Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.47750/jptcp.2023.30.06.047

Fetuin-A levels and Insulin Resistance in Obese and Non-Obese Iraqi Children

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Submitted: 17 February 2023; Accepted: 20 March 2023; Published: 02 April 2023

ABSTRACT

The study's objective was to assess fetuin-A serum levels in persons with and without obesity and their potential relationships with other laboratory and clinical factors. In this case-control study, 60 obese Iraqi children (30 boys and 30 girls) participated, with 30 non-obese Iraqi children serving as the control group (15 boy, 15 girl). The subject's age ranges from nine to sixteen. Obese subjects had higher serum fetuin-A levels than lean subjects. Significant correlations were seen between greater serum fetuin-A levels and metabolic syndrome patients. In obese children with IR, there are positive correlations between Fetuin-A and SBP, DBP, weight, BMI, FBG, HOMA-IR, TG, and LDL-C, but a negative significant association with HDL-C. It can conclude that obese kids have higher fetuin-A concentrations than normal kids. These results support the idea that fetuin-A and Met S have a functionally relevant relationship in obesity and play a significant role in the pathophysiology of metabolic disease in obese children. Insulin resistance and other characteristics of the Metabolic syndrome, Significant correlations exist between fetuin-A and other factors, such as elevated BMI, elevated blood pressure, and lowered HDL-C.

Keywords: *Fetuin A, Insulin Resistance , Lipid Profile, Obesity*

INTRODUCTION

The prevalence of high-calorie diets and sedentary lifestyles in children is gradually increasing the incidence of obesity in this population. Obesity, dyslipidemia, hypertension, and a change in glucose metabolism are all aspects of the metabolic syndrome(Demiral, 2021). The chronic disease of obesity is multifactorial and is impacted by a number of genetic, endocrine, and psychological variables(Organization, 2012).

The term "obesity" refers to an excessive amount of body fat, which is typically measured using the body mass index . A person is considered obese if their BMI is equal to or higher than 30 kg/m2. Compared to patients with peripheral obesity, those with visceral/central obesity are more prone to cvd and metabolic diseases(Rodríguez et al., 2007). In general, metabolic alterations linked to obesity and weight gain raise the risk of non-communicable diseases(Scorletti, Calder and Byrne, 2011).

The hepatic fat and protein metabolism is altered by obesity, particularly visceral obesity. Because the presence of increased adipose tissue makes it easier for proinflammatory mediators like macrophages and cytokines to infiltrate the adipose tissue, obesity is strongly linked to the buildup of liver fat that could lead to non-alcoholic fatty liver disease(Weston et al., 2005).

Obesity and the medical state known as insulin resistance (IR) are closely related. Clinically speaking, it is described as the inability of a known quantity of exogenous or endogenous insulin to boost glucose absorption and utilization in a person to the same extent that it does in a normal population.(Tagi, Giannini and Chiarelli, 2019),(Lebovitz, 2001). Circulating insulin antagonists, aberrant beta cell secretory products, The three primary factors that lead to insulin resistance are target tissue defects in insulin action. Regarding obesity and non-insulin-dependent diabetic mellitus Obese children and adolescents of all ages (T2D) exhibit a significant association between IR and a higher prevalence of T2DM(Caprio, 2002),(Tagi, Giannini and Chiarelli, 2019).

Fetuin-A-Alpha-2-Heremans-Schmid glycoproteins (2HSG), also referred to as Fetuin A, is a plentiful circulating glycoprotein released by the liver, tongue, and placenta to a lesser amount. It is a 64-kDa glycoprotein, and human serum contains quite large amounts of it (300–1000 g ml)(Stefan et al., 2006). Because fetal serum had the largest quantity of this protein, fetal serum received its name when it was initially identified in 1944 in bovine calves(Trepanowski, Mey and Varady, 2015). Two polypeptide chains, a big A-chain and a tiny B-chain, a short connecting peptide, and an interchain disulfide bridge, collectively make up the 2HSG molecule in humans. One mRNA transcript encodes both chains, and the linking peptide is only partially or not transcribed by the other chain,(Pérez-Sotelo et al., 2017).

It has been demonstrated that phosphorylation of 2HSG is particularly important for its IR tyrosine kinase inhibitory action. It has been established that 2HSG also affects adipose tissue (AT), inducing whole-body insulin resistance by promoting the release of pro-inflammatory cytokines from adipocytes and macrophages. As a result, it was discovered that circulating levels of 2HSG were associated with poor glucose tolerance, insulin resistance, and T2DM in people, demonstrating its function as a biomarker for inflammatory and chronic diseases(Trepanowski, Mey and Varady, 2015).

In the epidemiologic literature, associations between Fet-A level and factors associated to obesity are frequently observed. (Ou et al., 2012)According to them, the association between fetuin A and obesity can be explained by the fact that obesity is often associated with fat accumulation in the liver, which is associated with upregulation of fetuin A secretion and insulin resistance and type May lead to an increase in 2. Diabetes. FetA is associated with abnormal insulin receptor signaling, Toll-like receptor 4 (TLR4) activation, macrophage migration and polarization, adipocyte dysfunction, triacylglycerol accumulation in hepatocytes, liver inflammation, and fibrosis. Given that they are related, FetA may have a causal role in the development and progression of obesity-related complications.(Khadir et al., 2018) It has been demonstrated that diet, surgery, and aerobic activity are all effective ways to reduce FetA(Coen, Carnero and Goodpaster, 2018).

The study's objective was to assess fetuin-A serum levels in persons with and without obesity and their potential relationships with other laboratory and clinical factors.

MATERIALS AND METHODS

Sixty obese Iraqi children (30 boys, 30 girls) participated in the case-control study, and 30 non-obese Iraqi children (15 boys, 15 girls) served as the control group. The topic is between the ages of (9 to 15). Between November 2021 and the end of August 2022, this work was completed.

Measurements: Anthropometric Assessment

The clinical evaluation included a number of anthropometric measurements.

1- Determining blood pressure in accordance with WHO recommendations(Subcommittee and Organization, 1999).

2- Body Mass Index (BMI) calculation: performed in accordance with (Barlow, no date)

Biochemical Parameters Assessment

- Trinder, P. Modified assay method for estimating serum glucose employing (Trinder, 1969)
- Serum Triacylglycerol (TG): This method is based on the enzymatic hydrolysis of triglycerides to glycerol and (F.F.A) by (L.P.L)(Fossati and Prencipe, 1982).
- Serum HDL is directly determined using the accelerator selective detergent approach .(Burstein, Scholnick and Morfin, 1970)
- Insulin levels were measured using the DRG insulin ELISA kit (JUDZEWITSCH et al., 1982) and insulin resistance was calculated using the formula HOMA-IR= (fasting insulin (U/mL)) (fasting glucose (mmol/L))/ 22.5) was used to evaluate. (Tara, Jonathan and David, 2004).
- A Biosource/USA ELISA kit was used to determination of the fetuin-A levels.

Statistical Analysis

The 2010 Excel work sheet for Microsoft Office was used for the statistical work. statistically significant and highly significant, respectively, based on the p-values at $P<0.01$ and $P<0.05$. All analyzed parameters are related using Pearson's connection coefficient (r).

RESULTS

Figure (1): shown the distribution of Fetuin-A in children with obesity between boys and girls in all participant.

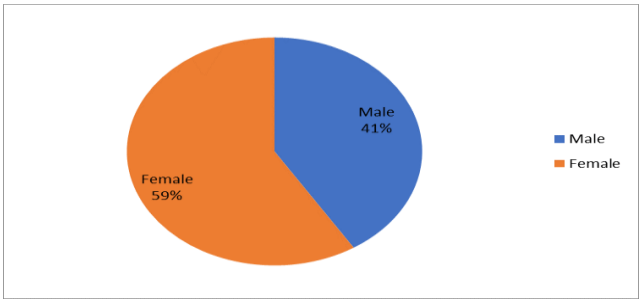

FIGURE 1: Distribution of Fetuin-A level in children with obesity between boys and girls in all participant.

Anthropometric measurements between obese children and normal control are listed in table 1. There were no differences between these two groups : Age , Hight while there were significant elevation in SBP ,DBP ,FBG ,Insulin ,HOMA-IR , TC , HDL-C ($P<0.05$) and highly significant elevation : weight , BMI , fetuin -A , TG and LDL-C($p<0.001$) .

TABLE 1: Mean±SD of the study groups between obese children and normal control.

Variables	Obese Children Mean±SD (n=60)	Control Mean±SD (n=30)	P Value
Age (Years)	12.44±3.58	11.92±3.66	0.108
SBP(mmHg)	130.00±2.76	110.00±2.75	*0.05
DBP(mmHg)	75.00±5.00	65.10±2.02	0.05 *
Kg)(Weight	50.75±4.95	38.76±2.83	0.01**
High (cm)	141.14±4.85	123.56±3.20	0.161
BMI (Kg/m2)	28.44±1.32	23.10±2.45	0.01**

FBG (mg/dl)	108.56±5.65	80.45±5.41	0.05*
Insulin (µU/ml)	16.62±2.74	9.81±2.25	0.05*
HOMA-IR	5.45±1.02	2.11±0.73	0.05*
Fetuin-A (ng/ml)	29.52±2.82	16.55±4.62	0.01**
TC (mg/dl)	173.01±10.31	138.22±10.15	0.05*
TG (mg/dl)	163.02±19.55	90.51±5.56	0.01**
HDL-C (mg/dl)	41.93±2.14	58.41±2.11	0.05*
LDL-C (mg/dl)	112.42±12.21	80.55±9.75	0.01**

As detailed in table 2, there were highly significant elevation in TAG ,HDL-C (P<0.01) in the obese children with IR compared to obese children without IR, In addition significant elevation s in SBP , DBP , W.t, FBG , Insulin , HOMA-IR, and LDL-C were found in the obese children with IR compared with obese children without IR table 2.

TABLE 2: Mean±SD between obese children with and without IR :

Variables	Mean±SD		P Value
	Obese Children with IR	Obese Children without IR	
Gender (boy/girl)	)16/14(	(15/15)	-
SBP(mmHg)	135.00±5.25	112.00±5.00	0.05*
DBP(mmHg)	70.38±3.75	65.88±20	0.05*
Kg)(Weight	52.55±5.55	33.03±4.25	0.05*
High (cm)	126.21±4.12	113.25±5.26	0.231
BMI (Kg/m2)	27.52±2.14	23.27±2.01	0.70
FBG (mg/dl)	101.25±5.41	85.8±5.11	0.05*
Insulin (µU/ml)	14.42±3.69	11.5±3.25	0.05*
HOMA-IR	5.10±1.33	2.59±1.92	0.05*
Fetuin-A (ng/ml)	36.31±4.41	28.5±3.82	0.02
TC (mg/dl)	170.25±10.12	165.81±9.91	0.124
TAG (mg/dl)	168.20±10.51	110.17±8.55	0.01**
HDL-C (mg/dl)	42.23±3.02	55.21±3.25	0.01**
LDL-C (mg/dl)	115.25±10.70	82.25±7.45	0.05*

As detailed in Table 3 showing the positive Correlations between Fetuin-A, with SBP, DBP, weight, BMI, FBG, HOMA-IR, TAG, and C LDL-C in obese children with IR, while negative significant correlation with HDL-C.

TABLE 3: Correlations between Fetuin-A and different Variables in obese children with (IR).

Parameters	Fetuin	
	r	P
Age (Years)	0.122	0.136
SBP(mmHg)	0.928	0.01**
DBP(mmHg)	0.723	0.01**
Kg)(Weight	0.321	0.05
High (cm)	0.214	0.167
BMI (Kg/m2)	0.516	0.05*
FBG (mg/dl)	0.506	0.05*
Insulin (µU/ml)	0.223	0.356
HOMA-IR	0.925	0.01**

J Popul Ther Clin Pharmacol Vol 30(6):e414–e420; 02 April 2023.

TC (mg/dl)	0.333	0.125
TAG (mg/dl)	0.301	0.05*
HDL-C (mg/dl)	-0.313	0.05*
LDL-C (mg/dl)	0.333	0.05*

DISCUSSION

Obesity is the most common risk factor for metabolic syndrome (MS), which is characterized by weight gain, hypertension, dyslipidemia, and impaired glucose metabolism.(Ix, Shlipak, et al., 2006). The release of adipose tissue-derived mediators, particularly proinflammatory cytokines, is prompted by obesity, which is also a significant elicitor of diabetes linked with IR.(Pérez-Sotelo et al., 2017).

Fetuin-A contributes to the etiology of IR by inhibiting insulin receptor activation by proteolyzing the -chain and constitutively stimulating the activity of insulin receptor tyrosine kinase, which causes a breakdown in the insulin cascade pathways . Obesity and insulin resistance interact in the development of type 2 diabetes. (Bourebaba and Marycz, 2019)Studies on the tissue-specific effects of fetuin inhibition on the human insulin receptor tyrosine kinase or alternative pathway may shed new light on the regulatory mechanisms behind dyslipidemia, hypertension, and abnormal glucose metabolism . (Ix, Chertow, et al., 2006)

Fetuin-A levels were greater in metabolically healthy obese children than in non-obese controls, as shown in table 1. This finding suggests that juvenile obesity may be linked to a rise in fetuin-A levels even in the absence of IR.. However, Nagwa A.I et al., 2012 (Ismail et al., 2012) found a discernible difference in fetuin-A levels between obese and normal weight children.

In comparison to children who were not fat, table 2 indicated a strong association between fetuin-A and IR. According to Christian et al., 2008(Reinehr and Roth, 2008), A lifestyle intervention for overweight children resulted in a significant decrease in fetuin-A levels and lower insulin resistance. According to this study, obese kids with MS had higher levels of fetuin-A than obese kids without MS. According to studies done on adults(Xu et al., 2011), fetuin-A has a correlation with various MS characteristics, including blood pressure, FBG, TG, LDL-C, and HDL cholesterol. Previous studies linking fetuin-A to insulin resistance in animal models showed that fetuin-A inhibits the effects of insulin on peripheral tissues by interacting with insulin receptors (Kalabay et al., 1998) .

These results support the theory that fetuin A plays a role in the pathogenesis of human MS and insulin resistance. Fetuin-A appears to interfere with insulin action on peripheral tissues through interaction with insulin receptors. (Vionnet et al., 2000)hypothesized that fetuin-reduction A's of adiponectin production may be the cause of the link between fetuin-A and the MS(Hennige et al., 2008). It has recently been shown that fetuin-A inhibits the synthesis of adiponectin in both humans and animals. An key factor in whole-body sensitivity and cardiovascular disease, adiponectin is an adipocytokine. Additionally, low grade inflammation caused by fetuin-A [Hennige., 2008] is linked to the MS and an atherogenic lipid profile.(Kadowaki et al., 2006),(Dahlman et al., 2004).

In conclusion, obese kids have higher fetuin-A concentrations than normal kids. A results support the idea that S. fetuin A and MS have a functionally relevant relationship in obesity and play an important role in the pathophysiology of metabolic diseases in obese children. Insulin resistance and other features of MS such as increased BMI, increased blood pressure, and decreased HDL cholesterol levels were also significantly correlated with fetuin A.

REFERENCES

1. Demiral, M. (2021) ‘A novel diagnostic tool in determining insulin resistance in obese children: Triglyceride/HDL ratio’, J Surg Med, 5(11), pp. 1144–1147.
2. Organization, W. H. (2012) ‘Fact Sheet No. 311 (May 2012)’.
3. Rodríguez, A. et al. (2007) ‘Visceral and subcutaneous adiposity: are both potential

therapeutic targets for tackling the metabolic syndrome?', Current pharmaceutical design, 13(21), pp. 2169–2175.
4. Scorletti, E., Calder, P. C. and Byrne, C. D. (2011) 'Non-alcoholic fatty liver disease and cardiovascular risk: metabolic aspects and novel treatments', Endocrine, 40, pp. 332–343.
5. Weston, S. R. et al. (2005) 'Racial and ethnic distribution of nonalcoholic fatty liver in persons with newly diagnosed chronic liver disease', Hepatology, 41(2), pp. 372–379.
6. Tagi, V. M., Giannini, C. and Chiarelli, F. (2019) 'Insulin resistance in children', Frontiers in endocrinology, 10, p. 342.
7. Lebovitz, H. E. (2001) 'Insulin resistance: definition and consequences', Experimental and clinical endocrinology & diabetes, 109(Suppl 2), pp. S135–S148.
8. Caprio, S. (2002) 'Insulin resistance in childhood obesity.', Journal of pediatric endocrinology & metabolism: JPEM, 15, pp. 487–492.
9. Stefan, N. et al. (2006) 'α2-Heremans-Schmid glycoprotein/fetuin-A is associated with insulin resistance and fat accumulation in the liver in humans', Diabetes care, 29(4), pp. 853–857.
10. Trepanowski, J. F., Mey, J. and Varady, K. A. (2015) 'Fetuin-A: a novel link between obesity and related complications', International journal of obesity, 39(5), pp. 734–741.
11. Pérez-Sotelo, D. et al. (2017) 'Visceral and subcutaneous adipose tissue express and secrete functional alpha2hsglycoprotein (fetuin a) especially in obesity', Endocrine, 55, pp. 435–446.
12. Ou, H.-Y. et al. (2012) 'Increased fetuin-A concentrations in impaired glucose tolerance with or without nonalcoholic fatty liver disease, but not impaired fasting glucose', The Journal of Clinical Endocrinology & Metabolism, 97(12), pp. 4717–4723.
13. Khadir, A. et al. (2018) 'Fetuin-A levels are increased in the adipose tissue of diabetic obese humans but not in circulation', Lipids in health and disease, 17, pp. 1–13.
14. Coen, P. M., Carnero, E. A. and Goodpaster, B. H. (2018) 'Exercise and bariatric surgery: an effective therapeutic strategy', Exercise and sport sciences reviews, 46(4), p. 262.
15. Subcommittee, G. and Organization, W. H. (1999) 'International Society of Hypertension guidelines for the management of hypertension', J Hypertens, 17(2), pp. 151–183.
16. Barlow, S. E. (no date) 'Expert, Committee.(2007). Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: Summary report', Pediatrics, 120(4), pp. 164–192.
17. Trinder, P. (1969) 'Determination of glucose in blood using glucose oxidase with an alternative oxygen acceptor', Annals of clinical Biochemistry, 6(1), pp. 24–27.
18. Fossati, P. and Prencipe, L. (1982) 'Serum triglycerides determined colorimetrically with an enzyme that produces hydrogen peroxide.', Clinical chemistry, 28(10), pp. 2077–2080.
19. Burstein, M., Scholnick, H. R. and Morfin, R. (1970) 'Rapid method for the isolation of lipoproteins from human serum by precipitation with polyanions', Journal of lipid research, 11(6), pp. 583–595.
20. Judzewitsch, R. G. et al. (1982) 'Chronic chlorpropamide therapy of noninsulin-dependent diabetes augments basal and stimulated insulin secretion by increasing islet sensitivity to glucose', The Journal of Clinical Endocrinology & Metabolism, 55(2), pp. 321–328.
21. Tara, M. W., Jonathan, C. L. and David, R. M. (2004) 'Use and abuse of HOMA modeling', Diabetes care, 27(6), pp. 1487–1495.
22. Ix, J. H., Shlipak, M. G., et al. (2006) 'Association between human fetuin-A and the metabolic syndrome: data from the Heart and Soul Study', Circulation, 113(14), pp. 1760–1767.
23. Bourebaba, L. and Marycz, K. (2019) 'Pathophysiological implication of fetuin-A glycoprotein in the development of metabolic disorders: a concise review', Journal of Clinical Medicine, 8(12), p. 2033.
24. Ix, J. H., Chertow, G. M., et al. (2006) 'Fetuin-A and kidney function in persons with coronary artery disease—data from the Heart and Soul Study', Nephrology Dialysis Transplantation, 21(8), pp. 2144–2151.
25. Ismail, N. A. et al. (2012) 'Fetuin-A levels in obesity: differences in relation to metabolic syndrome and correlation with clinical and laboratory variables', Archives of Medical Science, 8(5), pp. 826–833.
26. Reinehr, T. and Roth, C. L. (2008) 'Fetuin-A and its relation to metabolic syndrome and fatty liver disease in obese children before and after weight loss', The Journal of Clinical Endocrinology & Metabolism, 93(11), pp. 4479–4485.
27. Xu, Y. et al. (2011) 'Serum fetuin-A is correlated with metabolic syndrome in middle-aged and elderly Chinese', Atherosclerosis, 216(1), pp. 180–186.
28. Kalabay, L. et al. (1998) 'Human recombinant alpha2-HS glycoprotein is produced in insect cells as a full length inhibitor of the insulin

receptor tyrosine kinase', Hormone and metabolic research, 30(01), pp. 1–6.
29. Vionnet, N. et al. (2000) 'Genomewide search for type 2 diabetes–susceptibility genes in French Whites: evidence for a novel susceptibility locus for early-onset diabetes on chromosome 3q27-qter and independent replication of a type 2–diabetes locus on chromosome 1q21–q24', The American Journal of Human Genetics, 67(6), pp. 1470–1480.
30. Hennige, A. M. et al. (2008) 'Fetuin-A induces cytokine expression and suppresses adiponectin production', PloS one, 3(3), p. e1765.
31. Kadowaki, T. et al. (2006) 'Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome', The Journal of clinical investigation, 116(7), pp. 1784–1792.
32. Dahlman, I. et al. (2004) 'α 2-Heremans–Schmid glycoprotein gene polymorphisms are associated with adipocyte insulin action', Diabetologia, 47, pp. 1974–1979.