How to Cite:
Malhotra, M., & Ahmed, F. (2022). Evaluation of PPAR-γ with lipid profiles and blood glucose in obese persons with DM type 2 and obese persons without DM type 2. *International Journal of Health Sciences*, *6*(S3), 778–785.
https://doi.org/10.53730/ijhs.v6nS3.5466

Evaluation of PPAR-γ With Lipid Profiles and Blood Glucose in Obese Persons with DM Type 2 and Obese Persons Without DM Type 2

Manish Malhotra
Associate Professor, Department of Biochemistry, Sri Ram Murti Smarak Institute of Medical Science, Bhojipura, Bareilly, Uttar Pradesh, India

Faruque Ahmed
Assistant Professor, Department of Biochemistry, I Q City Medical College & Hospital, Durgapur, West Bengal, India

***Abstract*---**PPAR-γ is expressed at high levels in adipose tissue and is a central regulator of adipocyte gene expression and differentiation. PPAR-γ is induced during adipocyte differentiation, and retroviral expression of PPAR-γ stimulates adipose differentiation of cultured fibroblasts. Several studies demonstrate that PPAR-γ is both necessary and sufficient to promote differentiation of fat cells both in vivo and in vitro. The present study has been conducted at the Department of Biochemistry, Shri Ram Murti Smark Institute of Medical Sciences (SRMS IMS), Bareilly U.P. India. Among 30 Adult normal persons, 30 Adult obese persons without DM type 2 and 30 Adult obese persons with DM type 2 were selected for the study. BMI was measured for each subject and proposed biochemical parameters were estimated in their blood samples. The Subject chosen were not on any drug treatment during days of blood collection. Age of the subject was between 25-65 years. For the present study 30 normal (control) and 60 obese cases were taken. Out of 60 obese cases, 30 were found to be without DM Type-2 and 30 cases with DM Type-2. The level of PPAR-γ in obese with DM-2 varies from 0.01mg/dl to 35.6mg/dl with mean 8.04mg/dl and control group varied from 0.2mg/dl- 8mg/dl with mean 2.45mg/dl. The difference in the level of PPAR-γ between obese with DM-2 and control group is significant (p value 0.008). The level of PPAR-γ in obese without DM-2 varied from 0.1ng/ml to 36ng/ml with mean 8.03ng/ml and control group varied from 0.2ng/ml-8.1 ng/ml with mean 2.45ng/ml. The difference in the level of PPAR-γ between obese without DM-2 and control group is significant (p value 0.01) Considering the wide range of actions on glucose, lipid metabolism and cell proliferation/apoptosis, PPARs and

their modulators are suggested for the treatment of metabolic disorders such as hyperglycaemia, dyslipidemia and atherosclerosis. The prevention and treatment of both lipid and glucose profile disorders should consider the potency and affinity of selective PPARs and their potential influences.

***Keywords*---**PPAR-γ, lipid profiles, blood glucose, DM type 2.

Introduction

The incidence of obesity (defined as having a body mass index (BMI) of greater than 30 kg per m^2) is increasing dramatically in virtually all societies of the world, and with it come important pathological consequences such as type 2 diabetes mellitus and cardiovascular disease[1]. The global incidence of type 2 diabetes is projected to double to 350 million cases by the year 2030[2]. Although progression to type 2 diabetes occurs more frequently in obese humans compared with lean individuals, this association is highly dependent on genetic background. Inbred mouse strains vary widely in their metabolic response to high-fat diets and to the impact of obesity on insulin sensitivity and development of diabetes[3,4].

Likewise, despite an increased risk, many obese human subjects do not progress to the diabetic state, which suggests that genetic and/or environmental factors also play a part. Nonetheless, it is generally accepted that two features are particularly critical for obesity to elicit type 2 diabetes. First, impaired responsiveness of skeletal muscle to insulin is a primary condition in obesity and a precondition for the onset of type 2 diabetes. The association between obesity and skeletal muscle insulin resistance is probably a causal relationship, as studies in humans and animals indicate thatweight loss and gain correlate with increasing and decreasing insulin sensitivity, respectively[5]. In insulin-resistant individuals that are not diabetic, glycaemic control can be maintained by compensatory increases in insulin secretion by pancreatic β-cells.[6] Thus, a second defect required for progression from insulin resistance to type 2 diabetes is the failure of β-cells to secrete the required levels of insulin that maintain normal fasting blood glucose levels[7].

PPAR-γ is expressed at high levels in adipose tissue and is a central regulator of adipocyte gene expression and differentiation.[8] PPAR-γ is induced during adipocyte differentiation, and retroviral expression of PPAR-γ stimulates adipose differentiation of cultured fibroblasts.[9] Several studies demonstrate that PPAR-γ is both necessary and sufficient to promote differentiation of fat cells both in vivo and in vitro.[10] In contrast, PPAR-γ antagonists inhibit adipocyte differentiation.[11] Consistent with these findings, humans with dominant-negative mutations in PPAR-γ manifest partial lipodystrophy and severe peripheral and hepatic insulin resistance because of increased triglyceride and fatty acid deposition into skeletal muscle and liver.[12]

Clearly, there would be great benefits if research could achieve effective prevention and therapies for obesity and associated type 2 diabetes. Hampering these efforts are many complexities in studying metabolic disease, including a

strong social influence on the incidence of obesity. This is reflected in the Indian by the striking inverse correlation between obesity and income. Furthermore, it is difficult to determine the molecular mechanisms that underlie metabolic disease from studies on human subjects.

Materials and Methods

The present study has been conducted at the Department of Biochemistry, Shri Ram Murti Smark Institute of Medical Sciences (SRMS IMS), Bareilly U.P. India. Among 30 Adult normal persons, 30 Adult obese persons without DM type 2 and 30 Adult obese persons with DM type 2 were selected for the study. BMI was measured for each subject and proposed biochemical parameters were estimated in their blood samples. The Subject chosen were not on any drug treatment during days of blood collection. Age of the subject was between 25-65 years. Subjects were taken from out-patient Department and Indoor-patient Department of Medicine, SRMS IMS Bareilly U.P. India. Subjects were of both sexes coming from reasonable distance around Bareilly city, U.P. India. They were from lower and middle class of rural area having moderate physical activities, with vegetarian as well as non-vegetarian dietary habits.

The Height (meters), weight (kg) and BMI were recorded. Obese subjects had a BMI equal or greater than 25 and normal subject had a BMI less than 25. The waist (waist circumference was measured with a soft tape a standing subject mid way between the lower rib and iliac crest) (hip circumference was measured over the widest part and gluteal region) and therefore waist to hip ratio measured. The detailed history of all the subjects were taken, and it was insured that the patient were not any drug treatment and were on overnight fasting for statistical significance and comparison, all these cases were divided into four different groups.

Group-1: Control Group
Serum PPAR- γ level along with lipid profile and fasting Blood glucose was done in 30 normal healthy individuals of both sexes. Each individual of this group was examined clinically and was included in the study after finding them a normal individual.

Group-2: Obese Group: Serum PPAR-γ level along with lipid profile and fasting Blood glucose was estimated in 60 cases of obese persons.

Group-3: Obese without DM type-2
Out of 60 cases of obese, 30 were obese without DM type-2 selected as the basis of fasting Blood glucose level.

Group-4: Obese with DM type-2
Out of 60 cases of obese, 30 were obese with DM type-2, selected on the basis of fasting Blood glucose level.

Inclusion Criteria

1. All the patients were without any drugs treatment during blood sample collection.
2. Had some symptoms of Diabetes Mellitus.
3. Obese on the basis of BMI i.e. more than 25

Exclusion Criteria

1. Cases taking same drug treatment for same disease.
2. Cases suffering from chronic diseases.

Following estimation were done in Department of Biochemistry, SRMS IMS Bareilly U.P. India.

1. Fasting Blood Glucose level in serum.
2. Serum PPAR-γ

Local Research Ethic Committee approval was taken for the study before it commenced. Written consent was taken from the subject included in the study.

Sample processing

Before collecting venous blood sample using standard venipuncture into vial subjects were asked to have a fasting period of 12 hrs. for the standardization blood was drawn in sitting position from anticubital vein. These samples were collected in three different vial are for measuring factor included in the study i.e. PPAR-γ. Blood was allowed to clot and was immediately centrifuged at 5000rpm for 10 minutes. Serum was collected and stored immediately at -20c until assay performed.

Method of serum PPAR-γ level estimation

The qualitative estimation of PPAR-γ in human serum was done by ELISA method using ELISA kit from E lab science Biotechnology co.ltd.

Result

Table 1
Phenotypic characters of the studied groups

	Group 1	Group 2	Group 3	Group 4	
Age Range	30-57	21-65	35-60	33-56	
(year) Mean±SD	44.8± 8.1	43.5± 14	47.4± 7.8	46.2± 6.5	p= 0.75
Fasting bl. glucose Range(mg/dl)	60 - 90	65 - 95	90 - 120	95 - 125	
Mean±SD	64.8± 5.35	69.09 ± 5.6	98.79 ± 9.69	104.76± 9.6	<0.001
Post prandial glucose.	100-130	105 – 135	118 - 137	158 – 210	

Range (mg/dl) Mean±SD	105.34±10.38	112.36 ± 10.97	124.4 ± 12.5	166.6 ± 12.3	<0.001
Fasting Insulin. Range (µu/ml)	5.9 -10	7 -15	8.2 -15.5	12 -15.5	<0.001
Mean±SD	7.98 ± 1.1	8.4 ± 1.6	9.8 ± 1.14	14.57 ± 0.99	

BMI: Body Mass Index HOMA-IR homeostasis model assessment of insulin resistance.

Table 2
The distribution of cases taken

Group	BMI (Kg/m^2)	No. of cases
Group 1	<25	30
Group 2	>25	60
Group 3	>25	30
Group 4	>25	30

For the present study 30 normal (control) and 60 obese cases were taken. Out of 60 obese cases, 30 were found to be without DM Type-2 and 30 cases with DM Type-2. This is shown in Table-2

Table 3
Lipid profile of the studied groups

Lipid profile	Group 1	Group 2	Group 3	Group 4	p-value
Cholesterol	211.01±18.1	231.12 ±17.5	241.01±18.2	281.01 ±19.2	<0.001
Triglycerides	149.7 ±12.1	150.1 ±11.3	268.9±12.4	279.2 ±13.1	<0.001
HDL	42.9 ±3.1	43.1 ±4.2	40.6 ±4.1	37.9 ±3.9	<0.048
LDL	126.2 ±8.9	127.2 ±8.9	117.6 ±9.2	128.3 ±9.4	<0.001
VLDL	158.3 ±9.3	159.1 ±11.4	147.8 ±12.1	159.6 ±13.2	<0.037

Table 4
Statistical analysis of level of PPAR-γ in obese cases with DM-2 and control group. (Non obese non Diabetic)

Group	No. of cases	PPAR-γ (ng/ml)			P-value	Remark
		Range	Mean	SD		
Obese with DM Type 2	30	0.1-35.6	8.04	10.94	0.008	S
Control group- Non obese Non Diabetic	30	0.2-8.1	2.45	1.99		

Table 4 shows level of PPAR-γ in obese with DM-2 varies from 0.01mg/dl to 35.6mg/dl with mean 8.04mg/dl and control group varied from 0.2mg/dl-8mg/dl with mean 2.45mg/dl. The difference in the level of PPAR-γ between obese with DM-2 and control group is significant (p value 0.008)

Table 5
Statistical analysis of level of PPAR-γ in obese cases without DM-2 and control group. (Non obese non Diabetic)

Groups	No. of cases	PPAR-γ (ng/ml)			P-value	Remark
		Range	Mean	SD		
Obese without DM-2	30	0.1-36	8.03	11.16	0.01	S
Control group	30	0.2-8.1	2.45	1.99		

Table 5 shows the level of PPAR-γ in obese without DM-2 varied from 0.1ng/ml to 36ng/ml with mean 8.03ng/ml and control group varied from 0.2ng/ml-8.1 ng/ml with mean 2.45ng/ml. The difference in the level of PPAR-γ between obese without DM-2 and control group is significant (p value 0.01)

Discussion

Obesity and diabetes mellitus, significant risk factors for the development of CAD, are becoming a global epidemic, which is related to environmental, behavioral, and genetic factors.[13] Although changes in lifestyle are effective in preventing both diabetes and obesity in high-risk adults with impaired glucose tolerance, achieving modifications in lifestyle have proven to be difficult.[14] Current recommendations suggest that in addition to nonpharmacological methods, drug therapy should be considered for patients with a BMI ≥30 kg/m^2 or a BMI of 27 to 30 kg/m^2 with ≥1 obesity-related disorders.[15] Currently available antiobesity medications either decrease food intake or reduce intestinal fat absorption. However, short-term clinical trials evaluating antiobesity medications demonstrated only modest weight loss compared with placebo, and there are no long-term clinical trials to examine mortality and cardiovascular morbidity. [16]
The adipose tissue plays a crucial role in the regulation of food intake, because it secretes a number of endocrine and paracrine mediators, including leptin, adiponectin, resistin, and TNF-α, which have been shown to influence appetite. Understanding the complex signaling system that underlies appetite control will likely offer new approaches for treatment strategies. The ability of PPAR-δ agonists to induce adaptive thermogenesis and protect against both diet-induced and genetically predisposed obesity in animal models suggest that PPAR-δ might be an exiting new target in the treatment of obesity. Of particular interest are the dual PPARs, a single ligand activating both γ and α and the pan PPARs, activating α, γ, and δ. [17]

All 3 of the PPAR isotypes attenuate inflammatory responses, which is important, because inflammation is intimately connected to appetite, insulin resistance, obesity, and atherosclerosis. These antiinflammatory actions result in improvement of atherosclerosis in some animal models, although the effect on atherosclerosis is also related to the PPAR ability to regulate foam cell formation. Future studies are required to elucidate these interactions and the role of PPAR ligands as potential candidates for treatment of obesity, type 2 diabetes, and atherosclerosis. [18]
PPARγ function might be modulated by inflammatory signalling is through its interactions with co-activators and corepressors. Numerous such activities have been found in association with PPARγ and other nuclear receptors. [19] The net

effect of PPARγ on energy storage (as triglyceride) compared with energy use (through oxidative pathways) depends in part on the balance among coregulators, which favour distinct pathways. Co-activators of PPARγ include steroid receptor co-activator-2 (SRC-2) and C-terminal-binding protein (CBP), which promote adipogenesis and energy storage[95]. The nuclear hormone corepressor receptor-interacting protein-140 (RIP140), however, negatively regulates oxidative pathways in adipocytes at least in part through interaction with PPARγ. [20] Conversely, PPARγ activity can be enhanced by the PPARγ co-activator-1α (PGC-1α), initially identified through its interaction with PPARγ in brown fat. [21]

Conclusion

Considering the wide range of actions on glucose, lipid metabolism and cell proliferation/apoptosis, PPARs and their modulators are suggested for the treatment of metabolic disorders such as hyperglycaemia, dyslipidemia and atherosclerosis. The prevention and treatment of both lipid and glucose profile disorders should consider the potency and affinity of selective PPARs and their potential cancerogenic influences. Therefore, natural compounds and their close derivatives are being targeted as future drugs against metabolic diseases. Even though early preclinical data are very promising, it is necessary to evaluate the clinical properties of new PPAR agonists and their influence on patient health.

References

1. Neschen S, Morino K, Dong J, Wang-Fischer Y, Cline GW, Romanelli AJ, Rossbacher JC, Moore IK, Regittnig W, Munoz DS, Kim JH, Shulman GI: n-3 Fatty acids preserve insulin sensitivity in vivo in a peroxisome proliferator-activated receptor-alpha-dependent manner. Diabetes 2007, 56(4):1034–1041.
2. Delerive P, Furman C, Teissier E, Fruchart J, Duriez P, Staels B: Oxidized phospholipids activate PPARalpha in a phospholipase A2-dependent manner. FEBS Lett 2000, 471(1):34–38.
3. Rao MS, Kashireddy P, Musunuri S, Okonkwo A: Prevention/reversal of choline deficiency-induced steatohepatitis by a peroxisomeproliferatoractivated receptor alpha ligand in rats. In Vivo 2002, 16(2):145–152.
4. Krey G, Braissant O, L'Horset F, Kalkhoven E, Perroud M, Parker MG, Wahli W: Fatty acids, eicosanoids, and hypolipidemic agents identified as ligands of peroxisome proliferator-activated receptors by coactivator-dependent receptor ligand assay. Mol Endocrinol 1997, 11(6):779–791.
5. Margeli A, Kouraklis G, Theocharis S: Peroxisome proliferator activated receptor-gamma (PPAR-gamma) ligands and angiogenesis. Angiogenesis 2003, 6(3):165–169.
6. Plutzky J: Peroxisome proliferator-activated receptors in vascular biology and atherosclerosis: emerging insights for evolving paradigms. Curr Atheroscler Rep 2000, 2(4):327–335.
7. Berger J, Moller DE: The mechanisms of action of PPARs. Annu Rev Med 2002, 53:409–435.
8. Boitier E, Gautier JC, Roberts R: Advances in understanding the regulation of apoptosis and mitosis by peroxisome-proliferator activated receptors in pre-

clinical models: relevance for human health and disease. Comp Hepatol 2003, 2(1):3.
9. Rogue A, Lambert C, Jossé R, Antherieu S, Spire C, Claude N, Guillouzo A: Comparative gene expression profiles induced by PPARγ and PPARα/γ agonists in human hepatocytes. PLoS One 2011, 6(4):e18816.
10. Rogue A, Spire C, Brun M, Claude N, Guillouzo A: Gene expression changes induced by PPAR gamma agonists in animal and human liver. PPAR Res 2010, 2010:325183.
11. Lo Verme J, Fu J, Astarita G, La Rana G, Russo R, Calignano A, Piomelli D: The nuclear receptor peroxisome proliferator-activated receptor-alpha mediates the anti-inflammatory actions of palmitoylethanolamide. Mol Pharmacol 2005, 67(1):15–19.
12. Sheu SH, Kaya T, Waxman DJ, Vajda S: Exploring the binding site structure of the PPAR gamma ligand-binding domain by computational solvent mapping. Biochemistry (Mosc) 2005, 44(4):1193–1209.
13. Medina-Gomez G, Gray SL, Yetukuri L, Shimomura K, Virtue S, Campbell M, Curtis RK, Jimenez-Linan M, Blount M, Yeo GSH, Lopez M, Seppänen-Laakso T, Ashcroft FM, Orešič M, Vidal-Puig A: PPAR gamma 2 prevents lipotoxicity by controlling adipose tissue expandability and peripheral lipid metabolism. PLoS Genet 2007, 3(4):e64.
14. Wang YX, Lee CH, Tiep S, Yu RT, Ham J, Kang H, Evans RM: Peroxisomeproliferator-activated receptor delta activates fat metabolism to prevent obesity. Cell 2003, 113(2):159–170.
15. Willson TM, Brown PJ, Sternbach DD, Henke BR: The PPARs: from orphan receptors to drug discovery. J Med Chem 2000, 43:527–550.
16. Viswakarma N, Jia Y, Bai L, Vluggens A, Borensztajn J, Xu J, Reddy JK: Coactivators in PPAR-regulated gene expression. PPAR Res 2010, 2010:2050126.
17. Heikkinen S, Auwerx J, Argmann CA: PPARγ in human and mouse physiology. Biochim Biophys Acta 2007, 1771(8):999–1013.
18. Feige JN, Gelman L, Michalik L, Desvergne B, Wahli W: From molecular action to physiological outputs:peroxisome proliferator-activated receptors are nuclearreceptors at the crossroads of key cellular functions. Prog Lipid Res 2006, 45(2):120–159.
19. Ren D, Collingwood TN, Rebar EJ, Wolffe AP, Camp HS: PPARgamma knockdown by engineered transcription factors: exogenous PPARgamma2 but not PPARgamma1 reactivates adipogenesis. Genes Dev 2002, 16(1):27–32.
20. Werman A, Hollenberg A, Solanes G, Bjorbaek C, Vidal-Puig AJ, Flier JS: Ligand-independent activation domain in the N terminus of peroxisome proliferator-activated receptor gamma (PPARgamma). Differential activity of PPARgamma1 and −2 isoforms and influence of insulin. J Biol Chem 1997, 272(32):20230–20235.
21. Sertznig P, Seifert M, Tilgen W, Reichrath J: Present concepts and future outlook: function of peroxisome proliferator-activated receptors (PPARs) for pathogenesis, progression, and therapy of cancer. J Cell Physiol 2007, 212(1):1–12.