SUBCUTANEOUS FAT: A PROTECTOR FROM METABOLIC DYSREGULATION

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BACKGROUND

Adipose tissue distribution stemming from genetics and lifestyle is a major determinant in obesity-related diseases [1]. Peripheral adiposity in the subcutaneous/gluteofemoral region is considered protective against metabolic dysregulation. It is proposed this tissue acts as a metabolic sink to sequester and store lipid from circulation, protecting insulin sensitive tissues from ectopic deposition [2]. While subcutaneous adipose tissue (SAT) has been associated with improved insulin sensitivity and lower risk of adverse metabolic outcomes, the relationship has not been fully examined.

We have previously demonstrated that removal of lower body SAT leads to skeletal muscle, but not liver, lipid accumulation in mice [3]. Fat removal resulted in worsening of glucose intolerance in high-fat, high-sucrose, westernized diet (HFD) fed mice[3]. We sought to examine this further by systematically removing various amounts of SAT. Here we measured outcomes on insulin sensitivity and muscle lipid accumulation in mice. In addition, we identified a distinct lipid profile that correlated with diet-induced impaired glucose tolerance.

Our outcomes will advance the field of adipose tissue biology by supporting that peripheral adipose tissue links to a reduced risk of adverse metabolic outcomes. By linking fat distribution and insulin sensitivity, we will be prepared to better treat and prevent diseases like type 2 diabetes and hyperlipidemia typically observed with central obesity [4].

EXPERIMENTAL METHODS

Subjects: C57/BL6 *mice*

Surgery: Sham or LipX

Diet: CHOW or HFD for 5 or 13 weeks

GTT: Glucose Tolerance Test

Termination: tissue collection

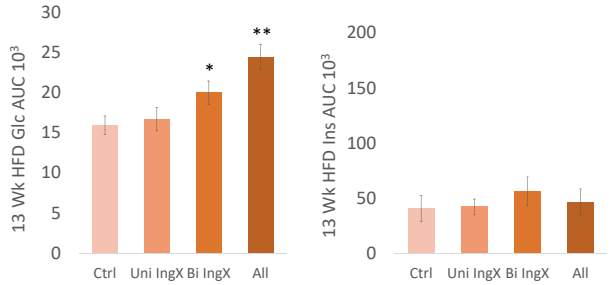
Analysis: outcome measures

HYPOTHESIS

LipX induces a dose-response effect on systemic glucose tolerance → Reduced glucose disposal is due to decreased muscle insulin sensitivity → Detrimental lipid profile is associated with metabolic dysregulation

SURGERY GROUPS

RESULTS

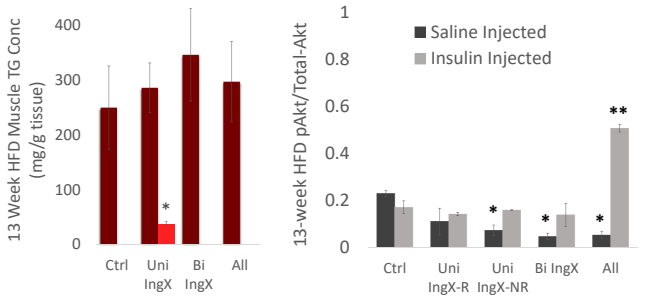


Glucose and Insulin Response to GTT: Terminal GTT was performed one week prior to termination. No effects of surgery were observed at 4 weeks for either diet. Progressive surgery altered glucose regulation in a dose-dependent manner after 12 weeks on HFD. There were no surgery differences in insulin response. *p<0.05, **p<0.001

	Sham	Uni IngX	Bi IngX	All
SAT removal	NA	~20%	~40%	~80%
Weekly kcals	≈	≈	≈	≈
Body Wt	≈	≈	≈	↓
Fasting Glc	≈	≈	≈	≈
Fasting Ins	≈	≈	≈	≈
Leptin	≈	≈	≈	≈
Resistin	≈	≈	≈	↓
PAI1 total	≈	≈	≈	≈
IL-6	≈	≈	≈	↓
Liver TG	≈	≈	≈	≈
AT Depot Mass	≈	≈	≈	≈
Cell size	≈	≈	≈	≈

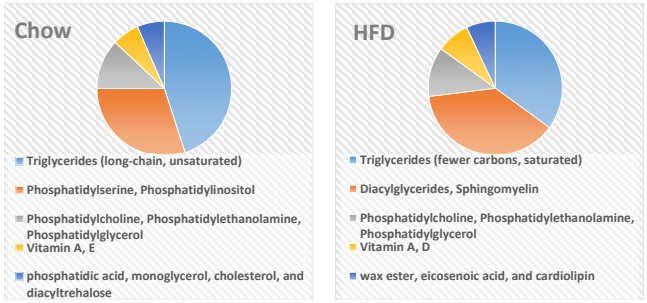
Factors Involved in Glucose Regulation: Components of glucose metabolism were investigated as contributing factors in glucose excursion with increasing SAT removal. No consistent pattern was observed that matches the response to GTT. Food intake, final body weight, fasting glucose/insulin, circulating adipokines, and liver triglycerides were not significantly different among surgery groups. There was no significant regrowth of excised tissue nor compensation in non-excised adipose tissue depots. Adipocyte size and distribution in intra-abdominal depots did not differ from controls with SAT removal.

FEMORAL MUSCLE



Femoral Muscle Insulin Sensitivity: Triglyceride deposition in muscle was substantially increased at 13 weeks with HFD, but no surgery effect. Insulin-stimulated phospho-Akt did not decrease with increasing fat removal, yet femoral muscle was hypersensitive to insulin when dorsal SAT was removed. However, basal muscle insulin sensitivity decreased in a dose-dependent way with progressive fat removal. *p<0.01, **p<0.0001

LIPIDOMICS



CONCLUSIONS

Body mass index alone is a poor predictor of metabolic disease risk, rather body fat distribution is considered influential more so than overall fatness. SAT makes up ~85% total fat mass and plays an important role in glucose homeostasis. Incremental removal of SAT produces a dose-response effect on systemic glucose tolerance and muscle basal insulin sensitivity, independently. We show that not only does SAT function as a "metabolic sink", but that the sink is partitioned and has a dose-dependent relationship to glucose tolerance. HFD induced decreases in femoral muscle function are associated with harmful lipids and decreases in healthful ones.

REFERENCES

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