Hepatobiliary and Metabolic Changes Occurring during Weight Loss and Subsequent Weight Maintenance in Obese Subjects: Implications for NASH Clinical Trials

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Background

Obese humans commonly cycle between weight loss, weight maintenance, and weight gain. The changes in bile acid metabolism, biliary lipids, serum lipids, liver tests, gallbladder function, and hepatic versus peripheral response to insulin that occur during periods of weight loss followed by weight maintenance have not been completely defined.

Objective

To define differences in hepatic and total body insulin sensitivity during weight loss and weight maintenance and to relate these changes to changes in bile acid metabolism and biliary lipids.

Methods

The three study periods were baseline (BL), weight loss (WL, day 61 ± 12), and weight maintenance (WM, day 102 ± 9). The following procedures were scheduled to be done at each time point: insulin sensitivity measured by euglycemic-insulin clamp, bile acid kinetics by Lindstedt technique using deuterated cholate and chenodeoxycholate, biliary lipids by naso-duodenal intubation and collection of fasting (hepatic) and CCK-stimulated (gallbladder) bile, and realtime gallbladder motility ultrasonography.

Subjects

27 subjects underwent study by one or more of the above procedures. Their demographics were:

Age – 38.7 ± 7.9 years (mean ± SD)

M:F – 6:21

Race/ethnicity as Non-Hispanic-White:Hispanic: Black:Unknown – 15:4:7:1

Results:

			BASELINE	BL→WL	WEIGHT LOSS	WL→WM	WEIGHT MAINTENANCE	BL→WM
	BMI	kg/m^2	38.8 ± 3.5	(p<0.0001)	34.3 ± 3.2	(p=NS)	33.1 ± 4.0	(p<0.0001)
Metabolism	Serum Insulin	µU/mL	15.0 ± 7.0	(p<0.002)	8.7 ± 4.8	(p=NS)	10.3 ± 4.2	(p<0.004)
	Fasting Glucose Production (Hepatic Insulin Sensitivity)	mg/kg/min	1.91 ± 0.63	(p<0.001)	1.56 ± 0.47	(p<0.0002)	2.02 ± 0.54	(p=NS)
Hepatobiliary Function	Bile Acid Synthesis	µmol/day	1665 ± 1908	(p<0.009)	672 ± 349	(p<0.004)	1070 ± 602	(p=NS)
	Lithogenic Index (Gallbladder Bile)	-	1.10 ± 0.20	(p<0.04)	1.44 ± 0.73	(p=NS)	0.84 ± 0.21	(p<0.05)
	Gallbladder Ejection Fraction	%	71.4 ± 11.9	(p<0.003)	53.8 ± 17.7	(p<0.003)	68.4 ± 11.0	(p=NS)
	LDL and HDL Cholesterol	mg/dL	184.7 ± 31.2	(p<0.0001)	143.9 ± 25.3	(p<0.007)	155.4 ± 34.4	(p<0.0002)
Standard Liver Tests	ALP	U/L	86.0 ± 33.5	(p<0.001)	63.2 ± 24.9	(p=NS)	65.8 ± 24.3	(p<0.05)
	AST	U/L	21.2 ± 8.8	(p=NS)	23.7 ± 10.6	(p<0.04)	16.9 ± 4.7	(p<0.05)
	ALT	U/L	24.9 ± 19.6	(p=NS)	25.7 ± 21.7	(p<0.02)	13.4 ± 6.3	(p<0.03)

Implications for NASH:

1. In obesity, hepatic insulin sensitivity improves but is not sustained during weight maintenance (in contrast to peripheral insulin action which continues to improve during weight maintenance).
2. Reduced gallbladder motility during weight loss can affect bile acid cycling but is unlikely to reduce bile acid synthesis.
3. Reduced bile acid synthesis and increases in biliary cholesterol and bile acid secretion may be due to FXR activation.
4. FXR inactivation may drive the increase in bile acid synthesis during weight maintenance.
5. Reductions in liver enzymes may suggest subclinical NASH in obesity and improvement with weight loss/maintenance.

Conclusions

Cycles of weight loss and weight maintenance are associated with major significant changes in hepatobiliary functions and metabolism and must be considered in the interpretation of the results of drug and placebo effects in the treatment of NASH.

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