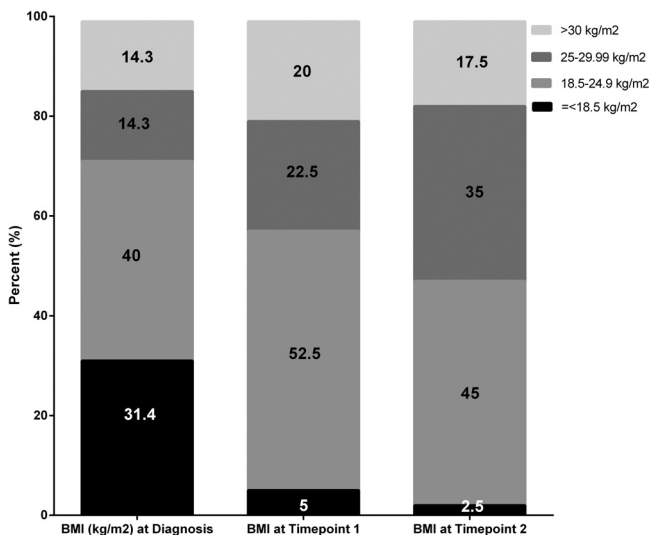


Longitudinal Changes in Body Mass Index and Abdominal Obesity in Crohn's Disease - Associations With Inflammatory Markers and Disease Course

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CONTEXT: Although traditionally associated with weight loss, there is now evidence that increasing body mass index (BMI) and overweight are emerging features of Crohn's disease (CD) and may be associated with more severe disease course. Both abdominal obesity and increased BMI are associated with inflammation. The aim of the study was to assess longitudinal changes in BMI in a cohort of patients with CD and examine the potential effect of abdominal adiposity on disease severity, inflammatory markers and health care use. METHODS: The study comprised of 40 adults with CD diagnosed at median age 26.5 yrs, who were assessed 7 years [time-point 1 (T1)] and again at 14 years [time-point 2 (T2)] after diagnosis. Height (m2), weight (kg), WC (cm), BMI (kg/m2), CD activity index (CDAI), biochemical, clinical and lifestyle data were recorded. Overweight and obesity was classed as BMI ≥ 25 kg/m2. Abdominal obesity was defined as WC ≥ 102 cm for men and WC ≥ 88 cm for women. Ethical approval was granted and participants gave informed written consent. RESULTS: The current CD cohort (n=40) comprised 26 females and 14 males, with mean (sd) age of 45.1 (11.9) yrs and mean follow-up of 14.9 (6.6) yrs. Over half, 52.5% of CD patients were overweight or obese, with no gender difference (p=0.194). Mean (sd) BMI (kg/m2) significantly increased over time from 22.3 (6.1) at diagnosis to 25.2 (5.5) (T1), to 26.3 (5.7) (T2) [14 yrs post diagnosis] (p=0.000 and p=0.015). Overweight and obesity prevalence increased over the 3 time points (fig 1). Increases in BMI between T1 v T2, however were not associated with significant changes in CDAI [mean, (sem) 117.7 (15.3) v 131.7 (18.5), p=0.437] or CRP [5.91 (0.60) v 5.12 (1.08) mg/l, p=0.601] or sedentary behaviours (hours of TV watching/wk) [mean (sd) 21.5 (10.0) v 18.5 (12.6) hours, p=0.09]. Mean WC in men was 98.4 (3.8) cm and 87.5 (3.1) cm in women. Overall 60% of CD were classified as centrally obese and prevalence was similar in men and women [64% v 58% of women (p=0.685)]. Of note, WC was significantly associated with systemic inflammation as measured by CRP (r= 0.536, p=0.010). Current BMI was not associated with markers of health care utilisation [frequency of IBD out-patient visits (r= -0.224, p=0.165), or endoscopy investigations (rho= -0.115, p=0.480) however WC was significantly associated with longer hospital stay (r= 0.319, p=0.045). CONCLUSION: The prevalence of obesity and overweight in CD significantly increased over 14 years across 3 longitudinal time-points. This incremental increase in BMI alone had no apparent significant effects on markers of inflammation or disease course. Central obesity, however, was significantly associated with higher CRP and increased hospitalization. The potential long-term implications of central adiposity for CRP and inflammatory load merit further study.

Fig1. Changes in BMI (kg/m2) category in patients with Crohn's disease (n=40) over 3 longitudinal time-points



Progressive Increase in Large Intestine Transcellular but Not Paracellular Permeability Correlates With Plasma Endotoxemia in Diet-Induced Obese Rats

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Background: High fat diet-induced obesity is characterized by increased intestinal paracellular permeability, increased plasma lipopolysaccharide (LPS), low-grade inflammation and metabolic alterations. Whether the increase in plasma LPS is due to the increased paracellular permeability is unclear. Moreover, the contribution of altered paracellular versus transcellular transport in different regions of the intestine to the obese phenotype has not been determined. Since LPS is a large molecule (>10 kDa), we hypothesized that it crosses the epithelium via a transcellular route. The aims of this study were to determine 1) the route of LPS passage and 2) the temporal relationship between alterations in small and large intestinal permeability and endotoxemia in rats fed a high fat diet. Methods: Route of LPS passage was evaluated in cell culture models (Caco-2 and T84) and in rat intestinal tissues mounted in Ussing chambers using LPS-FITC, horseradish peroxidase (HRP, marker of transcellular permeability) and electrical conductance (marker of paracellular permeability). Diet-induced obesity was induced by feeding rats a high fat diet (HF, 45% fat) or normal chow (NC, 10% fat) for 1, 3 or 6 weeks. FITC-dextran 4000 (FD-4, marker of paracellular permeability)

and HRP fluxes across intestinal tissues were evaluated in Ussing chambers. Plasma LPS-binding protein (LBP) was measured by ELISA. Results: In Caco-2 and T84 cells and rat intestine, FITC-LPS flux correlated significantly with HRP flux (P < 0.05) but not with electrical conductance (P > 0.05), suggesting LPS crosses the gut epithelium through the transcellular rather than paracellular route. In the small intestine, FD-4 flux was higher in HF than NC rats at wk1 (jejunum P=0.08, ileum P=0.004) then returned to normal values; HRP flux was not affected by HF diet (Table 1). In the large intestine, FD-4 flux was increased in the HF rats (Table 1). HRP flux was increased in the caecum and colon of HF compared to NC rats at wk3 (P=0.03 and 0.04) and wk6 (P=0.009 and 0.02) but not wk1 (Table 1). Plasma LBP was increased in HF rats at wk3 and wk6 (P=0.03 and 0.04, Table 1). Plasma LBP significantly correlated with caecum and colon HRP flux (P=0.006 and 0.01), which correlated significantly with adiposity (P < 0.001). Conclusion: HF feeding induces an early increase in paracellular permeability in both small and large intestine. HF feeding induces a later onset (wk3) increase in transcellular transport in the large intestine that correlates with plasma LBP and adiposity. These data support the hypothesis that alteration of transcellular but not paracellular transport in the large intestine is involved in the metabolic endotoxemia and phenotype of diet-induced obesity in rats.

	week 1		week 3		week 6		P-value		
	NC	HF	NC	HF	NC	HF	diet	time	diet x time
body weight, g	399±4	415±6*	446±10	476±9*	483±10	543±8*	<0.001	<0.001	0.03
adiposity, %	3.7±0.3	5.8±0.2*	4.3±0.4	7.1±0.3*	4.4±0.2	9.7±0.3*	<0.001	<0.001	<0.001
Paracellular permeability (FD-4 flux, ng/cm2/h)									
jejunum	2331±300	3501±478#	2266±322	3090±461	843±236	2583±736	0.02	ns	ns
ileum	2536±651	4151±191*	2694±170	3204±374	909±388	2361±254	0.08	ns	0.02
caecum	1529±193	2035±191	1349±168	2128±306	1525±105	1926±286	0.005	ns	ns
colon	2911±370	3440±510	2577±387	4972±995	2321±419	3672±648	0.006	ns	ns
Transcellular permeability (HRP flux, ng/cm2/h)									
jejunum	877±171	983±138	604±175	670±88	555±176	772±243	ns	ns	ns
ileum	629±232	928±198	708±217	716±153	1033±260	437±119	ns	ns	ns
caecum	134±4	184±56	84±28	325±83*	188±44	530±96*	0.004	0.03	0.08
colon	202±50	276±58	304±67	945±269*	150±34	825±219*	0.001	0.05	0.10
plasma LBP	703±33	747±21	506±65	794±92*	618±86	914±60*	0.004	ns	0.10

*P<0.05, #P=0.08, n=6 rats/group

Potential Role of Fatty Acid Synthase (Fasn) and Uncoupling Protein 2 (UCP2)

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Introduction: Obesity rates in the United States have reached epidemic proportions as one of the major contributors to the rising incidence of colorectal cancer (CRC) in young patients. The mechanism for the obesity-CRC risk remains unclear. Fatty Acid Synthase (FASN) has been linked to obesity-related breast cancer. In CRC, FASN is an established prognostic marker (progression) but there is no data on early colon carcinogenesis. The role of obesity may be accentuated due to the emerging evidence of a Warburg-like effect in the pre-dysplastic mucosa as evident by our and other studies on physiological abnormalities (reviewed in *Gastro* 2011, *Clin Gastro Hep* 2012). One potential mediator is uncoupling protein 2 (UCP2) but, like FASN, has only been noted in established CRCs and not pre-dysplastic mucosa which would be necessary to be implicated in initiation. Methods: Azoxy methane (AOM) and saline injected rats (n=6) were euthanized after 40 wks post injection. Polypops in rat colon (Pirc) rats and wild type rats were euthanized after 24 wks of age. Leptin deficient mice at 8, 12, and 18 months of age were used as a rodent obesity model. Colons from these rodents were sectioned for IHC analysis. Patients (n=103) undergoing screening/surveillance colonoscopies had 2 biopsies taken from the endoscopically normal rectal mucosa and analyzed for FASN and UCP2 by Real-Time PCR. This was correlated with colonoscopic findings and BMI. Results: In animal models, increased FASN and UCP2 expression was observed (in AOM, FASN and UCP2 was increased 1.5-fold and 2-fold, respectively, p<0.001; in Pirc FASN was induced ~90% and UCP increased by 48%, respectively, p<0.03). Leptin deficient mice also had an increase of FASN and UCP2, most notably at 18 months of age as compared to control (increase of staining intensity as by 3-fold and 1.1-fold, respectively, p<0.007). In patients, FASN was over expressed in non-adenoma bearing patient who were obese (BMIs>30) (figure 1). In non-obese patients with adenomas, there was a marked over expression in rectal FASN suggesting that it is a marker of field carcinogenesis (2.83-fold, 0.0002). However, the effect size of field effect was more dramatic in obese patients (4.3fold induction, p<0.0005). The data with UCP2 tightly mirrored FASN with regards to both the obesity and field carcinogenesis effect (figure 2). Conclusions: We demonstrate herein, for the first time, that FASN and UCP2 are over expressed in the pre-malignant mucosa and are accentuated by obesity. This provocative finding may provide fundamental insights into the mechanism behind obesity related CRC, especially in younger patients. It supports the concept of a Warburg like metabolic status in early colon carcinogenesis. Furthermore, it may yield a potential biomarker for risk stratification via field carcinogenesis detection in this higher risk population.