

Determinants of Cardiovascular Disease Risk in Obese Youth with Non-alcoholic Fatty Liver Disease

Ishita Jindal MD, Maurice Puyau, Anne Adolph, Nancy Butte PhD, Fida Bacha MD

USDA/ARS Children's Nutrition Research Center, Baylor College of Medicine, Houston, TX 77030



Background

- Autonomic dysfunction is an early independent predictor of cardiovascular disease risk and mortality.
- Non-alcoholic Fatty Liver Disease (NAFLD) is associated with markers of subclinical atherosclerosis in children.
- To understand the determinants of cardiovascular disease risk in obese Hispanic children with elevated ALT (as a surrogate measure of NAFLD), we evaluated markers of autonomic function (resting heart rate and blood pressure) and their relationship to cardiorespiratory fitness (CRF), inflammatory markers, and urinary catecholamines in youth with and without NAFLD.

Hypotheses

- Youth with elevated ALT have higher resting heart rate (RHR), systolic and diastolic blood pressure compared with equally obese Hispanic youth with normal ALT.
- This is related to lower CRF and higher urinary catecholamines in youth with elevated ALT compared with youth with normal ALT.

Methods

- Hispanic obese children (n=428) belonging to two age-groups (6-11 and 12-19 years) participated in the study.
- They were divided into two groups according to ALT levels (>26 U/L in males and >22 U/L in females).
- They underwent measurements of RHR (in resting supine position), systolic and diastolic blood pressure and CRF (VO₂ max determination during treadmill exercise test).
- Inflammatory markers (high sensitivity C-reactive protein [hs-CRP], TNF-α and interleukin-6 [IL6]) and urinary catecholamines (epinephrine, norepinephrine and dopamine) were obtained.
- General Linear Models (GLM) were used to examine determinants of cardiovascular disease risk such as resting heart rate and blood pressure accounting for ALT status, sex and age-group.

Table 1. Subject Characteristics

	6-11y		12-19y		p-value
	Normal ALT	Elevated ALT	Normal ALT	Elevated ALT	
Age* (years)	9.4 ± 1.7	9.5 ± 1.6	14.4 ± 1.9	14.7 ± 2.2	
BMI* (kg/m ²)	27.1 ± 4.5	28.9 ± 4.9	33.5 ± 5.3	36.0 ± 6.9	<0.001
BMI z-score^	2.2 ± 0.3	2.3 ± 0.4	2.2 ± 0.3	2.4 ± 0.4	<0.001
Lean mass* [^] (kg)	31.7 ± 7.8	33.9 ± 8.3	51.7 ± 9.5	54.4 ± 11.1	0.02
Fat mass* (kg)	21.3 ± 8.2	24.3 ± 9.0	34.5 ± 8.4	36.4 ± 8.1	0.003
Fat mass [^] (%)	39.3 ± 5.4	40.9 ± 4.8	39.8 ± 5.8	40.1 ± 5.2	0.03
Waist/Hip ratio* [^]	0.88 ± 0.06	0.90 ± 0.06	0.85 ± 0.06	0.89 ± 0.08	<0.001

Table 2. CVD Risk Markers

	6-11y		12-19y		p-value
	Normal ALT	Elevated ALT	Normal ALT	Elevated ALT	
ALT level* [^] (U/L)	16 ± 4	46 ± 28	15 ± 5	60 ± 43	<0.001
Systolic BP* [^] (mmHg)	108 ± 8	110 ± 8	115 ± 9	118 ± 10	0.009
Diastolic BP (mmHg)	51 ± 7	52 ± 7	51 ± 7	53 ± 8	
VO ₂ max* [^] (L/min)	1.7 ± 0.4	1.8 ± 0.4	2.5 ± 0.5	2.6 ± 0.5	
TNFα (pg/mL)	8.4 ± 2.4	8.0 ± 2.0	8.0 ± 2.6	8.4 ± 2.3	
IL-6 (pg/mL)	2.2 ± 2.4	2.2 ± 2.2	1.9 ± 1.5	2.4 ± 1.6	

Data are Mean ± SD
* : denotes p<0.05 for age group effect
^ : denotes p<0.05 for sex effect

Figure 1. Resting heart rate and ALT status

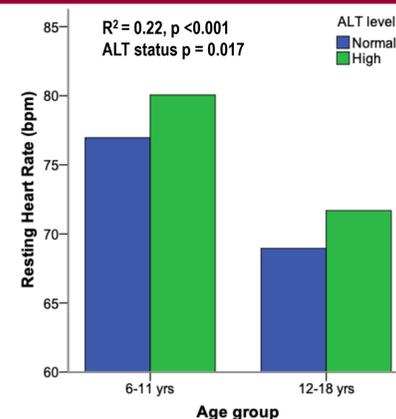


Figure 2. CRF and ALT status

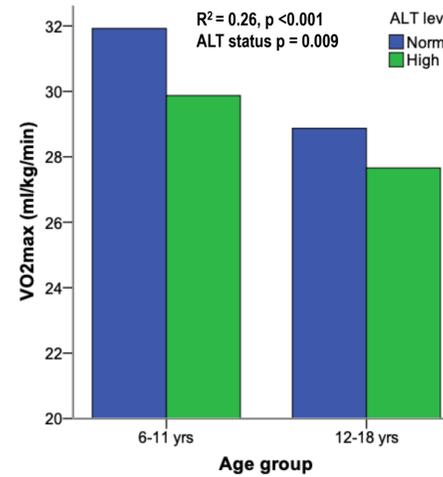


Figure 4. CRF and Resting Heart Rate

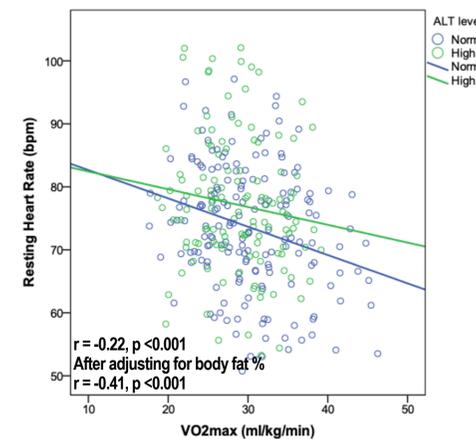


Figure 3. Hs-CRP and ALT status

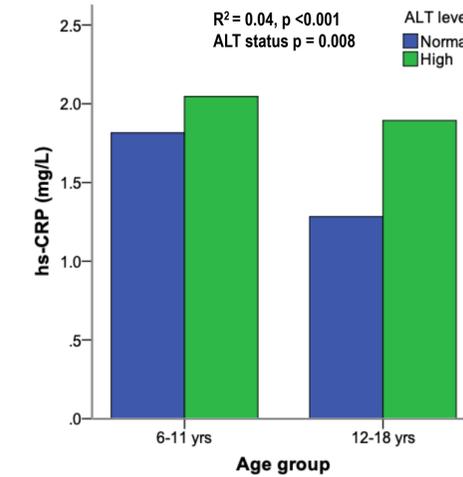


Figure 5. Epinephrine and Resting Heart Rate

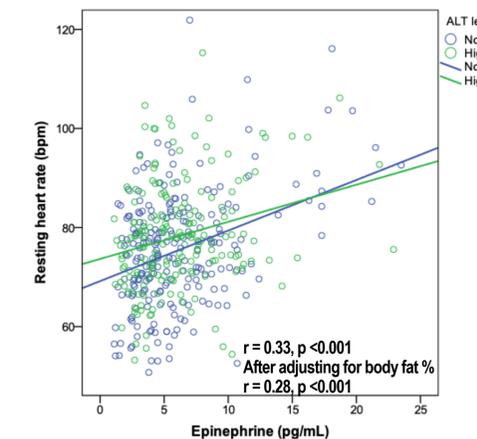


Table 3. Determinants of Resting Heart Rate

Variable	B	Std. Error	Beta	Sig.
Younger age group	7.80	1.12	0.37	<0.001
ALT status	2.47	1.05	0.11	0.02
Gender (female)	3.78	1.20	0.18	0.002
VO ₂ max/kg	-0.37	0.14	-0.19	0.01
Epinephrine	0.74	0.19	0.23	<0.001
Body fat (%)	21.25	13.47	0.11	0.12

$R^2 = 0.37, p < 0.001$

Results

- Systolic blood pressure was positively related to ALT, urinary norepinephrine, and hs-CRP; and correlated negatively with CRF.
- Diastolic blood pressure was positively related to ALT and urinary epinephrine.

Discussion

- Resting heart rate and systolic blood pressure were higher in children with elevated ALT compared to children with normal ALT.
- Resting heart rate was positively related to urinary catecholamines, hs-CRP; and inversely related to CRF.
- In addition to age and sex effects, higher resting heart rate was associated with elevated ALT, lower CRF and higher urinary epinephrine after adjusting for % body fat.
- Hs-CRP was significantly higher in youth with elevated ALT vs. normal ALT, however, no differences were noted in TNFα and IL-6 levels.

Conclusions

- Youth with elevated ALT manifest adverse cardiovascular disease risk markers including higher resting heart rate, systolic blood pressure, hs-CRP, and lower CRF compared with obese peers with normal ALT.
- Lower CRF, sympathoadrenal function and inflammation contribute to the adverse cardiovascular biomarkers suggestive of autonomic dysfunction in these youth.

References

- Aune D et al. Resting heart rate and the risk of cardiovascular disease, total cancer, and all-cause mortality - A systematic review and dose-response meta-analysis of prospective studies. Nutr Metab Cardiovasc Dis. 2017.
- Bacha F et al. Nonalcoholic Fatty Liver Disease in Hispanic Youth With Dysglycemia: Risk for Subclinical Atherosclerosis? J Endocr Soc. 2017.