Research Article

Impact of Family Background of Cardio-Metabolic Disorders and Associated Risk Factors on Total Adiponectin in Children

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Abstract

Background: Adiponectin is a novel hormone with unique biologic functions. Objective: Evaluating adiponectinpattern among children with a family history of cardio-metabolic diseases and risk factors may shed insight into the pathophysiologic mechanism behind these diseases among those at risk. **Methods:** 101 healthy children, aged 4 to 12 years, were enrolled in this study. Family history of diabetes, hypertension, obesity in both first and second degree relatives were established using Interviewer-administered questionnaires to the study participants' caregivers. Other data collated include the smoking history, occupation and highest educational attainment of the caregivers and birth weight of the study participants. Venous blood samples were assayed foradiponectin using ELISA kits. Data were analyzed using SPSS software version 21 with the significance level for tests of associations done set at $p<0.05$. **Results:** Of 101 children, 53 subjects were males (52.5%) with a male to female ratio of 0.9:1. The mean age of all subjects was 7.8 ± 2.3 years. Children with a positive family history of type 2 diabetes mellitus, hypertension and obesity had higher mean adiponectin values than those without a family history, but these differences were not statistically significant. A negative trend was observed among subjects with a positive history of smoking and increased birth weight ($p>0.05$). No association was detected between adiponectin level and socioeconomic class. **Conclusion:** Future related studies conducted among subjects of African ancestry should explore the role of adiponectin resistance in the progression of cardio-metabolic diseases.

Keywords: Adiponectin; Children; Familial; Off-spring; African; Cardio-metabolic disorders; Obesity; Body mass index; Type 2 diabetes mellitus; Hypertension; Cardiovascular disorders; Atherosclerosis; Lipid disorders; Adipokine; Nigeria; Endocrinology

Introduction

Adiponectin gene is located at chromosome 3q27 of the human gene. [1] The translation of this gene yields a 244 amino-acid adipose-tissue protein named adiponectin which is recognized as the most abundant adipokine in the human body. Since its discovery, three isoforms have been isolated, namely Low Molecular Weight (LMW) trimers, Medium Molecular Weight (MMW) hexamers, and High Molecular Weight oligomers (HMW). [2] Together, these isoforms form total adiponectin with HMW oligomers proven to have the highest biologic potency. [2,3]

Adiponectin greatly enhances insulin sensitivity in target tissues. [4] It also has both anti-inflammatory and anti-oxidative properties, boosting a favorable lipid profile. [5] These biologic functions play an essential role in modulating certain chronic non-communicable diseases whose pathophysiologic mechanisms are in direct contradistinction to adiponectin functions. Some of these diseases include type 2 diabetes mellitus, cardiovascular diseases, and obesity-related illnesses, with most comparative researches demonstrating an inverse relationship between the aforementioned diseases and blood adiponectin levels. [6-9]

Several factors can regulate blood adiponectin levels. Higher adiponectin concentrations are observed in young children of prepubertal age. [10] Similarly, female gender and normal body mass indexes are associated with an increased adiponectin blood level. [11,12] Ethnicity also plays a crucial role, further demonstrating the impact of varied individual genomes on blood adiponectin level and function. [13,14] Notably, several studies have shown adiponectin heritability to account for 30%-93% of blood pattern. [15-19] In one of such studies conducted among African-Americans, adiponectin heritability pattern accounted for as high as 82% of its blood variability. [18] However, this study was confounded by mixed ancestry of European descent. A more recent study carried out among Afro-Caribbean populations in Tobago and primarily of West African descent reported a 33.2% influence on blood distribution. [20] Since lower adiponectin

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values is a risk factor of Type 2 diabetes mellitus, cardio-metabolic disorders and obesity-related illnesses, the above findings on adiponectin heritability on its blood distribution do shed a profound insight behind the increased risk of these diseases among offspring with a positive family history.

Thus, understanding the impact of a family history of these diseases on the blood adiponectin distribution of our study participants in apparent healthy state can add to the growing body of knowledge that seeks to comprehend adiponectin role in the evolution of associated metabolic diseases.

Materials and Methods

This study was carried out in Nnewi, a cosmopolitan town in Anambra State, Nigeria, where most of its residents are of Igbo ethnicity. 101 apparently healthy children aged 4 to 12 years were randomly recruited from primary schools in Nnewi to participate in this study. The researcher interviewed the caregivers of the study participants to establish a family history of Type 2 diabetes mellitus, hypertension, and obesity in both first and second-degree relatives. We also obtained a history of passive and active smoking within the subjects' residential area and birth weights [Figure 1]. The socioeconomic class was ascertained based on the highest educational attainment and occupation of both parents as described by Oyedeji. [21] Ethical approval from an independent Ethics committee was obtained prior to the start of this study. In addition, informed consent and assent were obtained from the caregivers of the study participants and subjects above six years respectively.

Blood sample collection and adiponectinassay

Five milliliters (5 ml) of venous whole blood was collected from each subject from 7 am to 9 am following an 8 hour overnight fast. The blood was stored in labelled plain sample bottles and spun in a centrifuge for 10 minutes at 3000 revolutions per minute. Two milliliters of the supernatant serum were harvested and stored at-25°C for a month before a two-batch analysis was conducted to avoid loss of bioactivity and contamination of the samples. [22] Total adiponectin was measured using Elabscience Human ADP/Acrp30 (Adiponectin) ELISA kits from Guangdong Science and Technology Industry Park, Wuhan, Republic of China; Catalog No.: E-EL-H0004). The kit's minimum detectable dose was 0.47 ng/ml with a detection range of 0.78-50 ng/ml. The coefficient of variation was <10%.

Statistical Analysis

All statistical analysis was performed using the Statistical Software Package SPSS version 22 (SPSS Inc. Chicago IL, USA). Categorical data were expressed as frequencies and percentages, while continuous data were presented as mean and standard deviations. Descriptive statistics were employed to summarize all socio-demographic characteristics of study participants. For comparison of means of parametric quantitative variables between two groups, student t-test was utilized while one-way analysis of variance (ANOVA) was applied in more than two groups. Data visualizations were obtained with the ggplot2 package in R programming version 3.6.3.[23]

Results

A total of 101 primary school children aged 4 to 12 years were randomly recruited for this study. Of this, 53 (52.5%) were males with a male to female ratio of 0.9:1. The mean age of all subjects was 7.8 ± 2.3 years with no significant difference in age across gender. In all, the body mass indexes of all subjects that participated in this study were within the normal range, with no significant difference observed across both genders. The mean total adiponectin level was 4.51 ± 2.08 g/ml [Table 1].

In Table 2, most of the caregivers reported no history of smoking, whereas the distribution of other reported disease

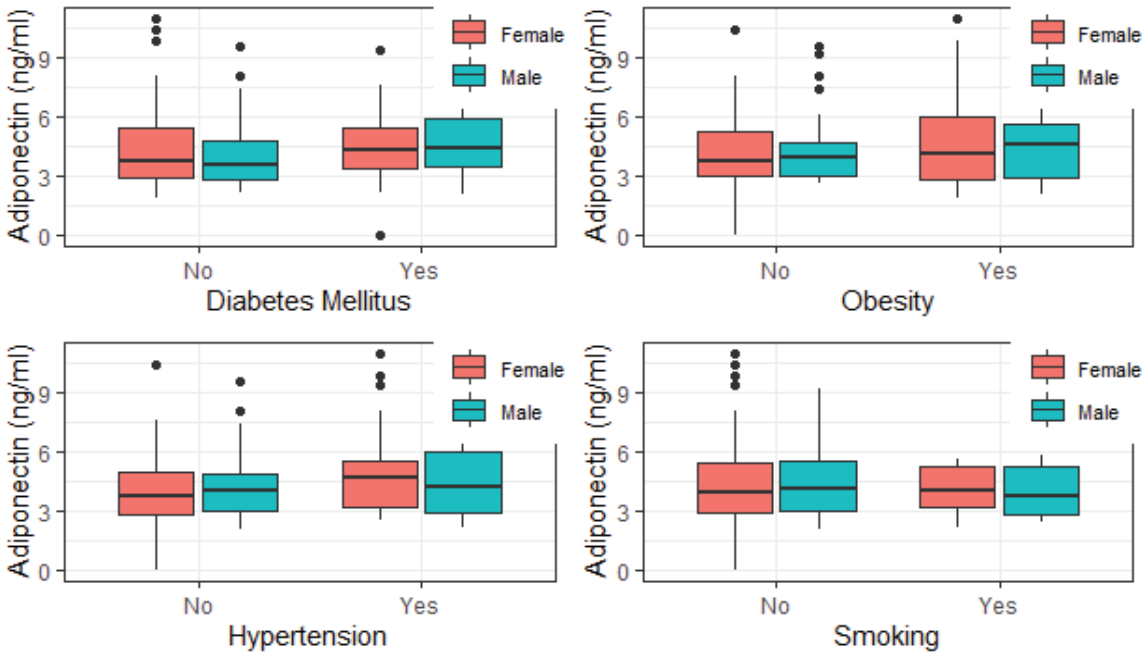

Figure 1: Boxplots showing the different adiponectin values across gender per family history of Type 2 diabetes mellitus, hypertension, obesity and smoking.

conditions was essentially the same. Higher adiponectin values were observed among subjects with a positive family history of Type 2 diabetes mellitus, hypertension and obesity, but this was not significant. In contrast, those with a positive history of smoking had lower adiponectin values [Tables 3 and 4]. No obvious pattern was observed among subjects of different social classes [Table 5].

Table 1: Basic characteristics of all subjects.

	All	Girls	Boys	p
No of Subjects (%)	101 (100)	48 (47.5)	53 (52.5)	0.287
Age (years)	7.8(2.3)	7.57(2.29)	8.15(2.29)	0.207
Weight (kg)	26.06(6.64)	25.14(6.09)	27.07(7.13)	0.144
Height (cm)	127.91(12.99)	126.02(12.33)	126.02(12.33)	0.125
BMI (kgm^{-2})	15.64(1.31)	15.59(1.18)	15.70(1.44)	0.666
Birth weight (kg)	3.23 (0.63)	3.22 (0.67)	3.23 (0.60)	0.941
Adiponectin (ng/ml)	4.51(2.08)	4.59(2.31)	4.45(1.86)	0.729

Table 2: Family history of associated cardio-metabolic disorders and risk factors.

	Cardio-metabolic diseases and risk factors	No history (%)	Positive history (%)
All subjects	Hypertension	49(48.5)	52(51.5)
	Obesity	57(56.4)	44(43.6)
	Type 2 Diabetes	55(54.5)	46(45.5)
	Smoking	84(83.2)	17(16.8)
Males	Hypertension	27(50.9)	26(49.1)
	Obesity	30(56.6)	23(43.4)
	Type 2 Diabetes	30(56.6)	23(43.4)
	Smoking	44(83.0)	9(17.0)
Females	Hypertension	22(45.8)	26(54.2)
	Obesity	27(56.3)	21(43.8)
	Type 2 Diabetes	25(52.1)	23(47.9)
	Smoking	40(83.3)	8(16.7)

Table 3: Distribution of adiponectin (ng/ml) based on family history of cardio-metabolic disorders and risk factors.

	Cardio-metabolic diseases and risk factors	No history (%)	Positive history (%)	p value
All Subjects	Hypertension	4.19(1.95)	4.82(2.16)	0.128
	Obesity	4.42(2.00)	4.63(2.19)	0.612
	Type 2 Diabetes	4.44(2.25)	4.60(1.86)	0.705
	Smoking	4.57(2.13)	4.26(1.83)	0.581
Males	Hypertension	4.30(1.81)	4.59(1.93)	0.576
	Obesity	4.46(2.00)	4.43(1.70)	0.948
	Type 2 Diabetes	4.21(1.92)	4.75(1.77)	0.296
	Smoking	4.46(1.79)	4.40(2.28)	0.937
Females	Hypertension	4.05(2.15)	5.05(2.38)	0.139
	Obesity	4.38(2.04)	4.86(2.65)	0.478
	Type 2 Diabetes	4.72(2.62)	4.45(1.98)	0.688
	Smoking	4.69(2.47)	4.10(1.29)	0.518

Table 4: Distribution of socioeconomic classes of the subjects.

Social Class	All Subjects (%)	Male (%)	Female (%)
Upper	38(37.6)	16(30.2)	22(45.8)
Middle	43(42.6)	22(41.5)	21(43.8)
Lower	20(19.8)	15(28.3)	5(10.4)
Total	101(100)	53(100)	48(100)

Tables 6 and 7 illustrated a higher trend in adiponectin values when the frequency of aggregated reports of a family history of cardio-metabolic diseases and smoking were greater, but this was not significant.

An inverse relationship was demonstrated between the subjects' birth weight and total adiponectin concentrations in both male and female children with correlation values of -0.106; p=0.466 and -0.010; p=0.948 respectively [Figure 2].

Discussion

Although many studies have established a significant influence of adiponectin heritability on blood variability, fewer studies have shown the impact of a family history of associated diseases and the risk factors on the adiponectin profile of the progeny. [24-27] To the best of our knowledge, this research is the first to address this research topic among Nigerian children. Elimination of known confounders, namely age, sex, puberty and increased body mass, was addressed through the random selection of prepubertal age subjects with normal body mass compositions. Adiponectin remains an area of global research interest due to its unique biological functions that possess the vast potential to unlock the nuances behind the pathophysiologic mechanisms and targeted therapy of non-communicable diseases of key public interest. [28,29]

Subjects with a family background of type 2 diabetes mellitus, hypertension, and obesity demonstrated higher mean adiponectin concentrations than their peers who did not share a similar history. Although this was not significant, we considered this paradoxical finding to be intriguing and at variance with other

Table 5: Adiponectin values across different socio-economic classes.

Social Class	All Subjects (SD)	p value	Male (SD)	p value	Female (SD)	p value
Upper	4.83(2.21)		4.79(2.07)		4.86(2.35)	
Middle	4.24(2.06)	0.444	4.01(1.59)	0.351	4.49(2.47)	0.658
Lower	4.50(1.85)		4.72(1.97)		3.84(1.43)	

Table 6: Frequency of aggregated family history of Type 2 diabetes mellitus, hypertension, obesity and smoking among the study participants.

Frequency	All Subjects (%)	Male (%)	Female (%)
0	23(22.8)	14(26.4)	9(18.8)
1	22(21.8)	10(18.9)	12(25.0)
2	31(30.7)	16(30.2)	15(31.3)
3	25(24.8)	13(24.5)	12(25.0)
Total	101(100)	53(100)	48(100)

Table 7: Distribution of adiponectin based on frequency of aggregated family history of Type 2 diabetes mellitus, hypertension, obesity and smoking among the study participants.

Frequency	All Subjects (SD)	p	Male (SD)	p	Female (SD)	p
0	4.32(1.91)		4.24(1.61)		4.44(2.41)	
1	4.41(2.32)	0.768	4.78(2.39)	0.411	4.10(2.32)	0.817
2	4.43(2.33)		3.94(1.94)		4.94(2.67)	
3	4.90(1.7)		5.03(1.52)		4.75(1.94)	

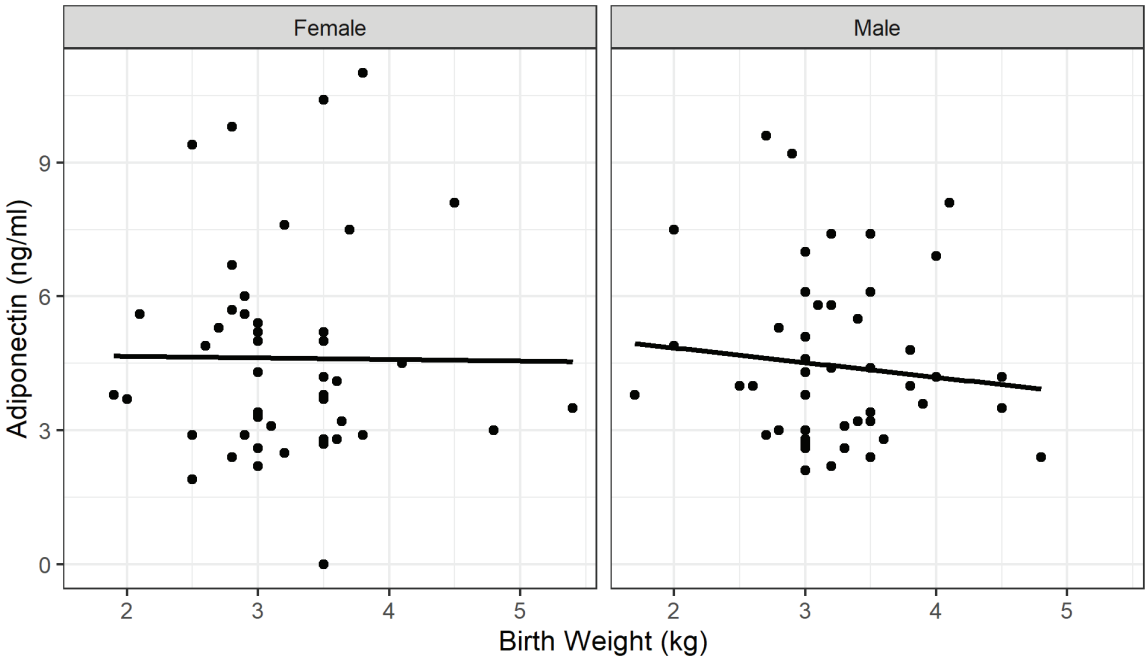

Figure 2: Scatterplots indicating the correlation pattern between birth weight and total adiponectin across gender.

published works. [24–27] An inverse relationship exists between adiponectin and markers of insulin resistance in Type 2 diabetes mellitus and obesity, pro-inflammatory mediators in obesity and atherosclerosis in hypertension. [30-35] Notwithstanding that adiponectin assay was not conducted for other family members with a background the diseases of interest, it stands to reason that a lower adiponectin level should be expected. Therefore, in keeping with adiponectin heritability pattern, which should account for a significant degree of adiponectin distribution in offsprings, a mean lower adiponectin was expected among subjects with a positive family history of type 2 diabetes mellitus, hypertension and obesity, thus providing some rare insight to the transmissibility of these diseases. Finally, lower adiponectin values can serve as a biomarker predicting an increased risk of cardio-metabolic disorders over time among children of apparent good health. [35,36] Hence, the discovery of a paradoxical outcome supports the possibility of an inherent adiponectin resistant state. In severe insulin resistance, receptor insensitivity to adiponectin can lead to hyperadiponectinaemia, which serves as an initial compensatory mechanism; however, persistence of this phenomenon may ultimately desensitiseadiponectin-producing adipocytes leading to lower blood adiponectin values. [23,37-39] Insulin resistance can occur in children with a positive family history of type 2 diabetes mellitus. [25,40] An alternative explanation to the paradoxical finding obtained may be attributed to a re-distribution in the quantitative values of the three isomeric forms of adiponectin in favor of the isomers with lesser biologic activity namely the trimer and hexamers, leading to a resistant state which can trigger an increase in hormone production. [41,42]

In this study, birth weight negatively correlated with adiponectin across both genders, but this was statistically insignificant. This observation is similar to the findings reported by Fonseca et al. [43] but is dissimilar to past studies, which demonstrated varied reports on the association of serum adiponectin levels and birth weights. [44-47] Studies that observed a significant positive correlation with increasing birth weight adduced that subjects with low birth weights have a greater risk of developing type 2 diabetes and cardiovascular diseases later on in adulthood than those with normal birth weights. [45,46,48] A similar explanation was proposed in studies that found a significant negative correlation with increasing birth weight. [44,47] It was speculated that large for gestational age birth weights could be associated with early obesity postnatally with a potential increase in cardiovascular and metabolic risk in adulthood. [49–51] The negative trend observed between birth weight and adiponectin in our study may also be related to the incidental discovery that the mean birth weight of subjects with a positive family history of Type 2 diabetes mellitus was significantly lower than those without a similar family history. Reasons for the higher birth weight among those with a family background of type 2 diabetes mellitus remains unknown.

Smoking, both active and passive, constitute a potential risk factor for cardio-metabolic illnesses. Smoking triggers the onset of atherosclerosis along the vasculature linings of exposed subjects. The present study found no statistically significant association between the family history of smoking and adiponectin levels. The observation is in agreement with the findings of Khanolkar and colleagues [52] from Sweden and Punthakee et al. [33] from Canada. It however differs from those of Papaioannou and co-workers [53] from Greece, who demonstrated a significant decrease in adiponectin level of children with a positive family history of smoking. Several other studies including an expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents, have consistently demonstrated the adverse effect of cigarette smoking, whether passive or active. [54-57] Also, an experimental animal study illustrated that smoking inhibits adiponectin secretion by reducing mRNA expression. [58] The lack of significance in this study may be explained by the lower

proportion of subjects with a positive smoking history. This limitation can confer statistically a reduced power to detect any difference if any.

Past research has demonstrated a paucity of evidence concerning the relationship between adiponectin levels and socioeconomic status. We found no association and this corroborates with those of Lausten-Thomsen and colleagues [59] and Khanolkar et al. [52], who both reported no significant difference in adiponectin across different socioeconomic classes. In contrast, Buchan et al. [30] and Davis and co-workers [60] observed significantly lower mean adiponectin values among subjects from the lower class than those from the upper class. However, it should be noted that these studies had utilized different methodological approaches in classifying social classes at variance to that used in this study, which may explain the conflicting results. Several published works have observed an increased incidence of non-communicable diseases such as hypertension, obesity, metabolic syndrome and type 2 diabetes mellitus and their risk factors among subjects from the lower class. [61-63] Cited reasons include reduced physical activity, poor dietary patterns, smoking and alcohol consumption. [63]

The validity of the self-reported family history of evaluated diseases and the subjects' birth weight could not be verified through existing health care records. In Nigeria, the prevalent culture of poor record-keeping and paper records poses a significant undertaking in confirming the validity of the reported histories among family members. Notwithstanding, this limitation does not invalidate completely the reports given as the rich social culture inherent in our society ensures that family members are mostly aware of their closest family unit's health conditions. More so, most of the caregivers in this study are educated as shown by the distribution of social classes, thus can recall their wards' birth weight values and understand the concept of the diseases of interest.

Conclusion

More exploratory studies are needed to investigate adiponectin distribution in subclinical states, particularly among children at risk. A key area of interests as it concerns our unique ethnicity should include adiponectin resistance and the distribution of its various isoforms.

Competing Interests

The authors declare that they have no competing interests.

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