Serum Adiponectin and its Relationship with Insulin Resistance in Nigerian Children

Chisom Adaobi Nri-Ezedi [1*], Henry Okpara [2], Chigozie Ozoemena Ifeadike [3], Achunam Simeon Nwabueze [3], Thomas Obiajulu Ulasi [1] and Amalachukwu Okwukweka Odita [1]

[1]Department of Paediatrics, Faculty of Medicine, Nnamdi Azikiwe University, Awka, Anambra State, Nigeria
[2]Department of Chemical Pathology, Nnamdi Azikiwe University, Awka, Anambra State, Nigeria
[3]Department of Community Medicine and Primary Health Care, Nnamdi Azikiwe University, Awka, Anambra State, Nigeria.

ABSTRACT

Background: Adiponectin, an excellent insulin sensitizer, holds immense potential in the management of Type 2 diabetes mellitus (T2DM) and other non-communicable diseases (NCDs). Despite insulin resistance being a known risk factor for NCDs, the precise association between adiponectin and insulin resistance in Nigerian children remains largely unexplored. **Objectives:** To examine the association between serum adiponectin and insulin resistance among Nigerian children. **Materials and Methods:** 172 primary school children aged 4-12 years were randomly enrolled in this study. Anthropometric measurements, including body mass index (BMI) and waist circumference, were recorded. Serum adiponectin levels, fasting blood glucose, and insulin levels were measured. Insulin resistance was assessed using HOMA-IR and FGIR. **Results:** Mean adiponectin levels were higher in females compared to males (p = 0.23). Insulin resistance was observed in 5.2% of children using HOMA-IR and in 1.7% using FGIR. Following adjustment for age, gender and BMI, a unit increase in adiponectin was associated with decreased odds of insulin resistance (OR: 0.956; 95% CI: 0.722-1.266). Increased adiposity was significantly associated with insulin resistance. **Conclusion:** This study offers significant contributions to our understanding of the association between serum adiponectin levels and insulin resistance in Nigerian children and explores the potential role of adiponectin in the management of T2DM and other NCDs. The insights gained from this study hold promise in informing targeted interventions and shaping future management strategies for NCDs in African populations.

Keywords: Adiponectin, Type 2 diabetes mellitus, insulin resistance, African children, HOMA-IR, FGIR

INTRODUCTION

Adiponectin has gained substantial recognition in clinical research worldwide due to its diverse biological functions, which may play a pivotal role in the management of Type II diabetes mellitus and other non-communicable diseases (NCDs).[1–5] Notably, adiponectin is an excellent insulin sensitizer and demonstrates anti-inflammatory and anti-atherogenic

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***Correspondence:**
Chisom Adaobi Nri-Ezedi, Department of Paediatrics, Faculty of Medicine, Nnamdi Azikiwe University, Awka, Anambra State, Nigeria.

***Tel:** +2348035068197*
Email:
ca.nri-ezedi@unizik.edu.ng

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properties, while also influencing a favourable plasma lipoprotein profile. These remarkable attributes have prompted investigations into the therapeutic potential of adiponectin in addressing conditions such as Type 2 diabetes mellitus, obesity, cardiovascular disorders and other NCDs.[6–8]

The escalating global prevalence of NCDs poses a significant health challenge across nations, accounting for a substantial proportion of global mortality, particularly in low- and middle-income countries.[9] Therefore, it is of utmost importance to prioritize the development and implementation of preventive and treatment strategies against NCDs.[9] In addition, recognizing the early signs of NCDs is crucial, as they often originate during childhood in the form of a subclinical phase known as insulin resistance.[10,11]

Insulin resistance, characterized by impaired glucose response to insulin, serves as a central pathological mechanism underpinning numerous NCDs.[10] Extensive research conducted in children consistently demonstrates a strong correlation between reduced serum adiponectin levels and the presence of insulin resistance.[12,13] These findings indicate that adiponectin holds promise as both a valuable marker and a potential therapeutic agent for conditions characterized by insulin resistance and its related comorbidities. However, there is currently a significant gap in knowledge within Nigeria regarding the specific role of adiponectin in relation to insulin resistance among the paediatric population. This knowledge deficit is especially critical to address due to the potential variations in metabolic profiles influenced by factors such as genetic predispositions, ethnicity, and environment. Therefore, our aim is to enrich the existing knowledge by offering valuable insights that can elucidate the potential role of adiponectin in the management of Type 2 diabetes mellitus and other non-communicable diseases (NCDs), with a specific emphasis on individuals of African descent.

MATERIALS AND METHODS

Study site

The present study was conducted in Nnewi, a cosmopolitan town and the second-largest settlement in Anambra State, Nigeria.

Study design

This is a cross-sectional descriptive study

Study population

This consist of primary school pupils in Nnewi, Anambra State, Nigeria randomly selected to participate in the study.

Eligibility criteria

Inclusion criteria

1. Primary school children registered in both public and private schools in Nnewi, Anambra state
2. Children whose caregivers gave an informed consent.

Exclusion criteria

1. Those with obvious clinical features such as generalized body swelling, jaundice or gross abdominal distension.

Sampling Technique

The study area, Nnewi, was divided into four clusters based on its quarters: Nnewichi, Otolo, Uruagu, and Umudim. From a total of 160 public and private primary schools in Nnewi, one school of each type was randomly selected from each cluster. The number of participants from each school was determined by the sampling fraction calculated using the total number of students in both public and private schools within each cluster.

Once the schools were chosen, necessary permissions were obtained from school authorities and teachers to involve the students. To select individual students, a systematic random sampling method was applied, ensuring an equitable representation of genders. Parents and guardians were then informed about the study, and students aged 6 years and above provided their assent. If consent was not obtained, another student was randomly selected as a replacement. This rigorous sampling approach aimed to assemble a diverse and

representative participant group for the study's comprehensive analysis.

Sampling Procedure

Selected participants were instructed to observe a fasting period of 8 to 12 hours prior to the collection of blood samples.[14] Weight measurements were taken using a calibrated weighing scale, while height measurements were recorded using a stadiometer integrated into the weighing scale.[15] These measurements were utilized to calculate the body mass index (BMI) of each participant. To determine BMI-for-age percentiles, Centres for Disease Control and Prevention (CDC) growth reference charts were employed.[16] Waist circumference was measured using a flexible non-elastic tape, and abdominal obesity was defined as a waist circumference equal to or greater than the 75th percentile for age and gender.[17]

Serum adiponectin levels were analysed using enzyme-linked immunosorbent assay (ELISA) kits.[18] Insulin resistance was assessed using fasting plasma glucose and insulin levels, calculated through the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) and the Fasting Glucose: Insulin Ratio (FGIR). In this study, HOMA-IR greater than 2.6 and FGIR less than 4.5 were employed as markers of insulin resistance.[19,20]

Statistical analysis

Statistical analysis was conducted with Python version 3.9.12. Categorical data were presented as frequencies and percentages, while continuous data were reported as means ± standard deviations (SD) for variables with a parametric distribution, and as medians and interquartile ranges (IQR) for variables with a non-parametric distribution. The student t-test was used to compare means of parametric quantitative variables between two groups, and one-way analysis of variance (ANOVA) was employed when there were more than two groups. The Mann-Whitney U test was utilized for non-parametric numeric variables between two groups, and the Kruskal-Wallis test was used for comparisons involving more than two groups. The association between qualitative variables was assessed using the chi-square test, with Fisher's exact test applied for small cell frequencies. Pearson's correlation coefficient was used for assessing the strength of linear relationships between parametric quantitative variables, and Spearman's correlation coefficient was employed for non-parametric variables. Scatter plots were created to visually represent linear relationships. A significance level of $p < 0.05$ was considered statistically significant.

RESULTS

One hundred and seventy-two (172) primary school children were enrolled in this study. Eighty-five (85) of the subjects were males (49.4%) yielding a male-to-female ratio of 0.97:1. The mean age of the subjects was 7.8 years ± 2.3 years with an age range of 4-12 years. Among the study participants, children aged between 10 and 12 years constituted the highest proportion (27.3%), while those aged between 4 and 5 years constituted the lowest proportion (19.2%) (Table 1).

There were no statistically significant differences observed in the age or BMI between male and female subjects (Table 1). However, females had a significantly larger waist circumference compared to males ($p = 0.045$) (Table 1).

Markers of Adiposity

Majority of the participants (85.4%) had a healthy BMI. A small percentage of participants were classified as underweight (6.4%), overweight (4.1%), and obese (4.1%).

Similarly, 155 (90.1%) of the participants had a healthy abdominal adiposity, while 17 (9.9%) were classified as abdominally obese. Although females were observed to have a larger waist circumference (WC) than males (56.92 ± 6.13 vs. 55.34 ± 3.85, $p = 0.045$), this finding was not consistent when WC was further categorised to delineate abdominal obesity (Table 1).

Metabolic Parameters of Study Participants

Serum Adiponectin concentration

Mean serum adiponectin value was 4.89 ± 2.67 ng/ml. Notably, no significant difference was observed across males and females (4.64 ± 2.50 ng/ml vs. 5.13 ± 2.82 ng/ml; p = 0.23) (Table 1).

Markers of insulin resistance

In total, 9 children (5.2%) were identified as having insulin resistance based on HOMA-IR, while 3 children (1.7%) were classified as insulin resistant using FGIR (Table 1).

Females showed a higher prevalence of insulin resistance using HOMA-IR (77.8%) compared to males (22.2%). Similarly, using FGIR, a greater proportion of females were insulin resistant compared to males (66.7% vs. 33.3%) but this was not statistically significant (Table 1).

Relationship between Measures of Adiposity and Metabolic Parameters

Adiponectin and Measures of Adiposity

In Table 2, subjects who were overweight were observed to have the lowest adiponectin values compared to other body mass categories. In contrast, subjects with abdominal obesity had a higher serum adiponectin concentration compared to subjects with normal abdominal adiposity (5.31ng/ml ± 3.71 vs. 4.84ng/ml ± 2.54) (Table 3).

HOMA-IR and Measures of Adiposity

Nearly half of overweight subjects were insulin resistant (Table 2). In contrast, none of the obese study participants were found to be insulin resistant. With regards to abdominal obesity, almost a third of study participants with abdominal obesity were found to be insulin resistant (p = 0.003) (Table 3).

A statistically significant positive linear correlation was found between the natural logarithmic transformation of HOMA-IR and BMI (r = 0.297, p < 0.001). Similarly, a positive correlation, with a stronger association, was observed between HOMA-IR and WC (r = 0.358, p = 0.0001) (Figure I).

FGIR and Measures of Adiposity

All insulin resistant subjects, detected by FGIR, were observed to be overweight (p < 0.001) (Table 2). Similarly, all subjects found to be insulin resistant had abdominal obesity (p < 0.001) (Table 3) Figure II depicts a significant negative linear relationship between the natural logarithmic transformation of FGIR and BMI was observed (r = -0.268, p < 0.001). Similarly, a negative correlation, albeit stronger, was observed between FGIR and WC (r = -0.301, p < 0.0001) (Figure II)

Relationship between Adiponectin Distribution and Markers of Insulin Resistance

The adiponectin concentrations of subjects who were not insulin resistant (HOMA-IR) were marginally lower than those who were insulin resistant (4.88 ng/ml ± 2.68 vs. 4.97ng/ml ± 2.68, p = 0.928).

Similarly, subjects who were not insulin resistant, as determined by FGIR, had lower levels of adiponectin in comparison with their counterparts with insulin resistance (4.85ng/ml ± 2.65 vs 7.1 ng/ml ± 3.64 vs; p-value = 0.418).

Predictor Variables of Insulin Resistance

Following adjustment for age, gender and BMI, a unit increase in adiponectin was associated with decreased odds of insulin resistance (OR: 0.956; 95% CI: 0.722-1.266). Compared to normal weight, obesity emerged as a positive significant predictor of insulin resistance (OR = 21.336, 95% CI = 2.362-192.692) (Table 4).

Table 1: Demographic, Adiposity and Metabolic Parameters of Primary School Children

Variables	Total (n=172)	Male (n = 85)	Female (n = 87)	pvalue
Mean Age (years)	7.8 ± 2.29	7.56 ± 2.37	8.02 ± 2.19	0.19
Age Group (years)				
45	33 (19.2)	21 (24.7)	12 (13.8)	
67	46 (26.7)	23 (27.1)	23 (26.4)	0.29
89	46 (26.7)	20 (23.5)	26 (29.9)	
10-12	47 (27.3)	21 (24.7)	26 (29.9)	
BMI (kg/m)^2	15.9 ± 2.06	15.71 ± 1.48	16.09 ± 2.5	0.218
WC (cm)	56.14 ± 5.18	55.34 ± 3.85	56.92 ± 6.13	0.045**
Body Mass Adiposity				
Underweight	11 (6.4)	4 (4.7)	7 (8.0)	
Healthy	147 (85.4)	76 (89.4)	71 (81.6)	0.495
Overweight	7 (4.1)	3 (3.5)	4 (4.6)	
Obese	7 (4.1)	2 (2.4)	5 (5.7)	
Abdominal Obesity				
Healthy	155 (90.1)	78 (91.8)	77 (88.5)	
Obese	17 (9.9)	7 (8.2)	10 (11.5)	0.645
Adiponectin (ng/ml)	4.89 ± 2.67	4.64 ± 2.5	5.13 ± 2.82	0.23
HOMAIR Category				
IR	9 (5.2)	2 (2.4)	7 (8.0)	
Not IR	163 (94.8)	83 (97.6)	80 (92.0)	0.182
FGIR Category				
IR	3 (1.7)	1 (1.2)	2 (2.3)	
Not IR	169 (98.3)	84 (98.8)	85 (97.7)	0.999

IR, Insulin Resistant; Not IR, Not Insulin Resistant; **p<0.05

Table 2: Relationship between Body Mass Index and Metabolic Parameters

	Total	Underweight	Healthy	Overweight	Obese	p-value
n (%)	172	11 (6.4)	147 (85.4)	7 (4.1)	7 (4.1)	-
Adiponectin (ng/ml)	4.0 (2.9 5.8)	4.6 (3.75.2)	4.0 (2.95.8)	3.3 (3.08.35)	4.0 (2.9 6.8)	0.999
HOMA-R Category						
IR	9 (5.2)	1 (9.1)	5 (3.4)	3 (42.9)	0 (0.0)	0.0001**
Not IR	163 (94.8)	10 (90.9)	142 (96.6)	4 (57.1)	7 (100.0)	
FGIR Category						
IR	3 (1.7)	0 (0.0)	0 (0.0)	3 (42.9)	0 (0.0)	0.0001**
Not IR	169 (98.3)	11 (100.0)	147 (100.0)	4 (57.1)	7 (100.0)	

n, number; IR, Insulin Resistant; Not IR, Not Insulin Resistant; ** p<0.05

Table 3: Relationship between Abdominal Adiposity and Metabolic Parameters

	Total	Healthy (n=155)	Obese (n=17)	p-value
Adiponectin (ng/ml)	4.89 ± 2.67	4.84 ± 2.54	5.31 ± 3.71	0.498
HOMA-IR Category				
IR	9 (5.2)	5 (3.2)	4 (23.5)	
Not IR	163 (94.8)	150 (96.8)	13 (76.5)	0.003**
FGIR Category				
IR	3 (1.7)	0 (0.0)	3 (17.6)	
Not IR	169 (89.3)	155 (100.0)	14 (82.4)	0.0001**

n, number; IR, Insulin Resistant; Not IR, Not Insulin Resistant; ** p<0.05

Table 4: Logistic Regression Analysis of Predictors for Insulin Resistance Among Primary School Children

Predictors	Univariate		Multivariate	
	OR	**95% CI**	**OR**	**95% CI**
Gender				
Female (ref)	-	-		-
Male	0.275	0.056-1.366	0.211	0.031-1.441
Age Categories (years)				
4-5 (ref)	-	-	-	-
6-7	0.344	0.03-3.966	0.218	0.015-3.253
8-9	0.705	0.094-5.275	0.189	0.014-2.577
10-12	1.442	0.248-8.373	1.889	0.252-14.145
BMI Categories				
Normal (ref)	-	-	-	-
Underweight	2.84	0.302-26.697	1.748	0.162-18.868
Obese†	7.745	1.632-36.758	21.336	2.362192.692*
Abdominal adiposity				
Healthy (ref)	-	-	-	-
Obese	9.231	2.205-38.638	18.345	2.819119.395**
Adiponectin	1.012	0.79-1.295	0.956	0.722-1.266

† Overweight and Obesity; ‡, * p<0.05. Note: Body mass index (BMI) categories and waist circumference were included as separate predictors in the multivariate logistic regression analysis to address multicollinearity concerns.

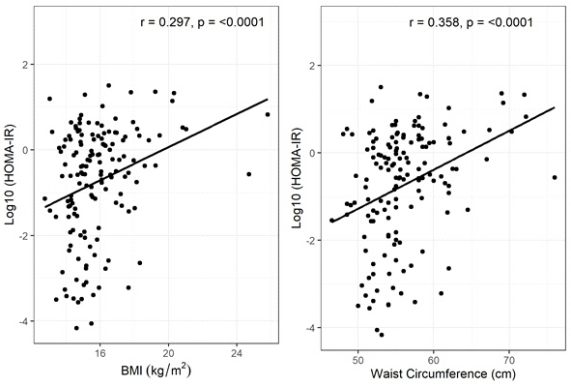

Figure I: Correlation between BMI and WC with HOMA-IR

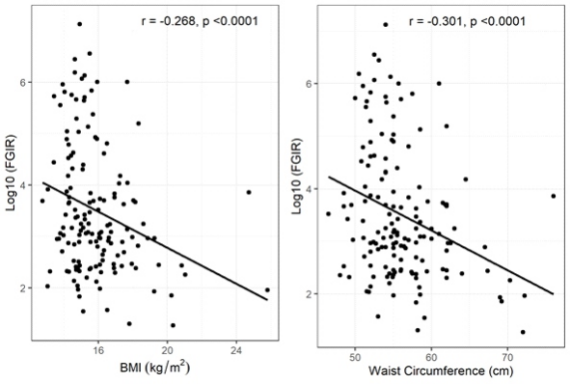

Figure II: Correlation between BMI and WC with FGIR

DISCUSSION

Insulin resistance is a recognized risk factor for the development of non-communicable diseases (NCDs) such as Type 2 diabetes, hypertension, and cardiovascular disease.[21] While no statistically significant difference was observed across genders, the study found that primary school females had an increased likelihood of developing insulin resistance compared to males. This gender-based disparity aligns with similar studies [22,23], and differs from other reports.[24,25] Notably, this study revealed that female subjects had a greater waist circumference than males, which could contribute to the heightened risk of insulin resistance observed among females.[23] Additionally, the onset of puberty is associated with a transient phase of insulin resistance in both genders. Given that the majority of insulin-resistant females were aged 8 years and above, whereas males were relatively younger on average, it is plausible that puberty may account for this divergence.[22]

Adiposity measures, BMI and WC, have been widely acknowledged to be associated with insulin resistance in both adults and children.[26–28] In our study, we found a robust correlation between these adiposity measures and insulin resistance. A stronger correlation was observed between waist circumference and insulin resistance compared to BMI and this portends that WC may be a more accurate marker of insulin resistance.[27]

Interestingly, despite the linear correlation observed between adiposity and insulin resistance, it is noteworthy that only a subset of individuals with increased adiposity (classified as overweight, obese, or abdominally obese) displayed insulin resistance within our categorized analysis. This finding underscores the heterogeneous nature of adiposity, indicating that not all individuals with increased adiposity manifest identical metabolic profiles.[27] Consequently, it becomes evident that additional factors beyond adiposity must be considered to comprehend the development of insulin resistance within our study population.

Although not statistically significant, subjects who were insulin resistant were found to have higher levels of adiponectin compared to those without insulin resistance. This is inconsistent with previous studies reporting lower adiponectin levels in individuals with insulin resistance, including both adult and children.[4,12,29,30] After adjustment for potential confounders, an increase in adiponectin was associated with decreased odds of insulin resistance (Table 4). Adiponectin is renowned for its insulin-sensitizing properties and is generally reduced in conditions associated with insulin resistance, such as Type 2 diabetes and obesity.[1,3] One plausible explanation for this weak relationship could be attributed to adiponectin resistance, which has been increasingly recognised in some individuals and animal models with insulin resistance.[31–34]Furthermore, adiponectin circulates in different forms, including high molecular weight (HMW) oligomers, medium molecular weight hexamers, and low molecular weight (LMW) trimers.[1] The HMW isoform of adiponectin is closely linked to insulin sensitivity, whereas the effects of the LMW isoform may be less pronounced.[1] Interestingly, studies have shown lower HMW adiponectin levels in African-American individuals compared to European-Americans, despite similar total adiponectin levels.[35] These findings suggest potential genetic differences in the distribution of adiponectin isoforms.[36] Therefore, it is plausible that the higher adiponectin levels observed in our insulin-resistant group might be influenced by an increase in the LMW isoform. Further research is needed to investigate the potential relationship between adiponectin polymorphism and insulin resistance in this unique population.

This research work has several strengths. Firstly, it addresses an underexplored aspect by investigating the relationship between adiponectin and insulin resistance in Nigerian young children, an area that has received limited attention in the current literature. By bridging this research gap, the study offers valuable insights into the potential significance of adiponectin in the management of non-communicable diseases (NCDs) within the

African population. Furthermore, the research contributes to the broader comprehension of adiponectin's biological functions and clinical implications, thereby holding substantial implications for preventive healthcare strategies aimed at tackling NCDs.

Limitations

One potential limitation of this study is its restricted scope to a particular geographical location or population, which may raise concerns regarding the generalizability of the findings to other regions or ethnic groups. Additionally, the absence of puberty assessment within the studied population is another potential limitation. Puberty significantly influences physiological changes related to adiponectin and insulin resistance. Its omission introduces the possibility of confounding variables which could affect the outcome of this study.

In conclusion, this study provides compelling insights into the complex interplay between serum adiponectin and insulin resistance among Nigerian primary school children. While a weak relationship between adiponectin and insulin resistance or adiposity was observed, a significant and positive association emerged between insulin resistance and adiposity, as measured by BMI and WC. These findings emphasize the utility of adiposity indicators in identifying insulin resistance among children. By elucidating the intricate interconnections between adiponectin, insulin resistance, and adiposity in young school children, this study makes a significant contribution to the existing body of knowledge, enriching our understanding of the underlying mechanisms and potential clinical implications involved.

Recommendations

1. Future studies should incorporate the assessment of puberty status in children. This would help elucidate the influence of puberty on the observed physiological changes related to adiponectin and insulin resistance.
2. The potential role of adiponectin isoforms should be investigated and genetic factors explored to determine their impact on adiponectin and insulin resistance.

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Authorship Contribution

CAN, HO, COI, ASN and TOU conceptualized and designed the study. CAN and ACO contributed to the implementation of the project and revision of the manuscript. All authors were involved in the writing and revision of the manuscript. The authors read, approved the final manuscript and agree to be accountable for all aspects of the work.

Data Availability: The data used to support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of Interest: None declared.

Ethical Approval: The study was approved by the Ethical Committee of Nnamdi Azikiwe University Teaching Hospital, Nnewi, Anambra State with reference number: NAUTH/CS/66/VOL.14/VER.3/194/2021/042. Informed consent and assent were obtained from caregivers and children above 6 years of age.

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