TACSM Abstract

Effects of Human Apolipoprotein E3 and E4 Genotypes on Cardiometabolic Disease Risk

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ABSTRACT

Apolipoprotein (apo) E isoforms have specific effects on the etiology of cardiovascular disease (CVD), but data is limited on the effects of these genotypes for the risk of type 2 diabetes mellitus (T2DM) and related cardiometabolic alterations. The purpose of this study was to determine the effects of human apoE3 and E4 genotypes on risk factors for T2DM and cardiac metabolism. Cardiac tissue from human apoE3 (n=8) and E4 (n=8) knock-in (KI) mice were compared to lean (n=11) and diet-induced obese (n=12) B6D2F1 mice to characterize the cardiac metabolic activity of AMPK, as well as for lipid and glycogen levels. Plasma was analyzed for lipid and lipoprotein concentrations, as well as glucose, insulin and HOMA-IR. An ANOVA was used to identify differences between groups. Statistical significance was set at a $P<0.05$. ApoE3 and E4 mice displayed mild insulin resistance (Table 1) despite for having a body mass similar to the lean mice. In addition, apoE3 mice had a 1.5 fold greater HOMA-IR than apoE4 mice. Interestingly, apoE3 and E4 mice had significantly lower TC, Tg and HDL-C than both lean and obese mice. In apoE3 mice, nonHDL-C was significantly lower than both the lean and obese mice and the apoE4 mice. In apoE3 mice, cardiac cholesterol was greater than both lean and obese controls and apoE4 mice. In contrast, apoE4 mice had 2.5 and 2.9 fold greater cardiac triglyceride levels than the lean and obese mice, respectively. In the absence of an obesogenic diet, apoE3 and E4 mice displayed an insulin resistant metabolic state combined with altered lipid and lipoprotein metabolism that paralleled an increase in cardiac lipid deposition. These alterations in cardiac metabolism may contribute to the increased risk of CVD observed in apoE3 and E4 genotypes.

Table 1. Metabolic characteristics of lean and obese B6D2F1 mice and human apo E3 and E4 KI mice.

Variables	Lean (n=11)	Obese (n=12)	Apo E3 KI (n=8)	Apo E4 KI (n=8)
Body weight (g)	34.0 ± 1.2	42.6 ± 2.4*	35.1 ± 3.3†	35.4 ± 2.2†
Glucose (mg/dL)	109.3 ± 34.3	190.7 ± 38.4*	187.5 ± 53.4*	160.7 ± 33.9*
HOMA-IR	4.9 ± 1.1	32.6 ± 4.5*	12.9 ± 2.8*†	8.5 ± 1.5*†
Tg (mg/dL)	150.6 ± 34.0	209.9 ± 40.0*	27.6 ± 15.1*†	22.2 ± 5.0*†
TC (mg/dL)	101.3 ± 7.3	179.7 ± 18.2*	52.3 ± 12.4*†	56.7 ± 16.7*†
HDL-C (mg/dL)	72.8 ± 106.7	106.7 ± 11.7*	32.1 ± 12.3*†	25.4 ± 9.9*†
nonHDL-C (mg/dL)	28.5 ± 4.2	73.0 ± 10.1*	20.3 ± 8.0*†	31.1 ± 8.0†‡
Cardiac Tissue				
pAMPK:AMPK	1.0 ± 0.0	1.8 ± 0.6*	1.4 ± 0.6	0.9 ± 0.5
Tg (µg/mg tissue)	28.5 ± 15.3	24.8 ± 18.9	68.1 ± 47.0	70.8 ± 28.2*†
Cholesterol (µg/mg tissue)	5.8 ± 1.3	7.9 ± 2.1	12.8 ± 1.5*†	7.7 ± 2.1‡
Glycogen (µg/mg tissue)	31.2 ± 6.1	22.6 ± 8.6	40.7 ± 34.1	26.7 ± 16.5

Data are mean ± SEM. *Significantly different than B6D2F1 lean group; †Significantly different than B6D2F1 obese group; ‡Significantly different than Apo E3 KI.