A Study of Adiponectin/Leptin Ratio in Adult Males with Metabolic Syndrome

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ABSTRACT:

BACKGROUND:

Metabolic syndrome is a disorder of energy utilization and storage. It is a multi-component disease brought on by a combination of life style and environmental factors, with some populations exhibiting a genetic predisposition and type 2 diabetes. It is marked by abdominal obesity, elevated levels of triglyceride, low levels of HDL (good) cholesterol, high blood pressure and high blood sugar levels. Metabolic syndrome is a significant risk factor for the development of both type 2 diabetes and heart disease, also associated with fatty liver, and polycystic ovary syndrome. Recently two adipocytokines secreted from visceral adipose tissue leptin and adiponectin, have been recognized as key regulators of various metabolic disorder.

OBJECTIVE:

The objective of this study was to use the adiponectin to leptin ratio as a parameter and a lab index to predict metabolic syndrome across adult males.

METHOD:

A total of 82 adult males with mean age of (38.47 $\pm$ 9.27) were included in the study. Fifty eight (58) adult males were the metabolic syndrome group depending on the presence of any 3 out of 5 of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII) criteria which include the following: (central obesity $\geq$ 102cm, triglyceride $\geq$150 mg/dl, HDL-Cholesterol <40 mg/dl, blood pressure $\geq$ 130/85 mmHg and fasting serum glucose $\geq$100 mg/dl) as compared to twenty four (24) healthy adult males as the control group.

RESULT:

The findings showed that adiponectin/ Leptin ratio is significantly lower in metabolic syndrome adult males as compared to healthy adult males.

CONCLUSION:

In conclusion data indicate that adiponectin/leptin ratio is a plausible index for detecting the presence of metabolic syndrome in adult males.

KEY WORDS: metabolic syndrome, cytokines, leptin, & adiponectin.

INTRODUCTION:

Metabolic syndrome is also known as syndrome X, cardio-metabolic syndrome, Insulin resistance syndrome. It was first recognized in the 1960 and information about it was first published in 1990. Metabolic syndrome and pre diabetes appear to be the same disorder, just diagnosed by different set bio markers (Gill H, et al, 2005). Several groups define metabolic syndrome including the World Health Organization (WHO) (Alberti K, et al, 1998), the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) (third report of the NCEP ATP III) and the International Diabetes Federation (IDF). They have proposed criteria to define this syndrome. The criteria serve as a simple tool for identifying patients at higher risk of diabetes and coronary heart disease. Metabolic syndrome is a significant risk factor for the development of both type 2 diabetes and heart disease; two of the most common and important diseases today. Metabolic syndrome is associated with fat accumulation in the liver (fatty liver) resulting in inflammation and the patient potential for cirrhosis. The kidneys can also be affected, as there is an association with micro albuminuria – the leaking of protein into the urine, a subtle but clear indication of kidney damage, other problems associated with metabolic syndrome include obstructive sleep apnea, polycystic ovary syndrome, risk of dementia with aging and cognitive decline in the elderly (Reaven G. 2006).

The criteria proposed by WHO include:

Impaired fasting glucose or insulin resistance and two of the following:-

- Blood pressure $\geq$ 140 / 90 mmHg.
- Dyslipidemia:-

Triglyceride $\geq$ 150 mg/dl (1.7 mmol/L).

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High density lipoprotein HDL-C < 40 mg/dl (up to 1.0) mmol/L for males and < 50 mg/dl (up to 1.3) mmol /L for females.

- Central obesity: waist measured in centimeters at the navel by placing a tape measure around the bare abdomen just above the hip bone: hip was measured in centimeters by wrapping the tape measure around the widest part of the hip. Ratio > 0.90 (male), > 0.85(female) or body mass index.
- Micro albuminuria: urinary albumin excretion ratio > 20 pg. /min or urinary albumin/Creatinine ratio ≥ 30 mg/g.

Metabolic syndrome is not a discrete entity known to be caused by a single factor. Moreover, it shows considerable variation in the components among different individuals. This variation is even greater among different racial and ethnic groups (AHA/NHLBI scientific statement 2005). The exact mechanisms of the complex pathways of metabolic syndrome are under investigation. The pathophysiology is very complex and has been partially elucidated. The most important factors are Genetic, Aging, Diet particularly sugar- sweetened, beverage consumption, Low physical activity, Disrupted sleep, Mood disorders and/or Medication use.

Leptin (from a Greek word meaning thin) is a product of the ob gene with molecular mass of a 16-KDa. This adipokine is secreted primarily by the adipocytes (Brennan Am, et al, 2006). Human leptin is a protein of 167 amino acids. It is manufactured primarily in the adipocytes of white adipose tissue, and the level of circulating leptin is proportional to the total of fat in the body; in addition to the white adipose tissue, the major source of leptin. It can also be produced by brown adipose tissue, placenta, ovaries, skeletal muscle, and fundus of the stomach, mammary epithelial cells, bone morrow, pituitary and liver**.** Leptin acts on the central nervous system, in particular the hypothalamus, suppressing food intake and stimulating energy expenditure (Margetic S. et al, 2002**).** The presence of receptors for leptin, not only in the hypothalamus, but also in peripheral tissues including adipose tissue, liver, skeletal muscle and islet cells suggest that leptin has peripheral, as well as central action (Tartaglia LA. et al, 1995) and (Muleen J. et al, 1997). Such actions have been confirmed by experimental studies which have suggested that leptin can impair insulin signaling both in skeletal muscle and adipocytes (Carvalheira JB. et al, 2003). To date, only leptin and insulin are known to act as adiposity signals that signify the amount of body fat, in general: Leptin circulates at levels directly proportional to body fat, it enters the central nervous system in proportion to its plasma concentration, it's receptors are found in brain nervous system involved in regulating energy intake and expenditure and it controls food intake and energy expenditure by acting on receptors in the mediobasal hypothalamus (Benoit Sc. et al, 2004) and (Williams KW. et al., 2009**).**

Adiponectin is an adipokine first described just over a decade ago, produced almost exclusively by adipocytes. It circulates in high concentration in human plasma. Researches into this hormone have revealed it has insulin-sensitizing, anti-inflammatory and cardiovascular roles (Fang X. et al, 2006). It is a protein hormone of a 244 amino acid long peptide. It circulates in high concentration in healthy adults accounting for 0.01 % of total plasma protein, and its plasma levels are a thousand times than leptin. Circulating level of adiponectin range between 8.8 and 14.4 µg/ml in humans and are generally higher in females than males (Koncsos P. et al, 2010). This sexual dimorphism has been attributed to the effect of testosterone on adiponectin secretion (XUA et. al, 2005). The gene encoding human adiponectin has been mapped to chromosome $3q^{27}$. In serum, adiponectin exists as three main forms, trimers, hexamers and high molecular weight (HMW) multimers.

It is well-known that adiponectin levels increase with age, however the cause of this is still unknown. Rises in age related adiponectin may be a result of a salvage mechanism against age related illness such as metabolic dysfunction, atherosclerosis and other inflammatory conditions. Satter and Nelson had given four different names by four independent groups. It was first discovered by (Scherer PE, et al 1994) who named it adipocyte complement-related protein of 30 KDa (ACRP30). Spiegelman and colleagues called the protein isolated Adipo Q (Hu. E et al, 1996). Adiponectin also called gelatin binding protein 28 (GBP28). Murine studies show half-life of circulating adiponectin to be 75 minutes with clearance mediated by the liver. HMW adiponectin has the slowest plasma clearance rate and serum levels remain constant. The initial clinical study of adiponectin measured its plasma levels in obese subjects who had significantly lower plasma adiponectin concentration than did non obese subjects. There is a negative correlation between plasma concentration of adiponectin and BMI in men and women (Arita Y. et al, 1999). Plasma adiponectin

concentration in humans correlated negatively with visceral fat area in both genders. This negative correlation was stronger with visceral adiposity than with subcutaneous adiposity (Wellen K.et al, 2003). Studies found that plasma adiponectin concentration were positively correlated with HDL-C levels. Adiponectin could reduce the release of Apo B and ApoE from hepatocyte resulting in reduced release of triglyceride rich lipoproteins from the liver thus preventing the formation of cholesterol rich LDL and leading to elevated systemic HDL (Neumelir M. et al, 2007). There is also relationship between plasma adiponectin levels and diabetes. The initial study with diabetic patient showed lower plasma adiponectin concentration. High levels of adiponectin offered stronger protection against type II diabetes (Weyer C. et al, 2001). Adiponectin mediates insulin-sensitizing effect through binding to its receptors adipoR1 and adipoR2, leading to activation of adenosine monophosphate dependent kinase (AMPK), peroxisome proliferator-activated receptor alpha (PPAR−∝) and presumably other yet unknown signaling pathways. These clinical studies provide an indication that adiponectin contributes to the development of insulin resistance and diabetes (Yadav A et al, 2013).

MATERIALS AND METHOD:

Fifty eight (58) adult males were included in this study as the metabolic syndrome group depending on the presence of any 3 out of 5 of the NCEP ATPIII criteria as compared to 24 healthy adult males (control group) by their anthropometric measurements, some biochemical parameters and hormones. Pre-tested questionnaire designed to obtain information on age, weight, height, hip, waist circumference and use of medication. Anthropometries measurements have been applied (weight, height, waist and hip circumferences), Body Mass Index, Blood pressure, Also Biochemical investigations (Blood Glucose, cholesterol, Triglyceride & HDL-Cholesterol) By spectrophotometer Device according to enzymatic cholorimetric test . And the Determination of the two hormones serum leptin and adiponectin levels have been done By Elisa. The serum extracted was used for measuring glucose and lipid profile at the same day, while the rest of the serum was stored in vials labeled and frozen at (-20) ℃ until used for hormonal analysis (leptin and adiponectin).

RESULTS AND DISCUSSION:

The study showed the leptin/Adiponectin ratio has positive correlation with HDL-Cholesterol. Also has negative correlation with BMI, glucose level, triglyceride and cholesterol, moderately negative correlation with waist circumference and weak negatively correlation between W/H ratio.

Table 1: Anthropometric measurements: a comparison between the control group and MS group.

Studied groups	NO.	BMI (Kg/ m^2)	Std. Error	WC (cm)	Std. Error	W/H ratio	Std Error
Apparently healthy (control)	24	25.95 ± 5.05	1.03	89.92 ± 8.40	1.71	0.86 ± 0.03	0.01
MS group	58	33.7 ± 5.9	0.77	115.1±9.66	1.29	1.006 ± 0.39	0.05
Total	82	----		----		---	---
P-value		P =0.00 HS (P<0.01)		P = 0.00 HS (p<0.01)		P = 0.087 NS (p>0.05)	----

Table 2: Biochemical serum analysis of FSG, Cholesterol, S.TG and HDL-C in the studied groups.

Investigated groups	FSG (mg/dl)	Std. Error	S. Cholesterol (mg/dl)	Std. Error	S.TG (mg/dl)	Std. Error	S.HDL-C (mg/dl)	Std. Error
Apparently healthy (Control)	79.83 ± 20.5	4.18	167.67 ± 22.6	4.61	102.5 ± 31.13	6.35	43.62 ±3.17	0.647
MS group	139.9 ± 70.14	9.21	208.2 ± 36.7	4.83	245.57 ± 112.1	14.72	35.60±3.4	0 .446
P-value	P=0.01 HS (p<0.01)		P=0.01 HS (p<0.01)		P=0.01 HS (p<0.01)		P=0.01 HS (p<0.01)	

Table 3: Hormonal assay and ratio in the studied groups.

Studied group	Adiponectin Mean(µg/ml)	Std. Error	Leptin Mean (ng/ml)	Std. Error	(A/L) ratio	Std. Error
Apparently healthy (control)	15.09 ± 9.95	1.97	6.76 ± 6.15	1.26	1.35 ± 2.18	0.50
MS group	5.3 ± 2.45	0.32	31.33 ± 24.1	6.63	0.54 ± 1.04	0.14
P-value	HS < 0.01	----	HS < 0.01	----	S < 0.05	----

Table 4: Coefficient correlations between adiponectin, leptin and Adiponectin/Leptin ratio with parameters of MS and anthropometric factors.

Parameters	Pearson correlation	Adiponectin (µg/ml)	Serum Leptin (ng/ml)	Adiponectin/Leptin ratio
Serum leptin	r	-.344		
	P-value	.028		
	Sig	S		
Adiponectin/Leptin ratio	r	.684	-.518	
	P-value	.000	.001	
	Sig	HS	HS	
Age / year	r	.076	-.060	-.072
	P-value	.569	.710	.593
	Sig	NS	NS	NS
BMI (kg/m^2)	r	-.293	.027	-.309
	P-value	.046	.881	.035
	Sig	S	NS	S
FSG (mg/dl)	r	-.342	.411	-.321
	P-value	.019	.016	.028
	Sig	S	S	S
S. Triglyceride (mg/dl)	r	-.709	.524	-.527
	P-value	.000	.021	.003
	Sig	HS	S	HS
S. HDL- cholesterol (mg/dl)	r	.321	-.597	.331
	P-value	.038	.000	.032
	Sig	S	HS	S
Waist / (cm)	r	-.664	.073	-.412
	P-value	000	.748	.016
	Sig	HS	NS	S
W/H	r	-0.192	0.178	-0.166
	P-value	0.148	0.265	0.212
	Sig	NS	NS	NS

Statistical analysis includes Chi-square, t-test & Pearson correlation (r).

CONCLUSION:

In general it can be concluded from this study that:

1. Adiponectin/leptin ratio can be used as a good parameter and laboratory index for prediction of metabolic syndrome in the Iraqi adult males population.

2. We can use simple measures like waist circumference (WC) and body mass index (BMI) for prediction of the metabolic syndrome in Iraqi adult males population.

REFERENCES:

1. Benoit Sc, clegg DJ, Seeley RJ, woods Sc. "Insulin and leptin as adiposity signals" Recent prog Horm. Res 2004:59: 267-85 PMID 14749506.
2. Fang X, Sweeney G. "Mechanisms regulating energy metabolism by adiponectin in obesity and diabetes". Biochem. Soc. Trans. 2006; 34:798-801.
3. Koncsos, P; Seres I; Harangi M, Illyës I, Jözsa L; Gönczi F, Bajnok L Paragh G. Human paraxonase -1 activity in childhood obesity and its relation to leptin and adiponectin levels. Pediatric Reserches, 2010; 67:309-13.
4. Scherer PE, Lisanti MP, Baldini G, Sargiacomo M, Mastick CC, Lodish HF: Induction of caveolin during adipogenesis and association of GLUT4 with caveolin-rich vesicles. J. Cell Biol 1994;127: 1233–43.
5. Hu E, Liang P, Spiegelman B.M. AdipoQ is a novel adipose-specific gene dysregulated in obesity. Journal of Biological chemistry 1996; 271:10697-703.
6. Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, Hotta K, Shimomura I, Nakamura T, Miyaoka K, et al: Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem Biophys Res commun 1999; 257:79-83.
7. Wellen K. and Hotamisligil G.. Obesity induced inflammatory changes in adipose tissue. J. Clin., invest. 2003;112:1785-88.
8. Weyer C.; Funahashi T.; Tanaka S.; Hotta; Marsuzawa Y. et al., Hypoadiponectinemia in obesity and type 2 diabetes. Close association with insulin resistance and hyperinsulinemia. J. Clin Endocrinal Metab 2001;86:1930-33.
9. XUA, Chan K W, HooR, Wang Y, Tan KC, Zhang J, Chen B, Lam Mc, Ts C, Cooper GJ, Lam Ks: Testosterone selectively reduces the high molecular weight form of adiponectin by inhibiting its secretion from adipocytes. J. Biol. Chem. 2005; 280: 18073-80.
10. Yadav A, Kataria MA, Saini V, Yadav A. Role of leptin and adiponectin in insulin resistance. Clin Chim Acta. 2013 Feb 18; 417:80-4. doi:10.1016/j.cca.2012.12.007. Epub 2012 Dec 22. Review. PMID 23266767.
11. Gill H. Mugo M. Whaley-Connell A. Stump C and Sowers J. the Key role of insulin resistance in the cardio metabolic syndrome. The American journal of medical sciences, 2005;330: 290-94.
12. Albright, A.L. and stern, J.S. adipose tissue in Encyclopedia of sports medicine and science 1998.
13. Reaven G. The metabolic syndrome: is this diagnosis necessary? Am J Clin Nutr. 2006;83:1237-47.
14. Margetic S. Gazzola C, Pegg GG, Hill RA. "Leptin: a review of its peripheral actions and interactions" Int. J. obes. Relat. Metab. Disord. 2002;26:1407-33.
15. Mullen J, M pre; bisch G. Leptin impairs metabolic reactions of insulin in isolated rat adipocytes. Biological chem. 1997:10585-93.
16. Tartaglia LA. Debski M. Weng X, Deng N, culpepper J, Devos R. Richards Gh, campfield LA, clark FT, Deesd J, Muiro smiker S, Molriarty A. MooremKJ, smut Ko JS, Mays GG, Moore CA. Teppr RI. Identification and expression cloning of a leptin receptor, OB-R cell 1995:1263-71.
17. Carvalheira JB, Ribeiro EB, Folli F, Velloso LA, Saad MJ.Biol Chem. 2003; 384:151-59.
18. Brennan AM, Mantzoros Cs Drug insight: "The role of leptin in human's physiology and pathology emerging clinical applications". Nat Clin pract Endocrinol Metab2.2006: 318-27.
19. Williams KW, Scoot MM, Elmquist JK "From observation to experimentation: Leptin action in the mediobasal hypothalamus" Am. J. clin Nutr . 2009;89: 9.