastinal ($4.8\,g\,ml^{-1}$, IQR 3.5–7.0, $P=0.0185$) and axillary depots ($4.1\,g\,ml^{-1}$, IQR 3.0–5.6, $P<0.0001$) (Fig. 1i). Lastly, maximum measured BAT activity positively correlated with the number of depots with BAT activity ($r=0.6510$, $P<0.0001$), indicating an association between abundance and activity (Fig. 1j). Patients were then categorized by presence or absence of BAT (BAT^+ and BAT^-, respectively) based on ^{18}F-FDG uptake on PET/CT, and an index scan was assigned as a reference point for data collection (Fig. 1a and described in the Methods). In patients without a BAT signature on any scan, the first ^{18}F-FDG PET/CT scan served

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Effect of Extended Pelvic Lymph Node Dissection on Oncologic Outcomes in Patients with D'Amico Intermediate and High Risk Prostate Cancer Treated with Radical Prostatectomy: A Multi-Institutional Study

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Abbreviations and Acronyms

BCR = biochemical recurrence
CSM = cancer specific mortality
ePLND = extended PLND
LNI = lymph node invasion
PCa = prostate cancer
PLND = pelvic lymph node dissection
PSA = prostate specific antigen
RP = radical prostatectomy

Purpose: Pelvic lymph node dissection represents the gold standard of lymph node staging in patients with prostate cancer. We sought to assess the effect of extended pelvic lymph node dissection on oncologic outcomes in patients with characteristics of D'Amico intermediate or high risk prostate cancer treated with radical prostatectomy.

Materials and Methods: In a multi-institutional database of 4 centers we identified 9,742 patients who underwent radical prostatectomy from 2000 to 2017 with or without pelvic lymph node dissection. Only patients with a greater than 5% probability of lymph node invasion according to the Briganti nomogram were included in study. We performed 2:1 propensity score matching to account for potential differences between the 2 cohorts. Cox regression models were used to test the effect of pelvic lymph node dissection on biochemical recurrence, metastasis and cancer specific mortality.

Results: Overall 707 patients (7.3%) did not undergo pelvic lymph node dissection, of whom 520 and 187 harbored D'Amico intermediate and high risk characteristics, respectively. A median of 14 lymph nodes (IQR 8–21) were removed in the pelvic lymph node dissection cohort and 1,714 of these cases (19.0%) harbored lymph node metastasis. After propensity score matching the biochemical recurrence-free, metastasis-free and cancer specific mortality-free survival rates were 60.4% vs 65.6% (p=0.07), 87.0% vs 90.0% (p=0.06) and 95.2% vs 96.4% (p=0.2) for pelvic lymph node dissection vs no pelvic lymph node dissection 120 months after radical prostatectomy. Multivariable Cox regression models adjusted for postoperative and preoperative tumor characteristics revealed that pelvic lymph node dissection

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Nutritional strategies and gut microbiota composition as risk factors for necrotizing enterocolitis in very-preterm infants

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ABSTRACT

Background: The pathophysiology of necrotizing enterocolitis (NEC) remains poorly understood.

Objective: We assessed the relation between feeding strategies, intestinal microbiota composition, and the development of NEC.

Design: We performed a prospective nationwide population-based study, EPIPAGE 2 (Etude Epidémiologique sur les Petits Ages Gestationnels), including preterm infants born at <32 wk of gestation in France in 2011. From individual characteristics observed during the first week of life, we calculated a propensity score for the risk of NEC (Bell's stage 2 or 3) after day 7 of life. We analyzed the relation between neonatal intensive care unit (NICU) strategies concerning the rate of progression of enteral feeding, the direct-breastfeeding policy, and the onset of NEC using general linear mixed models to account for clustering by the NICU. An ancillary propensity-matched case-control study, EPIFLORE (Etude Epidémiologique de la flore), in 20 of the 64 NICUs, analyzed the intestinal microbiota by culture and 16S ribosomal RNA gene sequencing.

Results: Among the 3161 enrolled preterm infants, 106 (3.4%; 95% CI: 2.8%, 4.0%) developed NEC. Individual characteristics were significantly associated with NEC. Slower and intermediate rates of progression of enteral feeding strategies were associated with a higher risk of NEC, with an adjusted OR of 2.3 (95% CI: 1.2, 4.5; $P = 0.01$) and 2.0 (95% CI: 1.1, 3.5; $P = 0.02$), respectively. Less favorable and intermediate direct-breastfeeding policies were associated with higher NEC risk as well, with an adjusted OR of 2.5 (95% CI: 1.1, 5.8; $P = 0.03$) and 2.3 (95% CI: 1.1, 4.8; $P = 0.02$), respectively. Microbiota analysis performed in 16 cases and 78 controls showed an association between *Clostridium neonatale* and *Staphylococcus aureus* with NEC ($P = 0.001$ and $P = 0.002$).

Conclusions: A slow rate of progression of enteral feeding and a less favorable direct-breastfeeding policy are associated with an increased risk of developing NEC. For a given level of risk assessed by propensity score, colonization by *C. neonatale* and/or *S. aureus* is significantly associated with NEC. This trial (EPIFLORE study) was registered at clinicaltrials.gov as NCT01127698. *Am J Clin Nutr* 2017;106:821–30.

Keywords: breastfeeding, clostridia, necrotizing enterocolitis, preterm infant, speed of increasing enteral nutrition

INTRODUCTION

Necrotizing enterocolitis (NEC) is one of the most dreaded diseases in neonatal intensive care units (NICUs) (1, 2). The

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Abbreviations used: EPIFLORE, Etude Epidémiologique de la flore; EPIPAGE 2, Etude Epidémiologique sur les Petits Ages Gestationnels; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; rRNA, ribosomal RNA.

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