



2014

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Receptor of Advanced Glycation Endproducts (RAGE) is Positively Correlated with Tumor Necrosis Factor- α in Adolescents with Obesity

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Abstract

Introduction: Obesity in childhood is associated with an increased prevalence of diabetes and other traditional cardiometabolic risk factors, suggesting an epidemic of premature cardiovascular disease among today's youth. Glycotoxins, known as advanced glycation end products (AGE's), activating via the membrane-bound receptors (mRAGE), have been implicated in the pathophysiology of inflammation, (increased tumor necrosis factor- α [TNF- α]), insulin resistance and vascular dysfunction in adults, but the role of RAGE in the early stages of metabolic disorders is unknown. In this study, we assessed relationship of cardiometabolic risk factors, mRNA expression of TNF- α and RAGE in peripheral monocytes in adolescents with obesity.

Methods: Thirty three adolescents, 11-16 years of age, with body mass index (BMI) Z-score ≥ 2 were admitted following a 12-hour overnight fast for anthropometrics, lipid profile, fasting peripheral blood sample collection, and a 2-hour 75 gm, oral glucose tolerance test (OGTT). Peripheral blood mononuclear cells (PBMC) positive for CD14 were isolated from blood. Cells were further analyzed by quantitative PCR for mRNA expression of RAGE and TNF- α . Pearson's coefficients were calculated to assess the associations between RAGE mRNA and cardiometabolic risk factors as well as TNF- α mRNA levels.

Results: The participants had a mean age of 12.7 ± 1.41 years and BMI-Z score 2.32 ± 0.35 SD with 81 % participants being female; 62 % were Black, 28% Caucasian, 10% were Hispanic. We observed a positive correlation between mRNA levels of RAGE and TNF- α in CD14⁺ monocytes in blood ($r=0.62$, $p<0.01$). However, we did not observe a correlation of BMI, cholesterol or triglyceride with RAGE mRNA levels.

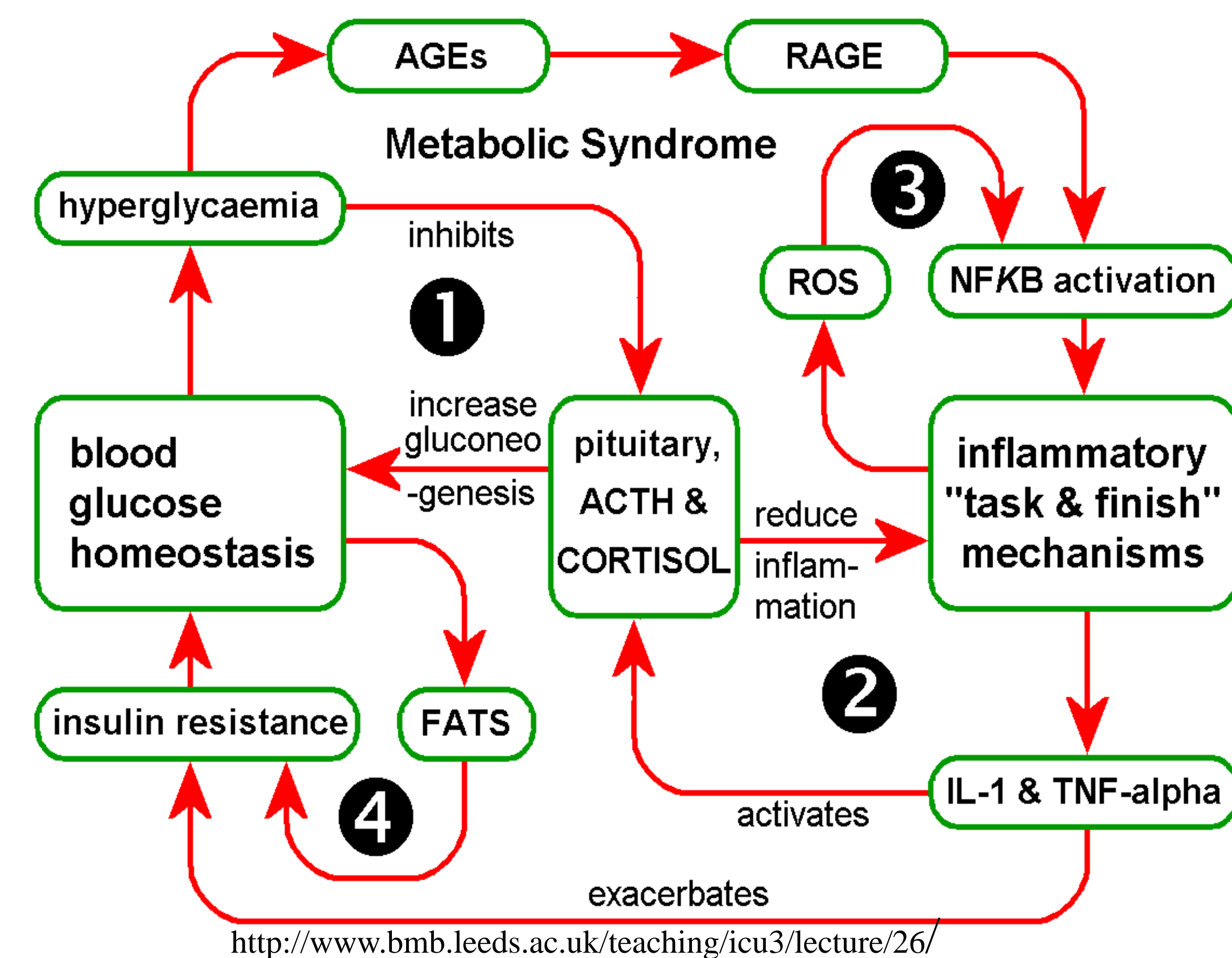
Conclusion: The positive relationship between the monocyte mRNA levels of RAGE and TNF- α suggest involvement of AGE- RAGE axis in obesity-associated inflammation and needs to be further investigated with larger sample size as well as studies in healthy adolescents.

Introduction

Receptor of Advanced Glycation End product is a signal transduction receptor associated with recognizing stress and inflammatory signals. It is a membrane bound recognition receptor that also works as a cell-adhesion molecule. RAGE is particularly involved in mediating pro-inflammatory actions of dietary glycotoxins known as Advance Glycation Endproducts (AGEs). Escalated levels of AGE-RAGE have been associated with both types of diabetes, obesity, metabolic syndrome and a number of degenerative diseases.

RAGE is expressed mostly in monocytes/macrophage. RAGE is responsible for enhanced expression of a key pro-inflammatory cytokine tumor necrosis factor alpha (TNF- α) which has been associated with the regulation of adiposity and insulin sensitivity. Both RAGE + TNF- α have been shown to play vital roles in the development of metabolic syndrome, a morbid combination of obesity, insulin-resistance, diabetes and hypertension.

AGE binding followed by activation of RAGE has been linked to diabetes, cardiovascular disease and obesity in both human and mice models. Blocking RAGE has been shown to suppress atherosclerosis. Therefore we hypothesized that enhanced RAGE gene expression in monocytes will correlate with cardiometabolic risk factors including glucose, cholesterol and triglyceride levels in adolescents with obesity.



<http://www.bmb.leeds.ac.uk/teaching/icu3/lecture/26/>

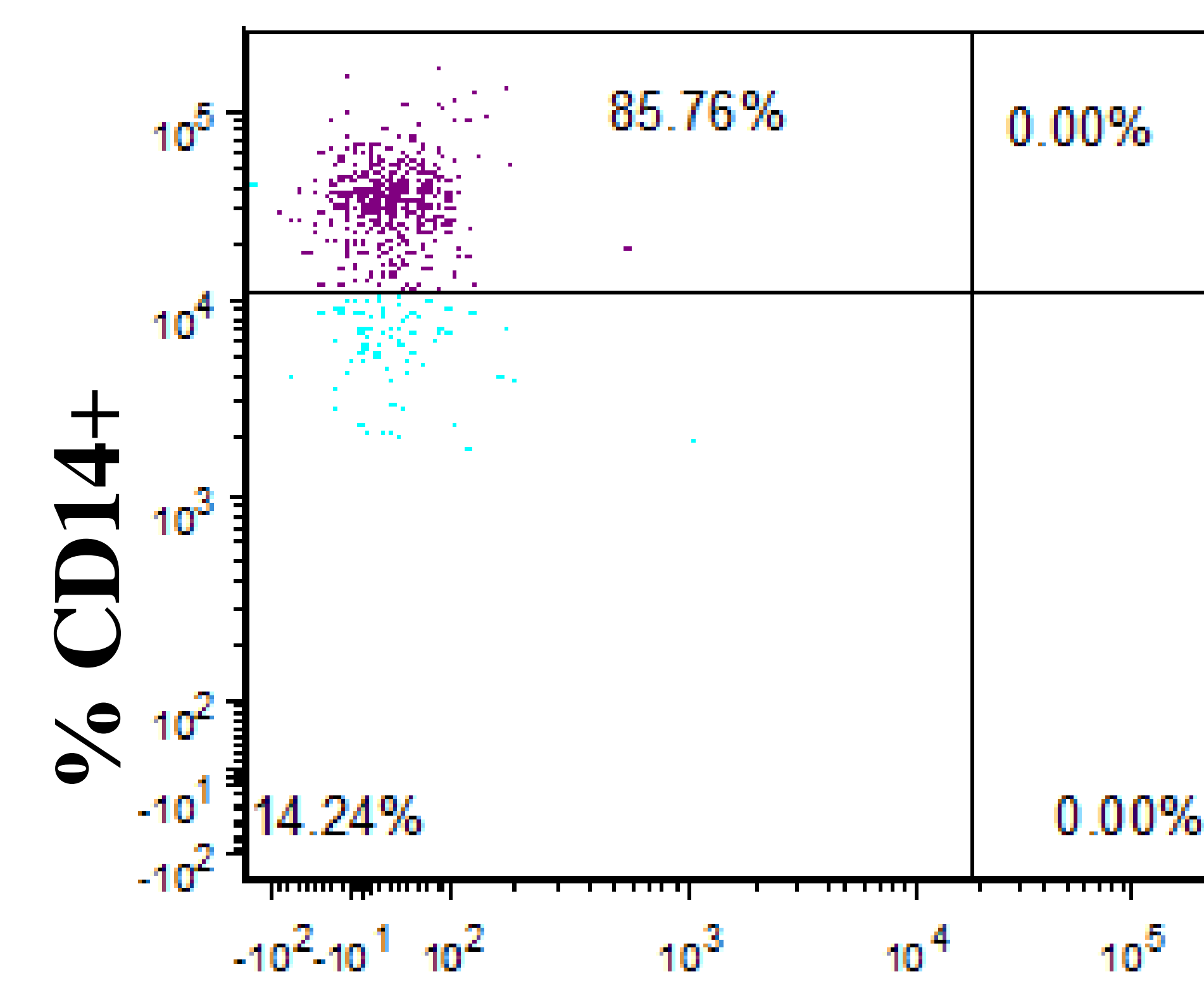


Figure 1: AGE-RAGE relationship in terms of Metabolic Syndrome. Obese individuals are persistently in an inflammatory stage enhanced by AGE-RAGE binding, which consequently increases expression of pro-inflammatory cytokines such as TNF- α and IL-1 exacerbating metabolic syndromes

Figure 3 (LEFT): CD14⁺ flow through was analyzed for representative purity by Flow Cytometry (Diva Software V.8, BD Canto Flow Analyzer). A satisfactory purity of 85.76% validated success of PBMC isolation and MACS column aspiration.

Figure 4 (BELOW): Correlation between % mRNA levels of RAGE and TNF- α in CD14⁺ monocytes in blood. ($r=0.62$, $p<0.01$)

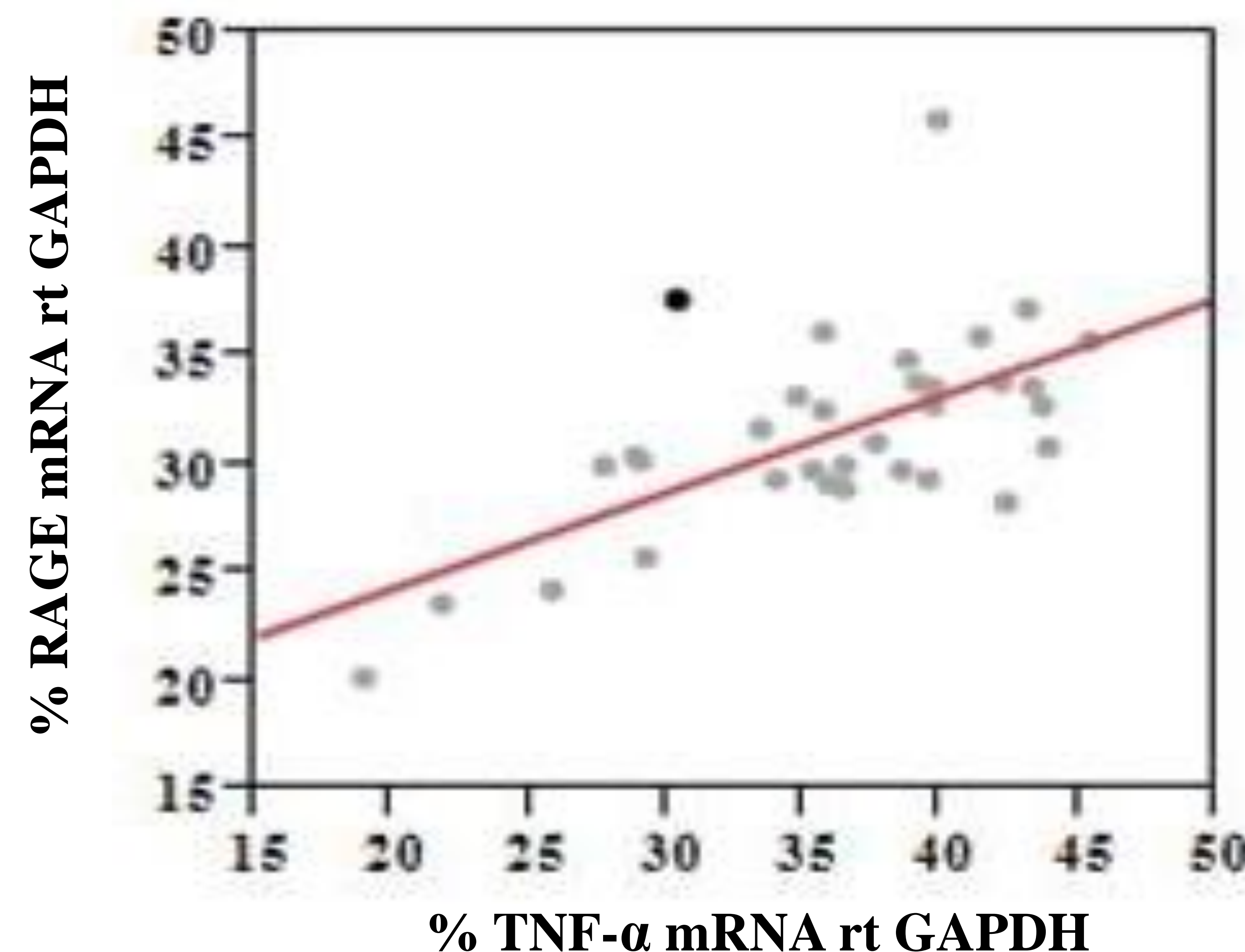
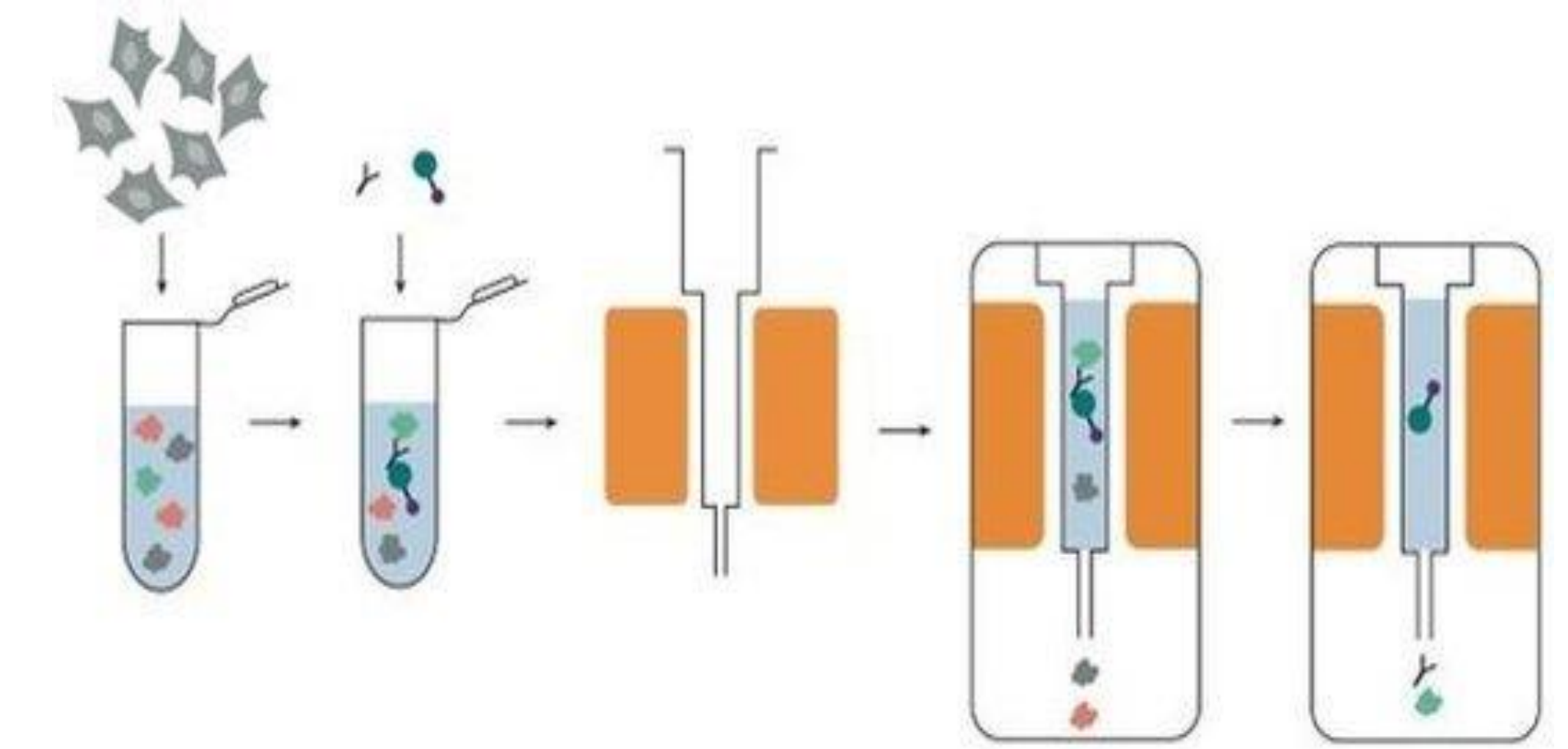


Figure 2: CD14⁺ monocytes isolation using MACS Column. PBMC incubated with CD14 beads was washed and aspirated in MACS MS column. CD14⁺ cells were used for RAGE and TNF- α expression by qPCR.



Results/Discussion

The cardiometabolic risk factors that were assessed with RAGE and TNF- α levels are BMI-Z score, cholesterol (LDL/HDL) and triglyceride levels.

Participants had a mean age of 12.7 ± 1.41 years and BMI-Z score 2.32 ± 0.35 SD with 81 % participants being female; 62 % were Black, 28% Caucasian, 10% were Hispanic.

%mRNA expression of RAGE and TNF- α were 31.06% and 34.29% respectively.

We saw a positive correlation ($r=0.62$, $p<0.01$) between RAGE and TNF- α expression.

Conclusion

- The positive correlation between RAGE and TNF- α expression suggests that RAGE is linked to inflammatory factors such as TNF- α in adolescents with obesity.
- Based on data so far so we do not see a relationship of RAGE gene expression with measures of obesity or dyslipidemia in our sample of adolescents with obesity.
- To our knowledge this is the first time expression of RAGE has been assessed in adolescents with obesity. However, it needs to be compared with RAGE expression in healthy adolescents. Therefore, we are recruiting for healthy adolescents and plan to compare the gene expression levels in the two groups.

Acknowledgements

This research received funding from U.S. National Institute of Health (UL1TR000058 and KL2TR000057). Flow Cytometry was supported by NIH Grant P30 CA16059).

We sincerely thank Julie Farnsworth, Jing Li and Lauren Folgosa Cooley for technical assistance.